

## Evidence-based management for preeclampsia

Peter von Dadelszen<sup>1,2,3</sup>, Jennifer Menzies<sup>1,3</sup>, Sarah Gilgoff<sup>1,3</sup>, Fang Xie<sup>1</sup>, M Joanne Douglas<sup>4</sup>, Diane Sawchuck<sup>5</sup>, Laura A Magee

<sup>1</sup> Department of Obstetrics and Gynaecology, <sup>2</sup> Department of Health Care and Epidemiology, <sup>3</sup> The CFRI Centre for Healthcare Innovation and Improvement, <sup>4</sup> Department of Anesthesiology, Pharmacology and Therapeutics, and <sup>6</sup> Department of Medicine, University of British Columbia <sup>5</sup> and British Columbia Reproductive Care Program, Provincial Health Services Authority, Vancouver, BC, Canada

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### 1. ABSTRACT

This review reflects both the variable presentation and the systemic nature of preeclampsia. Recommendations for the comprehensive evaluation and management of organ dysfunction associated with preeclampsia are included. The main points in the review are that: (1) Preeclampsia is a systemic disorder that may affect many organ systems. (2) For preeclampsia remote from term (<34 weeks), expectant management improves perinatal outcomes, but requires obsessive surveillance to mitigate maternal risks and is a “package.” (3) Initial assessment and ongoing surveillance of women with preeclampsia should include assessment of all vulnerable maternal organs as well as of the fetus. (4) Initiate antihypertensive drug treatment immediately if sBP  $\geq 160$ mmHg or dBp  $\geq 110$ mmHg, or if sBP 140-159mmHg and/or dBp 85-109mmHg (prepregnancy renal disease or diabetes). (5) The treatment of nonsevere pregnancy hypertension should include a treatment goal of dBp 80-105 mmHg (depending on practitioner preference), with one of the following agents, Methyldopa, Labetalol, Nifedipine, or, with special indications (renal or cardiac diseases), diuretics. (6) Drugs to avoid: angiotensin-converting enzyme inhibitors; angiotensin II receptor antagonists; and atenolol. (7) For the acute management of severe hypertension, initially reduce dBp by 10mmHg and maintain the blood pressure at or below that level with either Nifedipine or Labetalol. (8) For both prophylaxis against and treatment of eclampsia, MgSO<sub>4</sub> (4g IV stat, then 1g/hr). (9) For recurrent seizures, MgSO<sub>4</sub> (2g IV stat, then increase to 1.5g/hr). (10) Total fluid intake should not exceed 80ml/hr; tolerate urine outputs as low as 10ml/hr. (11) Early-onset and/or severe preeclampsia predict later cardiovascular morbidity and mortality; it would seem prudent to offer such women screening and lipid lowering interventions.

### 2. INTRODUCTION

This review reflects both the variable presentation and the systemic nature of preeclampsia and the other hypertensive disorders of pregnancy (1-9). The recommendations are derived from the pattern of investigation used in other centers of excellence, in response to international guidelines (10-14), in response to current practice across Canada (15;16), and from preliminary evidence that it may be possible to predict those women most at risk of doing poorly (5;17). It must be remembered that up to 40% of women who develop eclampsia (seizures) will not have had both hypertension and proteinuria in the week preceding their first seizure (18). Therefore, to proffer the greatest safety to women, we should consider (and continue to consider) preeclampsia in all women presenting with either hypertension or proteinuria in pregnancy, as well as those women who present with the symptoms of preeclampsia in the absence of both hypertension and proteinuria.

Preeclampsia remains the most common cause of maternal mortality in North America, and it is apparent that the surveillance of women with suspected or confirmed

pre-eclampsia is variable between practitioners. (15;16) In an era of effective blood pressure control (19;20), it is end organ failure (especially hepatic and respiratory complications) that most commonly causes women to die from preeclampsia (7;8). This review includes recommendations for the comprehensive evaluation of organ dysfunction.

The pattern of investigations aims to standardize the approach to care, with consideration that the choice of Mondays to Thursdays provides the best timing for delivery of infants (away from Friday evenings and weekends). Of course, some or all of these investigations may be performed at other additional times, at the discretion of the attending physician.

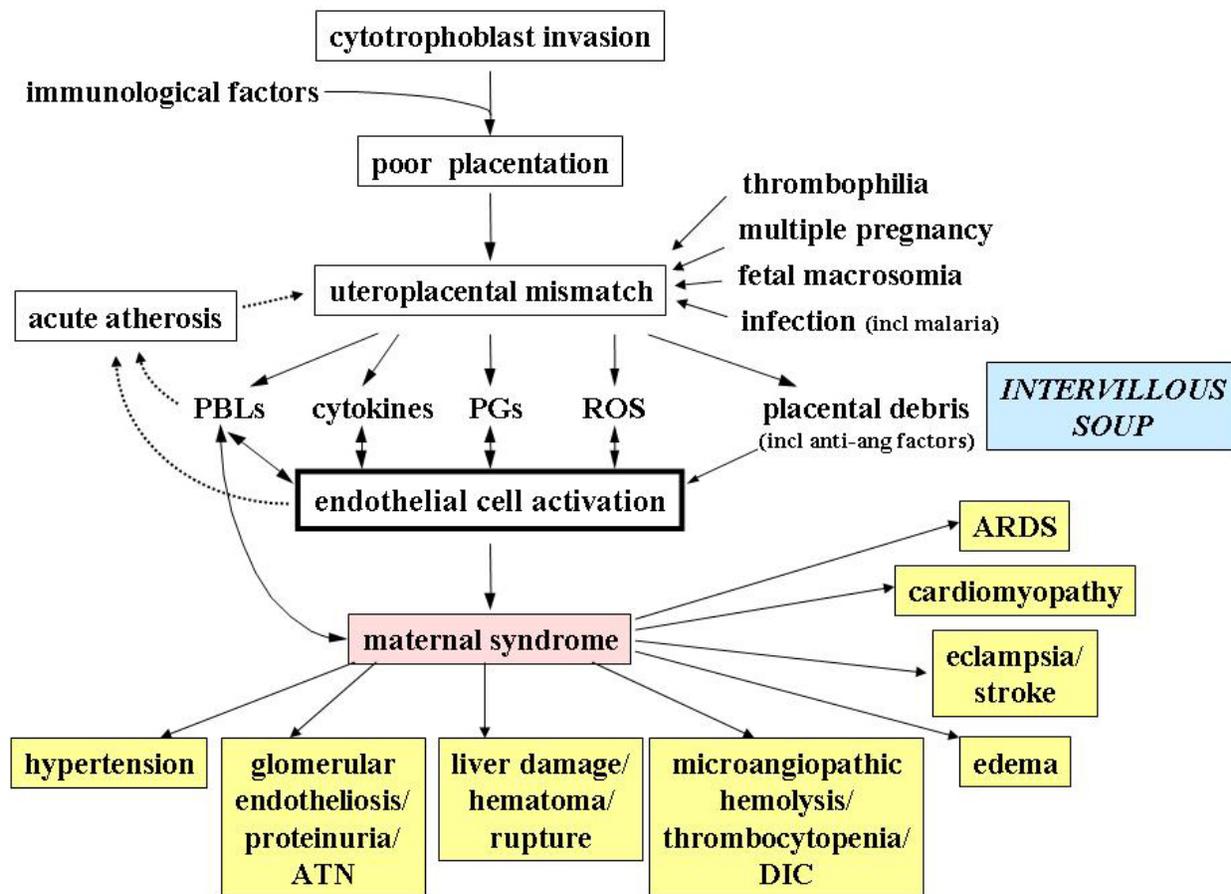
At BC Women's Hospital and Health Centre, since the introduction of the preprinted physician orders in September 2003, the incidence of an internationally-determined combined adverse maternal outcome has fallen from 5.1% to 1.2% Fisher's exact  $p < 0.05$  in those women admitted with preeclampsia for whom these orders were used (21).

Preeclampsia is a multisystem disease, with variable progression leading to signs and symptoms requiring imminent treatment (8;22). Preeclampsia is associated with generalized vasospasm and progressive involvement of essential organs such as the kidney, liver, brain, and hematological systems (8;22). Maternal endothelial cell damage associated with the release of substances from the poorly perfused placenta initiates a dysfunctional cascade of coagulation, vasoconstriction and intravascular fluid redistribution that results in the clinical syndrome of preeclampsia/eclampsia (Figure 1) (8;22).

When inadequate fetal vascular development, recurrent ischemia-reperfusion injury, and vasospasm affect the uteroplacental bed, fetoplacental demands outstrip the maternal circulatory supply (8). The fetus then becomes growth restricted and at increased risk of stillbirth and neonatal death. The incidence of IUGR in the context of pre-eclampsia ranges from 30-80%, and the majority of IUGR is associated with early-onset disease. At term, there is an increased incidence of preeclampsia in women with macrosomic fetuses (23).

### 3. INDICATIONS FOR OUTPATIENT ASSESSMENT AND OFFICE MANAGEMENT

While the threshold for managing women with preeclampsia as inpatients remains low, it is reasonable to offer outpatient surveillance to women whose systolic BP (sBP) <140 mmHg and diastolic BP (dBp) <90 mmHg, with 1+ or less proteinuria on dipstick on one occasion, a normal platelet count, and without adverse features. In the presence of any of the above signs, closer surveillance should include: frequent office visits (every 3 to 4 days), close maternal and fetal assessment, and patient education regarding decreased activity and home/childcare assistance. Patients should be assessed at least weekly with an assessment of: CBC, including platelets, uric acid (an



**Figure 1.** The pathogenesis of preeclampsia. In this model of preeclampsia, the maternal syndrome develops from a number of alternative pathways, leading to uteroplacental mismatch, whereby the fetoplacental demands outstrip the maternal circulatory supply. In response to the mismatch, and probably caused, in part, by recurrent ischemia-reperfusion injury within the intervillous (maternal blood) space of the placenta and accelerated placental apoptosis, a soup of endothelium-damaging substrates is released, with resulting endothelial cell activation and consequent development of the maternal syndrome of preeclampsia. Some elements of the soup—namely, activated peripheral blood leukocytes—can cause direct end-organ damage. There is cross talk between elements of the soup (not illustrated). Activated protein C could modify both the inflammatory and coagulation consequences of the endothelial cell activation. *anti-ang*, anti-angiogenic; *ARDS*, acute respiratory distress syndrome; *ATN*, acute tubular necrosis; *DIC*, disseminated intravascular coagulation; *PBLs*, peripheral blood leukocytes; *PGs*, eicosanoids; *ROS*, reactive oxygen species. Modified with permission from 8.

elevated uric acid helps with the diagnosis of gestational hypertension), and liver enzymes. Once hypertension and proteinuria have evolved, it is likely that a woman will be delivered for either maternal or fetal indications within two weeks (19).

#### 4. INDICATIONS TO CONSIDER HOSPITALIZATION

Once one of the following arise, then hospitalization should be considered. A sBP  $\geq 140$ mmHg and /or dBP  $\geq 90$ mmHg, repeated 1+ or greater proteinuria 1+ on dipstick or protein:creatinine ratio  $>30$  mg protein per mmol creatinine, hyperuricemia, platelet count  $\leq 100 \times 10^9/L$ , any adverse features, and/or ultrasound evidence of oligohydramnios or inadequate fetal growth. Once hospitalized, a decision should be made whether to pursue

conservative management or to proceed to immediate delivery.

#### 4.1. Indications for conservative hospital management (24-26)

Stable, well-controlled blood pressure (sBP  $<160$ mmHg / dBP  $<110$ mmHg), and on less than maximal oral antihypertensive therapy for at least two agents (i.e., 1200mg labetalol/d + 2000mg methyl dopa/d + nifedipine (Adalat PA/XL formulations) 90mg/d).

Proteinuria  $\leq 2+$  on dipstick ( $<1$ g/day or  $<100$  mg/mmol by PCR); this marker of disease severity may not exclude conservative management at gestational ages remote from term, a plasma albumin  $<20$ g/L places the patient at greatly increased risk of pulmonary edema, and

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should be considered a contraindication for conservative management.

Platelet count  $\geq 100 \times 10^9/L$ ; this marker of disease severity may not exclude conservative management at gestational ages remote from term, depending on the rate of platelet count fall, and the presence or absence of concomitant liver enzyme abnormalities or coagulopathy.

The most important factor in determining conservative management is gestational age. (19) The presence of gestational hypertension with proteinuria at a mature gestational age (i.e.,  $\geq 34$  weeks) may signify need for delivery, depending upon progression of the disease, assessment of the fetus, and status of the cervix. If the gestational age is  $< 34$  weeks, management must balance maternal risks against fetal benefits. Patient delivery may be delayed if blood pressure is controlled (i.e., sBP  $< 160$ mmHg and dBP  $< 110$ mmHg), fetal assessment remains within tolerable limits (see above), platelet count remains  $> 50 - 100 \times 10^9/L$ , depending on practitioner expertise, training and comfort.

Studies suggest that conservative management of patients at gestational ages  $\leq 24$  weeks is associated with serious maternal complications and pregnancy termination should be considered (24;25). Under these circumstances, the patient may be eligible for experimental therapy (8).

The evidence supports conservative management of patients with adverse features between gestational ages of 24 to 32 weeks in tertiary care centers in a closely monitored setting with physicians very familiar with disease process (25).

### 4.2. Conservative management

The essential elements of conservative management are bed rest, initial assessment and ongoing surveillance, fetal assessment including non-stress tests and / or ultrasound surveillance (full biophysical profile or AFL/umbilical artery Doppler), and daily assessment by the physician with close attention to: weight gain, blood pressure variation over the previous 24 hours, proteinuria levels, fetal movement, and general symptoms. Steroids should be used to accelerate fetal lung maturation if  $< 34$  weeks (27).

### 4.3. Fetal assessment (9;28-33)

This should include an assessment of the deepest amniotic fluid pocket ( $> 2$ cm on ultrasound), a non-stress test (accepting one without decelerations at gestational ages remote from term; although preferably including a computerized assessment), and umbilical artery Doppler. End diastolic flow should be present on umbilical artery Doppler; at gestational ages  $< 34$  weeks, absent end diastolic flow does not necessarily mandate delivery, but certainly does mandate very close surveillance. Reversed end diastolic flow on umbilical artery Doppler is an indication for delivery, unless an active decision has been made not to intervene at gestational ages remote from term and/or with severe IUGR.

## 5. SEVERE PREECLAMPSIA (9;10)

### 5.1. Definitions

Severe preeclampsia (generally synonymous with 'gestational hypertension with/without proteinuria with one or more adverse conditions') (11;14) is defined as the occurrence of one/more of the following elements:

Maternal symptoms: severe nausea and vomiting, frontal or occipital headache, visual disturbance, persistent epigastric or right upper quadrant pain, chest pain, and/or dyspnea.

Maternal signs: dBP  $\geq 110$ mmHg, oliguria ( $< 500$ ml/d), pulmonary edema, and/or suspected abruptio placentae. Severe systolic hypertension: sBP  $\geq 160$ mmHg (based on 3 blood pressure readings in a 15 minute period).

Maternal laboratory findings: platelets  $< 100 \times 10^9/L$ , elevated liver enzymes (AST and/or ALT), plasma albumin  $< 18$ g/L, and/or heavy proteinuria ( $> 3$ g/d).

Fetal assessment: intrauterine growth restriction, oligohydramnios, and/or absent or reversed end diastolic flow on umbilical artery Doppler.

In clinical practice there are no reliable clinical markers to predict eclampsia (seizures). (9) The following are thought to predict the onset of eclampsia. However, even when these symptoms are present, in most instances eclampsia does not develop: severe headaches (especially occipital headaches), brisk reflexes  $> 3+$  ( $3+$  is hyperactive without clonus,  $4+$  is hyperactive with unsustained clonus ( $< 4$  beats),  $5+$  is hyperactive with sustained clonus ( $\geq 4$  beats)), papilledema, and/or visual disturbances (9).

### 5.2. Management of severe preeclampsia (10)

#### 5.2.1. General measures

Women should be assessed and managed in a quiet, well-lit room in a high dependency care type situation. Ideally there should be one-on-one nursing care; at least initially, when the stability of the condition is being assessed.(9). After initial assessment, transfer should be considered for maternal or perinatal reasons depending on the capacity of the local facility (10).

Expectant management requires obsessive surveillance to mitigate maternal risks and is a "package". Critical care flow charts should be commenced to record all physiological monitoring and investigation results. All treatments should be recorded. Consider involving a consultant obstetrician (even if only by telephone) and, if possible, either a consultant anesthesiologist /GP anesthesiologist or consultant internist, depending on local practice. Consultants should be involved at an early stage in management (10).

When oral antihypertensive treatment is possible, it should be regarded as the route of choice. An intravenous cannula should always be inserted. Intravenous fluid should be by controlled volumetric pump. Fluid administration should be judicious (10)

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**Table 1.** Items present on BC Women’s Hospital and Health Centre guidelines for the initial assessment and ongoing surveillance of gestational hypertension and/or gestational proteinuria; with frequency of data ascertainment

Organ system	Variable(s)	Frequency of ascertainment <sup>1</sup>					
		Adm	Adm +1	Mon	Thurs	Del	Del +1
Maternal							
Hepatic	Aspartate transaminase (AST)	X	X	X	X	X	X
	Lactate dehydrogenase (LDH)	X	X	X	X	X	X
	Bilirubin	X	X	X	X	X	X
Cardiovascular	Albumin	X	X	X	X	X	X
	Systolic BP	X	X	X	X	X	X
	Diastolic BP	X	X	X	X	X	X
Renal	Albuminuria:						
	24h urine	X		X		X	X
	spot protein:creatinine ratio	X		X		X	X
	Urine output	X	X	X	X	X	X
	Uric acid	X	X	X	X	X	X
Respiratory	Creatinine	X	X	X	X	X	X
	SaO <sub>2</sub>	X	X	X	X	X	X
Hematological	Platelet count	X	X	X	X	X	X
	Mean platelet volume (MPV)	X	X	X	X	X	X
	MPV:platelet count ratio	X	X	X	X	X	X
Perinatal	Fibrinogen	X	X	X	X	X	X
	Growth (U/S)	Estimate of fetal weight	An ultrasound to include an estimate of fetal weight, amniotic fluid index, and umbilical and middle cerebral artery Doppler studies will be performed within 3d of admission, and will be repeated no less frequently than fortnightly thereafter				
	Abdominal circumference <sup>2</sup>						
Vascular adaptation (U/S)	Umbilical artery Doppler						
	Middle cerebral artery Doppler						
Renal perfusion (U/S)	Amniotic fluid index						
CNS/ cardiovascular		Deepest amniotic fluid pocket	Daily				
		Cardiotocography (non-stress test), computerised if possible					
		Short term variability on cCTG <sup>3</sup>					

<sup>1</sup>no less frequently than; *Adm*: day of admission; *cCTG*: computerised cardiotocography; *CNS*: central nervous system; *Del*: day of delivery; *U/S*: ultrasound. <sup>2</sup>The measurement of the abdominal circumference (AC) is a component of the ultrasound estimate of fetal weight; an AC<10%ile is diagnostic of intrauterine growth restriction antenatally. <sup>3</sup> Short term variability is the most predictive component of the output from the cCTG.

### 5.2.2. Basic investigations

Baseline investigations could follow those listed on Table 1. The pattern of investigation described is the minimum required, and may need to be repeated at more frequent intervals in response to changing symptoms or signs. As such, investigations may be repeated at the discretion of the clinician. Although this list is longer than standard for most units, the incremental increase in costs is small. Instituting this pattern of investigations has been associated with a significant improvement in maternal outcomes (incidence of a combined adverse maternal outcome has fallen from 5.1% to 1.2% (Fisher’s exact  $p < 0.05$ ) (21).

### 5.2.3. Maternal assessment and monitoring

Blood pressure and pulse should be measured every 15 minutes for a minimum of 4 hours until stabilized and then half hourly (i.e., every 15min for  $\geq 4h$ , then every 30min). At least initially, an indwelling catheter should be inserted and urine output measured hourly whenever intravenous fluids are given (i.e., hourly). All urine should be tested for proteinuria. Urine outputs as low as 10 ml/hour should be considered adequate in the absence of pre-existing renal disease. The UK Confidential Enquiries into Maternal Deaths have found that excess maternal mortality is associated with aggressive fluid use and not with transient renal compromise (34).

Fluid administration should be judicious and fluid balance should be monitored very carefully. Detailed input and output recordings should be charted (i.e., hourly). Careful fluid balance is aimed at avoiding fluid overload. Total intravenous input should be limited to 80ml/hour (approximately 1ml/kg/hr, using current weight). If oxytocin is used, it should be at high concentration (20U/500ml normal saline or Ringers) and the volume of fluid included in the total input. Oliguria at this point should not precipitate any specific intervention except to lower thresholds for considering early delivery. As these women are at high risk of Cesarean section, oral fluids should also be limited.

Oxygen saturation should be measured continuously and charted with the blood pressure. If saturation falls below 95% then medical review is essential. Respiratory rate should be measured every hour (count for a full minute). Temperature should be measured 4-hourly. When present, CVP should be measured continuously and charted with the blood pressure.

### 5.2.4. Fetal assessment

A baseline non-stress test (cardiotocograph) should be performed, prior to administration of MgSO<sub>4</sub>, if possible. Unless the situation mandates immediate delivery, an initial ultrasound for growth, amniotic fluid assessment, and umbilical artery Doppler flow velocity waveform is advised.

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### 5.3 Thromboprophylaxis

All women should have anti-embolic stockings and/or heparin whilst they are immobile during the entire antenatal, intrapartum, and postpartum periods. Women with pre-eclampsia are at particularly increased risk for thromboembolic disease as their condition resolves (19). Unfractionated heparin 5000 IU sc twice daily should be given until the woman is fully mobile. A prophylactic dose of low molecular weight heparin (LMWH) can be used postpartum (20;21). Many clinicians do not see the use of unfractionated heparin as a contraindication to the insertion of an epidural, providing there is no evidence of a coagulopathy. Ideally the epidural would be inserted 1 hour prior to the next dose of unfractionated heparin, as there is a subset of patients who become therapeutically anticoagulated during sc heparin therapy. As unfractionated heparin has its peak effect between 2 and 6hr following its administration it probably is wise to avoid that time period for insertion of an epidural unless the APTT is normal (20;21).

LMWH is being used more widely in obstetric patients. Monitoring of the anti-Xa level is not recommended as it is not predictive of the risk of bleeding. Regional anesthesia should not be done within 12hr of administration of LMWH for thromboprophylaxis. Women receiving LMWH for therapeutic anticoagulation should not receive regional anesthesia for 24hr after the last dose to ensure normal hemostasis. An epidural catheter should be removed 10-12hr after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2hr after catheter removal. If bleeding occurs during insertion of neuraxial anesthesia initiation of LMWH therapy should be delayed 24hr (20;21).

## 6. PHARMACOLOGICAL TREATMENT OF HYPERTENSIVE DISORDERS IN PREGNANCY (9;19;35-37)

It is clinically important to recognize that while acute hypertensive management to prevent maternal cerebral vascular accident is useful, rapid change in maternal perfusion pressure can cause profound alterations in uteroplacental perfusion and oxygen delivery that can precipitate non-reassuring FHR changes. All of these changes can be magnified in the presence of  $MgSO_4$  which also has the potential to produce peripheral vasodilatation. Care must be taken to avoid rapid and profound changes in maternal blood pressure. Therefore, each of these antihypertensive medications must be carefully titrated when considering acute management.

It must be noted that there is no evidence that antihypertensive agents alter fetal heart rate patterns (25). Therefore, should the fetal heart rate pattern deteriorate following the initiation of antihypertensive medication, those changes should be ascribed to deteriorating placental function, and not to the medications themselves (38).

Control of blood pressure is essential to prevent maternal morbidity. Antihypertensive drug usage should aim to decrease the dBP <110 mmHg. A significantly

lower diastolic blood pressure may cause decreased placental perfusion, and fetal compromise.

After severe hypertension has been addressed, there are insufficient data to determine the blood pressure associated with optimal maternal and perinatal outcomes. 'Less tight' control (i.e., dBP 90-109mmHg) is associated with more transient hypertension. Normalizing maternal blood pressure ('tight' control (i.e., dBP <90mmHg)) may adversely effect fetal growth (26-28).

Aim to reduce sBP <160mmHg and dBP <110mmHg, slowly and carefully.

### 6.1. Initiation of antihypertensive drug treatment (35-37)

#### 6.1.1. Immediately (in the absence of pre-pregnancy renal disease or pregestational diabetes)

Irrespective of pre-existing condition, BP should be lowered if either sBP  $\geq$ 160mmHg and/or dBP  $\geq$ 110mmHg. At sBP 140-159mmHg and/or dBP 85-109mmHg, the initiation of antihypertensive medication will be based on practitioner preference, training, and experience. There is increasing concern that 'tight' control of maternal hypertension may adversely affect perinatal outcomes (19;39-41).

#### 6.1.2. In the presence of pre-pregnancy renal disease or pregestational diabetes

Under these circumstances, every effort should be made to maintain normal BP to protect renal function; therefore the threshold for intervention should be either sBP  $\geq$ 140mmHg and/or dBP  $\geq$ 90mmHg (19;35-37).

### 6.2. Acute management of severe hypertension

As a guide, stabilisation of blood pressure is to reduce diastolic blood pressure (dBP) by 10mmHg in the first instance and to maintain the blood pressure at or below that level (9;10;19;20;35-37).

#### 6.2.1. First choice agents (19;20)

##### 6.2.1.1. Nifedipine (capsules or PA tablets)

Nifedipine is the first choice agent as many women who develop severe pregnancy hypertension are already on high/maximal doses of labetalol, so will be somewhat insensitive to further 'stat' dosing with labetalol. Also, nifedipine may more effectively control severely increased BP than does hydralazine and labetalol (19;20). However, nifedipine capsules should not be used in women with known atherosclerotic cardiovascular disease or at increased risk for atherosclerotic cardiovascular disease (e.g., insulin-dependent diabetes >15y duration, maternal age >45y) (42-44).

This can be given as either a 5mg capsule to swallow (in the first instance) or as a 10mg oral tablet ('PA') (not a slow release tablet, 'XL'). BP should be measured every 10 minutes in the first half hour after treatment, as there can be a very marked drop in pressure when severe pre-eclampsia is treated. The dose should be repeated if a satisfactory blood pressure response has not occurred by 30min (capsule) or 45min (PA tablet). If two

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5mg capsules are ineffective, 10mg capsules may be administered.

If nifedipine (capsules or PA) controls blood pressure, then it may be changed postnatally to a slow release preparation (Adalat XL), which lasts 12-24 hours. There has been some concern over interaction between magnesium sulphate and nifedipine, however, the risk is <1% (45).

After two 'stat' doses of nifedipine, regular antihypertensive agents (e.g. labetalol, nifedipine XL, alfamethyldopa) should either be instituted or increased in dose.

### 6.2.1.2. Labetalol

If the woman can tolerate oral therapy, dosing can be done immediately before venous access and so can achieve as quick a result as an initial intravenous dose. Initially, 200mg can be given orally. This should lead to a reduction in blood pressure in 30-60min, and peak at 2-3hr. A second oral dose can be given if needed (10;20;35).

If there is no initial response to oral therapy by 30min, or if it cannot be tolerated, control should be by a repeated bolus of labetalol or by a labetalol infusion. (10;20;35) Give a bolus infusion of 20mg over at least 2min. This should have an onset of effect by 5min and should be repeated if dBP has not been reduced within 30min. This can be repeated every 30min to a maximum dose of 200mg. If labetalol is given at a rate  $\leq$ 10 mg/min, continuous ECG monitoring is not required (10;20;35).

Following this, a labetalol infusion should be commenced at a rate of 20 mg/hr via a volumetric pump. The infusion rate should be doubled every half hour to a maximum of 160mg/hr until dBP has been reduced by 10mmHg and maintained at or below that level.

### 6.2.2. Alternative

#### 6.2.2.1. Hydralazine

Given the relationship between uncontrolled severe maternal hypertension and maternal death, the randomized controlled trial evidence of antihypertensive medications for use in severe pregnancy hypertension was reviewed (20). Of 21 trials (893 women), eight compared hydralazine with nifedipine and five compared hydralazine with labetalol. Hydralazine was associated with a trend towards less persistent severe hypertension than labetalol (RR 0.29 [95% CI 0.08, 1.04]; two trials), but more severe hypertension than nifedipine or isradipine (RR 1.41 [0.95, 2.09]; four trials); there was significant heterogeneity in outcome between trials and differences in methodological quality (20).

Hydralazine was associated with more maternal hypotension (RR 3.29 [1.50, 7.23]; 13 trials); more Caesarean sections (RR 1.30 (1.08 to 1.59); 14 trials); more placental abruption (RR 4.17 [1.19, 14.28]; five trials); more maternal oliguria (RR 4.00 [1.22, 12.50]; three trials);

more adverse effects on fetal heart rate (RR 2.04 [1.32, 3.16]; 12 trials); and more low Apgar scores at 1min (RR 2.70 [1.27, 5.88]; three trials). For all but Apgar scores, analysis by risk difference showed heterogeneity between trials. Hydralazine was associated with more maternal side effects (RR 1.50 [1.16, 1.94]; 12 trials) and with less neonatal bradycardia than labetalol (risk difference -0.24 [-0.42, -0.06]; three trials) (20).

The results of this meta-analysis are not robust enough to guide clinical practice, but they do not support use of hydralazine as first line for treatment of severe hypertension in pregnancy (20). Adequately powered clinical trials are needed, with a comparison of labetalol and nifedipine showing the most promise.

## 6.3. Recommended treatment of nonsevere pregnancy hypertension (9;19;35-37;39)

Due to increased rates of hepatic metabolism and renal clearance in pregnancy, and increased vascular reactivity associated with pre-eclampsia and other forms of gestational hypertension, maintenance doses may need to be split. For example, formularies state that labetalol is a twice daily medication; in women with preeclampsia it may need to be given up to four times per day to achieve a 'smooth ride' in blood pressure (10;19;35-37;39).

### 6.3.1. Treatment goal

The dBP goal will be dBP 80 - 105mmHg, depending on practitioner preference. Definitive data are required to identify what BP targets should be in hypertensive pregnancy (19;35-37;39-41).

### 6.3.2 First choice agents (10;19;35-37)

#### 6.3.2.1. Methyldopa (10;19;35-37)

Dosage: 250 mg p.o. 2 or 3 times a day in the first 48 hours (some experts administer a loading dose of 750-1000 mg p.o.). The daily dosage then may be increased or decreased, preferably at intervals of not less than 2 days, until the desired response is achieved. Maximum daily dose is 2000 mg (total). Support for methyldopa results from the 7 year follow-up neurodevelopmental data from a single randomized controlled trial (46).

#### 6.3.2.2. Labetalol (10;19;35-37)

Dosage: Recommended initial dose 100 mg p.o. twice daily. The dose should be adjusted semi-weekly or weekly according to the response. Maximal daily dose is 1200mg (total).

#### 6.3.2.3. Nifedipine (10;19;35-37)

Dosage: Adalat PA: Initiate at 10 mgs p.o. twice daily. Usual maintenance dose is 10 - 20 mgs p.o. twice daily. Adalat XL: Initiate at 30 mg daily. Usual maintenance dose is 30-60 mg given once or twice daily. Maximal daily dose of nifedipine is 90 mg (total).

### 6.3.3. Special indications (renal or cardiac disease)

In women with preexisting renal or cardiac disease, diuretics may have a place in their management (19;35-37).

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### 6.4. Drugs to avoid (35-37)

Angiotensin-converting enzyme (ACE) inhibitors should be avoided due to the recognized risk of stillbirth in the third trimester. By extension, angiotensin II receptor antagonists should not be used. There are no recognized teratogenic risks associated with these agents in pregnancy.

Due to its apparent adverse effect on fetal growth velocity, atenolol is less preferable than other beta-blockers or combined alfa- and beta-blockers.

## 7. Anticonvulsant therapy: magnesium sulfate (MgSO<sub>4</sub>)

### 7.1. Prophylaxis

Following the MAGPIE study, women considered to have severe preeclampsia should receive magnesium sulfate (MgSO<sub>4</sub>). The corollary to that is that if a woman is deemed to need MgSO<sub>4</sub>, then she needs to be assessed as having 'severe' disease (41). Give MgSO<sub>4</sub> as in section 7.4, below.

### 7.2. Management of eclampsia

Call appropriate personnel, including the anesthesiologist (if available). Commence MgSO<sub>4</sub> as outlined below; MgSO<sub>4</sub> is the drug of choice for both seizure termination and for the prevention of seizure recurrence (47). Give MgSO<sub>4</sub> as in section 7.4, below.

### 7.3. Management of recurrent eclampsia

Give a stat bolus dose of MgSO<sub>4</sub> 2g intravenously over 20-30min, and increase the MgSO<sub>4</sub> infusion rate from 1g/hr to 1.5g/hr intravenously. Continue observations and consider the need for ventilation.

### 7.4. MgSO<sub>4</sub> protocol

Briefly, give a stat bolus dose MgSO<sub>4</sub> 4g intravenously over 20-30min, followed by MgSO<sub>4</sub> 1g/hr intravenously. To facilitate this, units should consider creating an 'eclampsia box' for all obstetric areas (47). Once stabilized, undelivered women should be delivered, and oximetry should be instituted if not already in place. We recognize that the dose of MgSO<sub>4</sub> in this regimen is lower than most regimens used in North America; however, it is the regimen tested in well-designed and conducted RCTs, and found to be effective.

#### 7.4.1. Clinical assessment

The decision for continuing the infusion should be made every 4 hr and should be guided by: continuous pulse oximetry, hourly urine output, hourly respiratory rate, deep tendon reflexes (every 4hr), and level of consciousness every 4hr (Glasgow Coma Score).

The infusion should only continue if, after each 4 hour period: the biceps reflex is present, the respiratory rate is >12/min, and the urine output is greater than 100ml in the previous 4hr. There is no level to measure magnesium levels with this protocol.

#### 7.4.2. Side effects

Motor paralysis, absent tendon reflexes, respiratory depression and cardiac arrhythmia (increased conduction time) can all occur, but will be minimized if

MgSO<sub>4</sub> is administered slowly and the patient observed as above.

### 7.4.3. Antidote: 10ml of 10% calcium gluconate given slowly intravenously

97% of magnesium is excreted in the urine; therefore the presence of oliguria can lead to toxic levels. If the above criteria (biceps reflexes, respiratory rate, and urinary output) are not met, then further administration of MgSO<sub>4</sub> should be withheld. If magnesium is not being excreted then the serum levels should not fall and no other anticonvulsant is needed. Magnesium should be re-introduced if urine output improves.

## 8. DELIVERY GUIDELINES: "PLANNED DELIVERY ON THE BEST DAY IN THE BEST WAY" (9;10)

The delivery should be well planned, done on the best day, performed in the best place, by the best route, and with the best support team (9;10). Timing affects the outcome for both mother and baby. If the mother is unstable, then delivery is inappropriate and increases risk. Once stabilized with antihypertensive drugs and MgSO<sub>4</sub>, a decision should be made.

In the absence of convulsions, prolonging the pregnancy may be possible to improve the outcome of a premature fetus but only if the mother remains stable. This 'expectant management' is associated with markedly improved outcomes for the fetus, but does incur some, as yet unquantified, maternal risk (19;47;48). Continued close monitoring of mother and fetus is needed. It seems ideal to achieve delivery, particularly of premature infants, during normal working hours (i.e., 8 am to 5 pm).

Even a few hours may be helpful if it allows the neonatal unit to be more organized or to transfer a mother to a place where an ICU bed is available, assuming the mother is stable before transfer (see below).

### 8.1. Steroids

If the pregnancy can be prolonged in excess of 4hr, steroids help mature the fetal lungs and reduce neonatal mortality. Since the benefits to the fetus peak between 48 hours and 6 days then, after 48hr, further consideration should be given to delivery, as further delay may not be advantageous to the baby or mother (27;48). In all situations a planned elective delivery suiting all professionals is appropriate.

### 8.2. Mode of delivery (9)

The mode of delivery should be discussed with an obstetrician. Delivery is not necessarily by Cesarean section, but if gestation is less than 32 weeks it may be preferable, as the practice of expectant management will dictate that delivery is occurring in response to deteriorating maternal and/or fetal status. After 34 weeks, vaginal delivery should be considered in a cephalic presentation. Vaginal prostaglandins will increase the chance of success. Antihypertensive treatment should be

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continued throughout assessment, surveillance, labor, delivery, and the immediate puerperium (9;27;35;37;48).

If vaginal delivery is planned, then the second stage should be short with consideration given to elective operative vaginal delivery. An epidural will normally be used. The third stage should be managed with oxytocin; ergometrine should not be given in any form (9).

### 9. ANESTHESIA AND FLUIDS

Consider involving an anesthesiologist early in the care of women with preeclampsia. The anesthesiologist may be required to provide analgesia/anesthesia for labor and delivery, Cesarean section anesthesia, insertion of lines for invasive monitoring (arterial line, CVP), and management of care. Fluid management should be judicious with two purposes: avoidance of pulmonary edema and avoidance of hypotension. There is an excess of maternal mortality associated with aggressive hydration in women with preeclampsia (34). A fluid bolus is not necessary routinely prior to regional anesthesia for labor unless there is a compromised fetus or the woman is obviously dehydrated. One may consider a small bolus of colloid (pentastarch) to avoid hypotension during regional anesthesia for Cesarean delivery (49). Women with preeclampsia are not at increased risk for post-regional hypotension (50). There is no evidence that a bolus of crystalloid as a preload prevents hypotension (51;52).

Epidural, combined spinal epidural and spinal anesthesia are not specifically contraindicated in women with severe preeclampsia and, generally, are recommended unless there is evidence of coagulopathy, local or systemic sepsis, patient refusal or other contraindications (53;54). Studies have shown that the incidence of profound hypotension in women with severe preeclampsia is similar when either spinal or epidural anesthesia is used (55-57).

Hypotension during regional anesthesia can be treated with both ephedrine and phenylephrine, titrated in small bolus doses or as an infusion (51;52;56).

General anesthesia may be required in the setting of acute fetal compromise or when there is a contraindication to regional anesthesia. Considerations include a possible difficult airway that may require awake intubation as well as the need to ablate the hypertensive response to intubation (58). Labetalol 10 mg intravenously every 5-10min is effective; alternatives (to be used instead of or with labetalol) include: opioids (fentanyl 3-5 µg/kg, remifentanyl 0.5-1 µg/kg), lidocaine 1.5 mg/kg, and nitroglycerin 100-300 µg. A full induction dose of thiopental (5-7mg/kg) or propofol (2mg/kg) and full intubating dose of a muscle relaxant should also be used (58). Esmolol is best avoided due to fetal concerns (58). Prior to extubation, consider using labetalol (or a listed alternative, with the exception of an opioid).

Neonatology should be informed that the neonate may be depressed at birth.

### 9.1. Indications for central venous pressure (CVP) monitoring

A CVP may be indicated at Cesarean section, particularly if blood loss is excessive, and regardless of delivery mode, if blood loss is excessive or delivery is complicated by other factors such as abruptio placentae. Remember that a CVP may not reflect the true central hemodynamics (i.e. pulmonary capillary wedge pressure, PCWP) in women with preeclampsia (59).

### 9.2. Fluid management

Following delivery the woman should be fluid restricted in order to wait for the natural diuresis which usually occurs around 36-48hr post delivery. Total intravenous fluid should be given at 80ml/hr. This total includes normal saline, or equivalent, plus other infusions of drugs. After delivery, oral fluids can be given in a relatively unrestricted way (9).

Urine output should be recorded hourly and each 4hr block should be totaled, recorded on the chart, and exceed 40ml. If two consecutive blocks fail to achieve 40ml, then further action is appropriate, as follows: (1) If total input is more than 750 ml in excess of output in the last 24 hours (or since starting the regimen) then 20mg of intravenous furosemide should be given. Pentaspan should then be given as above if a diuresis occurs, or (2) if total input is less than 750 ml in excess of output in the last 24 hours (or since starting the regimen) then an infusion of 250ml of pentaspan over 20 minutes should be given. The urine output should then be watched until the end of the next four-hour block. If the urine output is still low then 20mg of iv furosemide should be given. If a diuresis in excess of 200 ml occurs in the next hour the fluid should be replaced with 250ml of pentaspan in addition to baseline fluids.

### 9.3. Oliguria

If oliguria persists (requiring fluid challenge or furosemide), then the electrolytes and creatinine need to be carefully assessed and checked 6-hourly.

### 9.4. Analgesia

Women with preeclampsia have vulnerable renal function. Therefore, non-steroidal anti-inflammatory agents should be avoided in women whose urine output is <40ml/hr.

## 10. POSTPARTUM

High risk women should not be placed onto low risk discharge pathways. Women should only be discharged when there is a clear trend towards improvement in clinical and laboratory assessments, when there is an ability to provide adequate outpatient surveillance, and when follow-up can be arranged within a week for clinical and blood pressure assessment. It is reasonable to discharge women with BP < 160/100 mmHg for at least 24hr; however, it must be remembered that BPs reach their maximum postpartum level on d3-5 (60).

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### 11. Special problems (ante- and postpartum)

#### 11.1. Dropping O<sub>2</sub> saturations

If the woman has dropping oxygen saturation, it is most likely to be due to fluid overload. Input and output should be assessed together with either clinical or invasive assessment of the fluid balance. Clinical assessment should include maternal symptoms, cardiovascular and respiratory status, and chest X-ray. However, the most appropriate treatment is likely to be furosemide (10 mg) and oxygen. If there is no diuresis and the oxygen saturation does not rise, then referral to a nephrologist should be considered (9).

#### 11.2. Blood products

Cases requiring large volumes of colloid such as fresh frozen plasma, blood, or platelets can lead to fluid overload. Significant hemorrhage or HELLP needs to be managed by an experienced specialist practitioner (9).

#### 11.3. Stabilization before transfer

When a woman is ill and requires delivery, transfer for fetal reasons is often considered. However if the woman requires transfer for delivery, it is even more important that her condition is stabilized. Therefore, we recommend the following as a minimum requirement before transfer: (1) Blood pressure should be stabilized at an acceptable level according to the above protocol. Also, when the woman is ventilated it is important to ensure ventilatory requirements are stable and oxygen saturations are being maintained. (2) All basic investigations should have been performed (Table I) and the results clearly recorded in the accompanying notes or telephoned through as soon as available. (3) Fetal well being should be assessed (Table I) to be certain that transfer is in the fetal interest before delivery. (4) Steroids should be given if the woman is preterm (<34<sup>+0</sup> weeks).

Appropriate personnel should be available to transfer the woman. This may mean at least a senior nurse, often with an anesthesiologist.

Transfer should be discussed with appropriate consultant medical staff and nursing leadership and all the relevant people at the receiving unit (e.g., the neonatal unit and neonatal medical staff, the obstetrician, the nurse in charge of delivery suite, intensive care, and the intensive care anesthesiologist (where appropriate)).

### 12. LONG-TERM SEQUELAE

Preeclampsia, especially early-onset disease, is an identifiable risk factor for later cardiovascular morbidity and mortality (61-64). Therefore, it would seem prudent to offer women who have suffered from either early-onset and/or severe disease cardiovascular risk screening (lipids and C-reactive protein) when they have their cervical screening (65-68). Along with lifestyle modification, hypercholesterolemia and hyperlipidemia are amenable to treatment with statins ± fibrates, with a consequent lowering in premature cardiovascular risk (65-68).

### 13. DISCUSSION

Preeclampsia remains a significant cause of maternal and perinatal morbidity and mortality. By recognizing preeclampsia as a condition of systemic endothelial and inflammatory activation, and managing it as such, it appears possible to reduce the burden of maternal risks.

Preeclampsia remote from term warrants consideration of expectant management to improve perinatal outcomes; such expectant management requires a total package of care as the explicit intent is to await maternal and/or fetal deterioration to provoke delivery. Steroids should be administered at gestational ages <34<sup>+0</sup> wks to accelerate fetal lung maturation.

Antihypertensive drugs do not alter the natural history of preeclampsia, but do reduce the risks of maternal stroke associated with severe hypertension (BP>160/110mmHg); it remains unclear at what blood pressures below 160/110mmHg (if any) therapy should be started and what blood pressure goals should be.

MgSO<sub>4</sub> is the treatment of choice both for preventing and treating the seizures of eclampsia.

There is an excess burden of maternal morbidity and mortality associated with pulmonary edema; therefore, women with preeclampsia should be kept 'dry' to reduce those risks.

Women who have suffered from either severe and/or early-onset preeclampsia are at increased risk for developing premature cardiovascular disease. Therefore, these women should be counseled about that risk, and a suggestion is made that they should undergo repeated cardiovascular risk profiling so that effective interventions can be employed.

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## **Management for preeclampsia**

**Send correspondence to:** Dr Peter von Dadelszen, MBChB, DPhil, FRCSC, FRCOG, Associate Professor of Obstetrics and Gynaecology, UBC, Interim Director, CFRI Centre for Healthcare Innovation and Improvement, Consultant in Maternal-Fetal Medicine, Children's and Women's Health Centre of BC, 2H30-4500 Oak Street, Vancouver, BC V6H 3N1, Canada, Tel: 604-875-3265, Fax: 604-875-2725, E-mail: pvd@cw.bc.ca

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