

## Maternity - Management of Hypertensive Disorders of Pregnancy

**Summary** All NSW Public Health Organisations providing maternity services and/or emergency department services must have clinical practice guidelines and protocols for the management of hypertensive disorders of pregnancy based on this policy directive.

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## MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

### PURPOSE

This policy provides direction to NSW maternity services, Emergency Departments, Ambulance Service of NSW and retrieval services regarding the management of hypertensive disorders of pregnancy. The NSW Maternal and Perinatal Committee and the NSW Maternal and Perinatal Health Priority Taskforce have endorsed *The Guidelines for the Management of Hypertensive Disorders of Pregnancy 2008* issued by the *Society of Obstetric Medicine of Australia and New Zealand* and it is now issued as NSW Health policy.

### MANDATORY REQUIREMENTS

All NSW Public Health Organisations providing maternity services and/or emergency department services must have clinical practice guidelines and protocols for the management of hypertensive disorders of pregnancy based on this policy directive.

Ambulance Service of NSW and all other retrieval services must also have protocols for the management of hypertensive disorders of pregnancy based on this policy directive.

### IMPLEMENTATION

The Chief Executives of Local Health Districts and the Ambulance Service of NSW are ultimately responsible for the implementation of this policy directive within their respective facilities.

### REVISION HISTORY

Version	Approved by	Amendment notes
October 2011 PD2011_064	Deputy Director- General Population Health	Revised policy directive replacing PD2011_020
March 2011 PD2011_020	Deputy Director- General Strategic Development	New policy directive replacing PD2005_239, PD2005_241 and PD2005_346
March 2004 PD2005_346	Director-General	Revised policy on Hypertension in Pregnancy issued as Circular 2004/14
February 2002 PD2005_241	Director-General	Protocol for administration of Intravenous Hydralazine for severe hypertension in pregnancy. Originally issued as Circular 2002/29
February 2002 PD2005_239	Director-General	Magnesium sulphate (mgs04) infusion protocol for eclamptic seizure prophylaxis. Originally issued as Circular 2002/27

### ATTACHMENTS

1. Maternity - Management of Hypertensive Disorders in Pregnancy: Procedures.

**Maternity - Management of Hypertensive Disorders of  
Pregnancy**



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## 1. BACKGROUND

### 1.1 About this document

Hypertension disorders of pregnancy are common affecting approximately 6% of pregnancies.<sup>1</sup> Hypertensive disorders of pregnancy are associated with increased maternal and perinatal morbidity and mortality. Previous guidance regarding the detection, investigation and management of hypertension, the use of intravenous hydralazine in severe hypertension, and the use of magnesium sulphate for eclamptic seizure prophylaxis was provided in separate policy documents. The primary reference for all three documents was a consensus statement from the Australasian Society for the Study of Hypertension in Pregnancy. This document has since been replaced by the *Guidelines for the Management of Hypertensive disorders of Pregnancy 2008* compiled by the *Society of Obstetric Medicine of Australia and New Zealand*.<sup>2</sup> These guidelines form the basis of this policy directive.

### 1.2 Key definitions

**Hypertension in pregnancy** is defined as:

1. Systolic blood pressure greater than or equal to 140 mmHg and/or
  2. Diastolic blood pressure greater than or equal to 90 mmHg (Korotkoff 5)
- These measurements should be confirmed by repeated readings over several hours.

**Severe hypertension in pregnancy** is defined as:

1. Systolic blood pressure greater than or equal to 170 mmHg and/or
2. Diastolic blood pressure greater than or equal to 110 mmHg.

**White Coat Hypertension** is defined as:

Hypertension in a clinical setting with normal blood pressure away from this setting when assessed by 24 hour ambulatory blood pressure monitoring or home blood pressure monitoring using an appropriately validated device.

**Pre-eclampsia** is defined as:

Hypertension that arises after 20 weeks gestation and is accompanied by one or more of the following:

- Renal involvement
  - Significant proteinuria – dipstick proteinuria subsequently confirmed by spot urine protein/creatinine ratio  $\geq 30\text{mg}/\text{mmol}$ . In view of the close correlation between spot urine protein/creatinine ratio and 24 hour urine excretion, the latter is rarely required (21).
  - Serum or plasma creatinine  $> 90 \mu\text{mol}/\text{L}$
  - Oliguria
- Haematological involvement
  - Thrombocytopenia
  - Haemolysis
  - Disseminated intravascular coagulation
- Liver involvement

<sup>1</sup> Centre for Epidemiology and Research, NSW Department of Health. NSW Mothers and Babies Report 2006. NSW Public Health Bulletin 2007; 18(S-1).

<sup>2</sup> [http://www.somanz.org/pdfs/somanz\\_guidelines\\_2008.pdf](http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf)

- Raised serum transaminases
- Severe epigastric or right upper quadrant pain
- Neurological involvement
  - Convulsions (eclampsia)
  - Hyperreflexia with sustained clonus
  - Severe headache
  - Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)
  - Stroke
- Pulmonary oedema
- Fetal growth restriction
- Placental abruption

**Gestational hypertension** is defined as:

The new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia, followed by return of blood pressure to normal within 3 months post-partum.

**Chronic or essential hypertension** is defined as:

A blood pressure > 140 mmHg systolic and/or > 90mm diastolic confirmed before pregnancy or before 20 completed weeks gestation without a known cause.

**Pre-eclampsia superimposed on chronic hypertension** is diagnosed when:

One or more of the systemic features of preeclampsia develop after 20 weeks gestation in a woman with chronic hypertension.

## 2. DEFINITION OF HYPERTENSION IN PREGNANCY

Normal pregnancy is characterized by a fall in blood pressure, detectable in the first trimester and usually reaching a nadir in the second trimester. Blood pressure rises towards pre-conception levels towards the end of the third trimester.

**Hypertension** in pregnancy is defined as:

1. Systolic blood pressure greater than or equal to 140 mmHg and/or
2. Diastolic blood pressure greater than or equal to 90 mmHg (Korotkoff 5)

These measurements should be confirmed by repeated readings over several hours.

Elevations of both systolic and diastolic blood pressures have been associated with adverse fetal outcome and therefore both are important.<sup>(1)</sup> There are several reasons to support the blood pressure readings above as diagnostic of hypertension in pregnancy:

- Perinatal mortality rises with diastolic blood pressures above 90 mmHg;<sup>(2)</sup>
- Readings above this level were beyond two standard deviations of mean blood pressure in a New Zealand cohort of normal pregnant women;<sup>(3)</sup> and
- The chosen levels are consistent with international guidelines and correspond with the current diagnosis of hypertension outside of pregnancy.

Detecting a rise in blood pressure from 'booking' or preconception blood pressure (> 30/15 mmHg), rather than relying on an absolute value, has in the past been considered useful in diagnosing pre-eclampsia in women who do not reach blood pressures of 140 or 90 mmHg. Available evidence however, does not support the notion that these women have an increased risk of adverse outcomes.<sup>(4,5)</sup> Nevertheless such a rise may be significant in some women, particularly in the presence of hyperuricaemia and proteinuria. Further data are required and in the meantime, closer monitoring of pregnant women with an increment in blood pressure of  $\geq 30$  mmHg systolic and/or 15 mmHg diastolic is appropriate.

**Severe hypertension** in pregnancy is defined as a systolic blood pressure greater than or equal to 170 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg. This represents a level of blood pressure above which cerebral autoregulation is overcome in normotensive individuals. It is generally acknowledged that severe hypertension should be lowered promptly, albeit carefully, to prevent cerebral haemorrhage and hypertensive encephalopathy.<sup>(6)</sup> This degree of hypertension therefore requires urgent assessment and management. It is important to acknowledge that systolic as well as diastolic hypertension increases the risk of cerebral haemorrhage. Certain experts have recommended lowering the cut-off for the definition of severe systolic hypertension to 160 mmHg. For now, in the absence of definitive data, the above definition should be retained as a clinically useful cut-off value to initiate urgent treatment (see Management of pre-eclampsia and gestational hypertension).

**White Coat Hypertension** is defined as hypertension in a clinical setting with normal blood pressure away from this setting when assessed by 24 hour ambulatory blood pressure monitoring or home blood pressure monitoring using an appropriately validated device. Women with this condition present early in pregnancy with apparent chronic hypertension, but their outcomes are better than those of women with true chronic hypertension. They may generally be managed without medication by using repeated ambulatory or home blood pressure monitoring. A small proportion will go on to develop preeclampsia.<sup>(7)</sup>

### 3. RECORDING BLOOD PRESSURE IN PREGNANCY

The woman should be seated comfortably with her legs resting on a flat surface. In labour, the blood pressure may be measured in the left arm in lateral recumbency. The supine posture should be avoided because of the supine hypotension syndrome. Measurement of blood pressure should be undertaken in both arms at the initial visit to exclude rare vascular abnormalities such as aortic coarctation, subclavian stenosis and aortic dissection. Generally the variation in blood pressure between the upper limbs should be less than 10 mmHg.

The systolic blood pressure is accepted as the first sound heard (K1) and the diastolic blood pressure the disappearance of sounds completely (K5).<sup>(8-10)</sup> Where K5 is absent, K4 (muffling) should be accepted. Correct cuff size is important for accurate blood pressure recording. A large cuff with an inflatable bladder covering 80% of the arm circumference should be used if the upper arm circumference is greater than 33 cm. This helps to minimise over-diagnosis of hypertension during pregnancy.<sup>(11)</sup>

#### 3.1 Measurement devices

Mercury sphygmomanometers remain the gold standard for measurement of blood pressure in pregnancy however occupational health concerns are limiting their availability. Automated blood pressure recorders have provided major advantages for treatment and diagnosis of hypertension in the general community and they have been advocated for use in pregnant women.<sup>(12)</sup>



Few studies have compared these self-initiated devices with mercury sphygmomanometry in pregnant women. While such automated devices may give similar mean blood pressure values to those obtained with mercury sphygmomanometry, there is wide intra-individual error and their accuracy may be further compromised in pre-eclamptic women.<sup>(13,14)</sup> Aneroid sphygmomanometers are also prone to error. Each unit should maintain a mercury sphygmomanometer for validation of automated and aneroid devices. All devices should be calibrated on a regular basis (ideally monthly), as recommended by the British Hypertension Society.

### 3.2 Twenty four hour Ambulatory Blood Pressure Monitoring (ABPM)

Normal blood pressure values recorded by ABPM have been established for different stages of pregnancy.<sup>(15,16)</sup> ABPM is useful in the evaluation of early (< 20 wks gestation) hypertension where approximately one third of these women will be shown to have “white coat” or “office” hypertension.<sup>(7)</sup> About half of these women will not require antihypertensive medication in pregnancy, while the other half develops true (ABPM confirmed) hypertension. ABPM is less useful in screening for white coat hypertension in the second half of pregnancy.<sup>(17)</sup> Twenty four hour ABPM has also been shown to predict those women at risk of developing hypertension later in pregnancy but its sensitivity and specificity for this purpose is low.<sup>(18)</sup>

## 4. CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

This classification of the hypertensive disorders in pregnancy reflects the pathophysiology of the constituent conditions as well as the risks and potential outcomes for both mother and baby. The following clinical classification modifies only slightly that proposed in the ASSHP consensus statement of 2000. It has subsequently been adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP).<sup>(19)</sup> In endorsing this classification the ISSHP committee examined the classifications proposed by the ASSHP, the National High Blood Pressure Education Programme (NHBPEP) in the United States<sup>(20)</sup> as well as earlier published criteria.

### 4.1 Preeclampsia

Preeclampsia is a multi-system disorder unique to human pregnancy characterised by hypertension and involvement of one or more other organ systems and/or the fetus. Raised blood pressure is commonly but not always the first manifestation. Proteinuria is the most commonly recognised additional feature after hypertension but should not be considered mandatory to make the clinical diagnosis. As this classification is based on clinical data, it is possible that women with another condition will sometimes be classified incorrectly as having preeclampsia during pregnancy. This is not usually a clinical problem as the diagnosis of preeclampsia should lead to increased observation and vigilance which is appropriate for conditions which may mimic preeclampsia. A diagnosis of preeclampsia can be made when hypertension arises after 20 weeks gestation and is accompanied by one or more of the following:

- Renal involvement:
  - Significant proteinuria – dipstick proteinuria subsequently confirmed by spot urine protein/creatinine ratio
  - $\geq 30\text{mg/mmol}$ . In view of the close correlation between spot urine protein/creatinine ratio and 24 hour urine excretion, the latter is rarely required.<sup>(21)</sup>
  - Serum or plasma creatinine  $> 90 \mu\text{mol/L}$
  - Oliguria



- Haematological involvement
  - Thrombocytopenia
  - Haemolysis
  - Disseminated intravascular coagulation
- Liver involvement
  - Raised serum transaminases
  - Severe epigastric or right upper quadrant pain.
- Neurological involvement
  - Convulsions (eclampsia)
  - Hyperreflexia with sustained clonus
  - Severe headache
  - Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)
  - Stroke
- Pulmonary oedema
- Fetal growth restriction
- Placental abruption

### Notes:

1. Oedema is not included in the diagnostic features of preeclampsia. It is a common feature of normal pregnancy and severe preeclampsia may be present in the absence of any oedema. Nevertheless rapid development of generalised oedema should alert the clinician to screen for preeclampsia.
2. Other rare disorders may present with some of the features of preeclampsia.<sup>(22)</sup> Disorders such as acute fatty liver of pregnancy, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura, exacerbation of systemic lupus erythematosus or cholecystitis may need to be excluded.
3. Rarely preeclampsia presents before 20 weeks gestation<sup>(23)</sup>, usually in the presence of a predisposing factor such as hydatidiform mole, multiple pregnancy, fetal triploidy, severe renal disease or antiphospholipid antibody syndrome.
4. Dipstick testing for proteinuria is a screening test with very high false positive and negative rates. The use of automated dipstick readers can significantly improve detection of proteinuria.<sup>(24)</sup> Although ideally all women with hypertension should have a urine protein/creatinine ratio performed; in practice, dipstick readings of 'nil' or 'trace' are unlikely to be significant. The presence of urinary tract infection should also be excluded.
5. Hyperuricaemia is a common but not diagnostic feature of preeclampsia; the degree of hyperuricaemia may correlate with fetal risk<sup>(25,26)</sup> although some studies have questioned this<sup>(27-29)</sup>. A rapidly rising plasma uric acid over a few days in the setting of hypertension usually indicates worsening preeclampsia, often in the presence of other markers of deterioration.
6. Serum transaminase levels are reduced in pregnancy (by approximately 20%) and the upper limits of normal should be based on local reference ranges.
7. The HELLP syndrome (Haemolysis, Elevated Liver enzymes and a Low Platelet count) represents a particular presentation of severe preeclampsia and separating it as a distinct disorder is not helpful.
8. Microangiopathic haemolysis although infrequent may cause a sudden fall in haemoglobin and the appearance of fragmented red blood cells on the blood film. It is accompanied by a rise in bilirubin and lactate dehydrogenase, as well as thrombocytopenia and elevated liver enzymes, sometimes with the appearance of red or black urine. This diagnosis should be considered after a fall in haemoglobin when there has been insufficient revealed bleeding to account for the anaemia. Despite this, anaemia is more often due to obstetric bleeding in these cases, including occult intra-abdominal haemorrhage.
9. Preeclampsia is a frequent cause of migrainous symptoms in pregnancy, the commonest cause in pregnancy of cerebral haemorrhage, and the only cause of eclampsia. Other rare neurological complications include cerebral haemorrhage, cerebral oedema, cortical and sinus vein thrombosis, retinal detachment and central serous retinopathy.

The above classification is a clinical one. Although it is recognised that women with preeclampsia may not show proteinuria,<sup>(30)</sup> for research purposes a more homogeneous group will be represented by women with both hypertension and proteinuria as this is less open to clinical interpretation and error.

The ISSHP research definition of preeclampsia<sup>(19)</sup> is as follows:

- De novo hypertension after 20 weeks gestation, returning to normal postpartum, and
- properly documented proteinuria.

### 4.2 Gestational Hypertension

Gestational hypertension is characterised by the new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia, followed by return of blood pressure to normal within 3 months post-partum. At first presentation this diagnosis will include some women (up to 25%) who are in the process of developing preeclampsia but have not yet developed proteinuria or other manifestations. Some women initially diagnosed in this category will manifest persistent blood pressure elevation beyond 12 weeks post-partum and eventually be classified as having chronic hypertension.

Gestational hypertension near term is associated with little increase in the risk of adverse pregnancy outcomes.<sup>(31)</sup> The earlier the gestation at presentation and the more severe the hypertension, the higher is the likelihood that the woman with gestational hypertension will progress to develop preeclampsia<sup>(32)</sup> or an adverse pregnancy outcome.<sup>(33)</sup> Severe hypertension ( $\geq 170/110$ mmHg) is associated with increased risk of adverse outcomes in pregnancy.<sup>(33)</sup>

### 4.3 Chronic Hypertension

*Essential hypertension* is defined by a blood pressure  $> 140$  mmHg systolic and/or  $> 90$ mm diastolic confirmed before pregnancy or before 20 completed weeks gestation without a known cause. It may also be diagnosed in women presenting early in pregnancy taking antihypertensive medications where no secondary cause for hypertension has been determined. Some women with apparent essential hypertension may have white coat hypertension (raised blood pressure in the presence of a clinical attendant but normal blood pressure otherwise as assessed by ambulatory or home blood pressure monitoring). These women appear to have a lower risk of superimposed preeclampsia than women with true essential hypertension but are still at an increased risk compared with normotensive women.<sup>(7)</sup>

Important *secondary* causes of chronic hypertension in pregnancy include:

- Chronic kidney disease e.g. glomerulonephritis, reflux nephropathy, and adult polycystic kidney disease.
- Renal artery stenosis
- Systemic disease with renal involvement e.g. diabetes mellitus, systemic lupus erythematosus.
- Endocrine disorders e.g. pheochromocytoma, Cushing's syndrome and primary hyperaldosteronism.
- Coarctation of the aorta.

In the absence of any of the above conditions it is likely that a woman with high blood pressure in the first half of pregnancy has essential hypertension. It is not possible to investigate these disorders fully during pregnancy, and complete appraisal may need to be deferred until after delivery.

### 4.4 Preeclampsia Superimposed on Chronic Hypertension

Pre-existing hypertension is a strong risk factor for the development of preeclampsia.<sup>(34)</sup> Superimposed preeclampsia is diagnosed when one or more of the systemic features of preeclampsia develop after 20 weeks gestation in a woman with chronic hypertension. In women with pre-existing proteinuria, the diagnosis of superimposed preeclampsia is often difficult as pre-existing proteinuria normally increases during pregnancy. In such women substantial increases in proteinuria and hypertension should raise suspicion of preeclampsia but the diagnosis is not secure without the development of other systemic features or fetal growth restriction.

## 5. INVESTIGATION OF NEW ONSET HYPERTENSION IN PREGNANCY

Any woman presenting with new hypertension after 20 weeks gestation should be assessed for signs and symptoms of preeclampsia. Initially, assessment and management in a day assessment unit may be appropriate. However, if features of preeclampsia are detected, admission to hospital is indicated. The presence of severe hypertension, headache, epigastric pain or nausea and vomiting are ominous signs which should lead to urgent admission and management,<sup>(35,36)</sup> as should any concern about fetal wellbeing.

The following investigations should be performed in all patients:

- Urine dipstick testing for proteinuria, with quantitation by laboratory methods if >'1+' (30mg/dL)
- Full blood count
- Urea, creatinine, electrolytes
- Liver function tests
- Ultrasound assessment of fetal growth, amniotic fluid volume and umbilical artery Doppler flow

Notes:

1. Blood test abnormalities should be interpreted using pregnancy-specific ranges, some of which are gestation dependent.
2. If features of preeclampsia are present, additional investigations should include:
  - Urinalysis and microscopy on a carefully collected mid-stream urine sample.
  - If there is thrombocytopenia or a falling haemoglobin, investigations for disseminated intravascular coagulation (coagulation studies, blood film, LDH, fibrinogen).
3. Patients with severe early onset preeclampsia warrant investigation for associated conditions e.g. systemic lupus erythematosus, underlying renal disease, antiphospholipid syndrome or thrombophilias. The timing of these investigations will be guided by the clinical features.
4. Although a very rare disorder, undiagnosed pheochromocytoma in pregnancy is potentially fatal and may present as preeclampsia.<sup>(37,38)</sup> Measurement of fasting plasma free metanephrines/ normetanephrines or 24 hour urinary catecholamines should be undertaken in the presence of very labile or severe hypertension.

Subsequent management will be based on the results of ongoing blood pressure measurement and these investigations (Tables 1 and 5).

Amongst women referred for assessment of new onset hypertension, a number will have normal blood pressure and investigations. These women are considered to have transient or labile hypertension. Repeat assessment should be arranged within 3-7 days as many will subsequently develop pre-eclampsia.

**Table 1: Ongoing investigation of women with hypertension in pregnancy**

	<b>Modality</b>	<b>Frequency</b>
Chronic Hypertension	Urinalysis for protein Preeclampsia bloods	Each visit If sudden increase in BP or new proteinuria
Gestational Hypertension	Urinalysis for protein Preeclampsia bloods	1 - 2 x per week Weekly
Preeclampsia	Urinalysis for protein  Preeclampsia bloods	At time of diagnosis:  If non-proteinuric, repeat daily Twice weekly or more frequent if unstable

## 6. MANAGEMENT OF PREECLAMPSIA AND GESTATIONAL HYPERTENSION

Preeclampsia is a progressive disorder that will inevitably worsen if pregnancy continues. Current therapy does not ameliorate the placental pathology nor alter the pathophysiology or natural history of preeclampsia. Delivery is the definitive management and is followed by resolution, generally over a few days but sometimes much longer. At mature gestational age, delivery should not be delayed. Even so, it is important to control severe hypertension and other maternal derangements before subjecting the woman to the stresses of delivery.

Prolongation of pregnancy in the presence of preeclampsia carries no benefit for the mother but is desirable at early gestations to improve the fetal prognosis as in general, fetal outcome is proportional to gestational age at delivery. In cases of preterm preeclampsia before 34 weeks, delivery should be delayed for at least 24-48 hours if maternal and fetal status permit, to allow fetal benefit from antenatal corticosteroids administered for lung maturation. A number of trials<sup>(39-42)</sup> have shown that 25-30% of women managed expectantly with preeclampsia will develop severe morbidity including HELLP syndrome, abruption, pulmonary oedema and eclampsia and that the mean duration of prolongation is less than 12 days. Continuation also carries fetal risk and some stillbirths will occur despite careful monitoring.<sup>(43)</sup> These trials have excluded women with the “HELLP” variant of preeclampsia and with other evidence of severe morbidity.

The management of women with preeclampsia between gestational ages of 24-32 weeks should be restricted to those centres with appropriate experience and expertise. Clear “endpoints” for delivery should be defined for each patient (Table 2), such that the decision to terminate the pregnancy is based on agreed criteria. In many cases, the timing of delivery will be based upon a number of factors, maternal and/or fetal rather than a single absolute indication for delivery.

A team approach, involving obstetrician, midwife, neonatologist, anaesthetist and physician provides the best chance of achieving a successful outcome for mother and baby. Regular and ongoing reassessment of both the maternal and fetal condition is required. Careful daily assessment for clinical symptoms and signs should be complemented by regular blood and urine tests as indicated (Table 1 and 5).

**Table 2: Indications for delivery in women with preeclampsia or gestational hypertension**

Maternal	Fetal
Gestational age > 37 weeks	Severe fetal growth restriction
Inability to control hypertension	Non-reassuring fetal status
Deteriorating platelet count	
Deteriorating liver function	
Deteriorating renal function	
Placental abruption	
Persistent neurological symptoms Eclampsia	
Persistent epigastric pain, nausea or vomiting with abnormal liver function tests	
Acute pulmonary edema	

The only controlled studies of bed rest for preeclampsia have shown no significant maternal or fetal benefit.<sup>(44)</sup> However, admission to hospital allows close supervision of both mother and fetus as progress of the disorder is unpredictable. Outpatient monitoring may be appropriate in milder cases after a period of initial observation.

## 6.1 Hypertension

### 6.1.1 Acute Treatment of Severe Hypertension

Antihypertensive treatment should be commenced in all women with a systolic blood pressure  $\geq$  170 mm Hg or a diastolic blood pressure  $\geq$  110 mm Hg because of the risk of intracerebral haemorrhage and eclampsia.<sup>(45)</sup> Whilst there is no controlled trial to determine how long severe hypertension may be left untreated, it is recommended that treatment be administered promptly aiming for a gradual and sustained lowering of blood pressure.

Drugs for the treatment of very high blood pressure in pregnancy have been the subject of a Cochrane review which concluded that no good evidence exists that any short acting antihypertensive is better than another.<sup>(46)</sup> Several rapidly acting agents are available to control severe hypertension (Table 3).

There is concern that a precipitous fall in blood pressure after antihypertensive treatment, particularly intravenous hydralazine, may impair placental perfusion resulting in fetal distress. This can be prevented by co-administration of a small bolus of fluid e.g. normal saline 250ml at the time of administration of antihypertensive therapy<sup>(52)</sup> Continuous CTG monitoring should be considered in these situations, particularly when there is evidence of existing fetal compromise. However, fetal distress as a result of such treatment is rare.

**Table 3: Acute blood pressure lowering for severe hypertension (47-51)**

	Dose	Route	Onset of action
Labetalol	20 - 50 mg	IV bolus over 2 minutes	5 mins, repeat after 15 - 30 mins
Nifedipine	10 - 20 mg	Oral	30 - 45 mins, repeat after 45 mins
Hydralazine <sup>3</sup>	5 - 10 mg	IV bolus	20 mins, repeat after 30 mins
Diazoxide	15 - 45 mg, max 300mg	IV rapid bolus	3 - 5 mins, repeat after 5 mins

<sup>3</sup> See Appendix 1 for principles and method of administration of intravenous hydralazine for severe hypertension in pregnancy

Persistent or refractory severe hypertension may require repeated doses of these agents or even an intravenous infusion of labetalol 20-160 mg/hr or hydralazine 5-10 mg/hr, titrated to the blood pressure response. The concurrent administration of longer acting oral agents (see Table 4) will achieve a more sustained blood pressure lowering effect. Infusions of sodium nitroprusside or glyceryl trinitrate are also effective but are recommended rarely, e.g. when other treatments have failed and delivery is imminent. Sodium nitroprusside may cause fetal cyanide and thiocyanate toxicity and transient fetal bradycardia. Such infusions may be considered with intra-arterial blood pressure monitoring in a high dependency care environment if the usual medications have failed to control the blood pressure, but only so as to effect safe operative delivery and not for prolonged use.

The most important consideration in choice of antihypertensive agent is that the unit has experience and familiarity with that agent. It is recommended that protocols for the management of severe hypertension should be readily accessible in all obstetric units.

### **6.1.2 Ongoing Treatment for Hypertension**

Treatment of hypertension in pregnancy does not cure preeclampsia but is intended to prevent cerebral haemorrhage and eclampsia and perhaps delay progression of proteinuria. Uncontrolled hypertension is a frequent trigger for delivery and control of hypertension may allow prolongation of pregnancy. There is controversy regarding the need to treat mild to moderate hypertension in women with preeclampsia. In favour of treatment is the fact that blood pressure may be extremely labile in preeclampsia and treatment at lower blood pressure levels will prevent or attenuate acute and severe rises in blood pressure. In addition, it is possible that pharmacologic arteriolar vasodilatation may help improve organ perfusion. Arguments against treatment include that there is little risk to the mother in having relatively mild hypertension for a short time (usually only a few days or at the most weeks), that fetal perfusion is dependent upon adequate maternal blood pressure and that lowering blood pressure suppresses an important sign of the severity or progression of preeclampsia.

There is as yet no controlled trial of the treatment of mild to moderate hypertension in pregnancy, although a pilot trial of such a study has been completed<sup>(53)</sup> One small Australian placebo-controlled randomised study examined the role of antihypertensive therapy in the management of mild hypertension.<sup>(54)</sup> Placebo-treated women were delivered significantly earlier, mainly as a result of severe hypertension or premonitory signs of eclampsia, and there was more neonatal morbidity secondary to prematurity.

In the absence of compelling evidence, treatment of mild to moderate hypertension in the range 140-160/90-100 mm Hg should be considered an option and will reflect local practice. Above these levels, treatment should be considered mandatory.

In terms of lowering blood pressure in preeclampsia, a number of drugs have demonstrated safety and efficacy (Table 4). First line drugs include methyldopa, labetalol and oxprenolol.<sup>(55-57)</sup> Second line agents are hydralazine, nifedipine and prazosin.<sup>(58-61)</sup> Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. Their use in the third trimester has been associated with fetal death and neonatal renal failure. All of the drugs in Table 4 along with enalapril, captopril and quinapril are considered compatible with breastfeeding.<sup>(62)</sup>

It is important to control severe hypertension at any gestation and post partum. Induction of labour or Caesarean section does not control hypertension even though delivery begins the



process of resolution of preeclampsia. Thus, antihypertensive medication will usually be required even when delivery has been arranged.

**6.1.3 Summary**

The intention in treating mild to moderate hypertension is to prevent episodes of severe hypertension and allow safe prolongation of the pregnancy for fetal benefit. It is reasonable to consider antihypertensive treatment when systolic blood pressure reaches 140-160 mmHg systolic and/or 90-100 mmHg diastolic on more than one occasion. If the blood pressure exceeds these levels, antihypertensive therapy should be commenced in all women. In view of this uncertainty, each Unit should develop protocols for the management of hypertension and regularly monitor and audit their outcomes.

**Table 4: Guidelines for Selecting Antihypertensive Drug Treatment In Pregnancy**

Drug	Dose	Action	Contraindication	Practice points
Methyl dopa	250-75mg tds	Central	Depression	Slow onset of action over 24 hour. Dry mouth, sedation, depression, blurred vision.  Withdrawal effect with clonidine
Clonidine	75-300 µg tds			
Labetalol	100-400mg tds	β blocker with mild alpha vasodilator effect	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling which usually resolves within 24-48 hours (labetalol only)
Oxprenolol	20-160mg tds	β blocker with ISA	Heart block	
Nifedipine	20mg bd– 60mg SR bd	Ca channel antagonist	Aortic stenosis	Severe headache associated with flushing, tachycardia  Peripheral edema, constipation
Prazosin	0.5 - 5mg tds	α blocker		Flushing, headache, nausea, lupus-like syndrome
Hydralazine	25-50 mg tds	Vasodilator		Flushing, headache, nausea, lupus-like syndrome

**6.2 Treatment of other manifestations**

**6.2.1 Thromboprophylaxis**

Preeclampsia is a risk factor for thrombosis, particularly in the presence of additional risk factors such as obesity, age above 35 years, previous thrombotic event, family history of thrombosis, nephrotic range proteinuria or likely inpatient stay more than a few days.<sup>(63)</sup> When women are admitted for observation in hospital they will usually be relatively immobile and graduated compression stockings should be considered, with or without prophylactic low molecular weight heparin (LMWH). Postnatal thromboprophylaxis should be administered to women with preeclampsia except where there is a surgical contraindication. Units should have clear protocols to deal with the timing of LMWH administration in regard to the insertion and withdrawal of epidural and spinal cannulae.<sup>(64)</sup>



### 6.2.2 Intravenous Fluids

Although maternal plasma volume is often reduced in women with preeclampsia<sup>(65)</sup> there is no maternal or fetal benefit to maintenance fluid therapy.<sup>(66)</sup> Administration of fluid at a rate greater than normal requirements should only be considered for:

1. Women with severe preeclampsia immediately prior to parenteral hydralazine, regional anaesthesia or immediate delivery
2. Initial management in women with oliguria where there is a suspected or confirmed deficit in intravascular volume.

As vascular permeability is increased in women with preeclampsia<sup>(67)</sup> administration of large volumes of intravenous fluid before or after delivery may cause pulmonary oedema and worsen peripheral oedema. This tendency is further aggravated by hypoalbuminaemia. Appropriate blood product replacement is necessary when there has been haemorrhage, as in cases of placental abruption.

Post-partum oliguria is a regular accompaniment of preeclampsia and care must be taken to avoid its over-treatment. Persistent oliguria beyond 24 hours post-partum with rising plasma creatinine suggests the possibility of post partum renal failure. There is no evidence that fluid manipulation is able to prevent this rare complication.

Monitoring in a high dependency care unit is ideal for these cases because of the risk of pulmonary oedema as mentioned above. Invasive monitoring should only be considered when there is developing renal failure or pulmonary oedema. In view of the reduced plasma volume in most women with preeclampsia, diuretics should not be used in the absence of pulmonary oedema.

### 6.2.3 Eclampsia

Eclampsia complicates 1 in 200-300 cases of preeclampsia in Australia. There are no reliable clinical markers to predict eclampsia and conversely, the presence of neurological symptoms and/or signs is rarely associated with seizures.<sup>(68)</sup> Seizures may occur antenatally, intra-partum or postnatally, usually within 24 hours of delivery but occasionally later. Hypertension and proteinuria may be absent prior to the seizure and not all women will have warning symptoms such as headache, visual disturbances or epigastric pain.<sup>(69)</sup>

The further from delivery that the seizure occurs, the more carefully should other diagnoses be considered. Cerebral venous thrombosis in particular may occur in the first few days of the puerperium. It should be remembered that eclampsia is not the commonest cause of seizures in pregnancy and the differential diagnosis includes epilepsy and other medical problems that must be considered carefully, particularly when typical features of severe preeclampsia are lacking.

### Management of eclampsia

Comprehensive protocols for the management of eclampsia (and severe hypertension) should be available in all appropriate areas. There are four main aspects to care of the woman who sustains eclampsia.

#### 1. Resuscitation:

Resuscitation requires institution of intravenous access, oxygen by mask, assuring a patent airway and removing regurgitated stomach contents from the mouth/pharynx.

These seizures are usually self-limiting. Intravenous diazepam (2mg/minute to maximum of 10mg) or clonazepam (1-2mg over 2-5 minutes) may be given whilst the magnesium sulphate is being prepared if the seizure is prolonged.

### 2. Prevention of further seizures

Following appropriate resuscitation, treatment should be commenced with magnesium sulphate heptahydrate (4g over 10-15 minutes) followed by an infusion (1-2g/hr)<sup>4</sup>. In the event of a further seizure, a further 2-4g of magnesium sulphate heptahydrate is given IV over 10 minutes. Magnesium sulphate is usually given as an intravenous loading dose although the intramuscular route is equally effective. Monitoring should include blood pressure, respiratory rate, urine output, oxygen saturation and deep tendon reflexes. Magnesium sulphate heptahydrate by infusion should continue for 24 hours after the last fit.<sup>(70,71)</sup> Magnesium sulphate is excreted renally and extreme caution should be used in women with oliguria or renal impairment. Serum magnesium concentration should be closely monitored in this situation. Magnesium is not universally successful and the recurrence rate of seizures despite appropriate magnesium therapy is 10-15%.<sup>(72)</sup>

### 3. Control of hypertension

Control of severe hypertension to levels below 160/100 mmHg by parenteral therapy is essential as the threshold for further seizures is lowered after eclampsia, likely in association with vasogenic brain oedema. In addition, the danger of cerebral haemorrhage is real.

### 4. Delivery

Arrangements for delivery should be decided once the woman's condition is stable. In the meantime, close fetal monitoring should be maintained. There is no role, with currently available treatment, for continuation of pregnancy once eclampsia has occurred, even though many women may appear to be stable after control of the situation has been achieved.

#### Prevention of eclampsia in the woman with preeclampsia

The drug of choice for the prevention of eclampsia is magnesium sulphate given as described above.<sup>(71)</sup> Although there is good evidence for the efficacy of this therapy, the case for its routine administration in women with preeclampsia in countries with low maternal and perinatal mortality rates is less than compelling. In some Units, the presence of symptoms or signs such as persistent headache, hyperreflexia with clonus, epigastric pain or severe hypertension are considered indications for prophylaxis with magnesium sulphate. It is appropriate for individual Units to determine their own protocols and monitor outcomes.

#### Hepatic and Haematological manifestations

Epigastric or right upper quadrant pain in a woman with preeclampsia often represents hepatic involvement. The pain responds poorly to analgesia but both the pain and associated increases in liver enzymes (AST, ALT) may subside (albeit temporarily) after blood pressure lowering, particularly with vasodilators. If the cause of epigastric or right upper quadrant pain is not clear, close ongoing assessment is required, with careful review of all indicators of maternal and fetal wellbeing (as above) and appropriate imaging of the liver and gallbladder.

<sup>4</sup> See Appendix 2 for magnesium sulphate infusion notes and example infusion protocols

Thrombocytopenia is the commonest hematologic abnormality seen in preeclampsia; the lower limit of the normal platelet count in pregnancy is approximately  $140 \times 10^9/L$  but the risk of spontaneous bleeding is not significantly increased until the count falls below  $50 \times 10^9/L$ . Even so, there are concerns with central neuraxial anaesthetic and analgesic techniques at higher levels ( $50-75 \times 10^9/L$ ), and surgical bleeding may be increased even with moderate thrombocytopenia.

Platelet transfusion is the only rapidly effective treatment for severe thrombocytopenia and this may be necessary at the time of Caesarean delivery or in the case of postpartum haemorrhage, wound or vulval hematoma or other bleeding as sometimes occurs in these cases. Fresh frozen plasma may be required for management of coagulopathy indicated by active bleeding and a prolonged APTT and INR. In this setting, fibrinogen levels should also be measured and cryoprecipitate administered if levels are low.

Steroid therapy (other than for fetal lung maturation) is not indicated for the management of thrombocytopenia or hepatic dysfunction in women with preeclampsia.<sup>(73)</sup> These abnormalities recover spontaneously postpartum within a few days of delivery, without specific treatment.<sup>(74-77)</sup> If abnormalities worsen or show no improvement after 72 hours post partum, differential diagnoses such as thrombotic thrombocytopenic purpura or antiphospholipid syndrome should be considered, and appropriate therapy instituted.

## 7. FETAL SURVEILLANCE

Adverse perinatal outcome is increased in women with all subcategories of hypertensive disease in pregnancy as compared to normotensive women.<sup>(78)</sup> The increase in adverse outcomes is greatest in those with early gestation at onset of disease, severe hypertension and/or chronic hypertension with superimposed preeclampsia.<sup>(78-80)</sup> Although fetal surveillance is commonly recommended and performed in women with hypertensive disease in pregnancy<sup>(6,81)</sup> there is no established consensus on how this should be performed.<sup>(82,83)</sup> Frequency, intensity, and modality of fetal evaluation will depend on individual pregnancy (maternal and fetal) characteristics. Individual obstetric units should devise their own protocols for monitoring the fetus in pregnancies complicated by hypertension. In compiling such protocols, the following issues should be considered.

1. Accurate dating of pregnancy is important for women with chronic hypertension or those at high risk of preeclampsia
2. Symphysis-fundal height measurement is a poor screening tool for detection of fetal growth restriction (FGR).<sup>(84)</sup> Therefore, ultrasound should be performed by an experienced operator to assess fetal size, amniotic fluid volume and umbilical artery Doppler flows in such women. Assessing growth trends by serial ultrasound is recommended if pregnancy continues.
  1. Umbilical artery Doppler flow is the only fetal surveillance modality that has been shown by systematic review to reduce the need for fetal interventions, improve neonatal outcome and predict adverse perinatal outcome.<sup>(85,86)</sup> Severe early onset FGR should be monitored at institutions experienced in advanced fetal Doppler waveform analysis. Absent or reversed end diastolic flow is unlikely to occur within 7-10 days after a normal umbilical artery Doppler waveform analysis. Umbilical artery Doppler flow studies have limited value after 36 weeks gestation.

2. Although numerous observational studies have suggested improved outcome in the high-risk pregnancy monitored using protocols that included Biophysical Profile, cardiotocography, and combinations of both<sup>(87-89)</sup>, none of these has shown significant benefit in systematic reviews.<sup>(90,91)</sup>
3. No fetal testing can predict an acute obstetric event such as placental abruption or cord accident.
4. Fetal Surveillance via a Day Assessment Unit is associated with good perinatal outcome in women with various obstetric complications, including women with well controlled hypertension (92).
5. An appropriately grown fetus in the third trimester in women with well-controlled chronic hypertension without superimposed preeclampsia generally is associated with a good perinatal outcome. Fetal monitoring using methods other than continued surveillance of fetal growth and amniotic fluid volume in the third trimester is unlikely to be more successful in preventing perinatal mortality/morbidity.

Table 5 demonstrates commonly used international and national protocols for fetal surveillance in women with hypertensive disease in pregnancy where immediate delivery is deferred. None of these protocols has been tested in prospective randomised trials, thus they are based only on the opinion and experience of the authors. As preeclampsia is an ever changing and unpredictable disease, for those women where expectant management is employed, the frequency and modality of fetal surveillance should be adjusted based on the current maternal and/or fetal condition. Each obstetric unit should develop an agreed institutional approach to fetal surveillance and/or fetal medicine referral.

**Table 5: Protocol for Fetal Surveillance In Women With Hypertension In Pregnancy**

Hypertension	Modality	Frequency
Chronic Hypertension	Early dating ultrasound	First trimester
	Ultrasound for fetal growth/AFV/Doppler	3 <sup>rd</sup> trimester: 4 - weekly
Gestational Hypertension	Ultrasound for fetal growth/AFV/Doppler	At time of diagnosis and 3 – 4 weekly
Preeclampsia	Ultrasound for fetal growth/AFV/Doppler	At time of diagnosis and 2 - 3 weekly
	Cardiotocography	Twice weekly
Preeclampsia with FGR	Cardiotocography	Twice weekly
	Doppler/AFV/Fetal growth	On admission and 2 weekly

## 7.1 Antenatal Corticosteroid Administration

Contrary to popular belief, accelerated fetal lung maturation does not occur in preeclampsia.<sup>(93)</sup> A systematic review has shown that a single course of antenatal corticosteroid given to women expected to deliver preterm reduces the risk of neonatal death, respiratory distress syndrome, cerebrovascular haemorrhage, necrotizing enterocolitis, respiratory support, and intensive care admission.<sup>(94)</sup> This systematic review showed that infants born to pregnancies complicated by hypertension syndromes treated with corticosteroids had significantly reduced risk of neonatal death, RDS, and cerebrovascular haemorrhage. There is insufficient evidence to support antenatal corticosteroids for those pregnancies that have reached 34 weeks gestation.<sup>(94)</sup> A recent randomized trial demonstrated a small benefit of antenatal corticosteroids to mothers undergoing a term (37 to 39 weeks gestation) elective Caesarean section.<sup>(95)</sup> In women with hypertensive disorders of pregnancy undergoing planned Caesarean section after 34 weeks gestation, urgent delivery should not be delayed for the benefits of corticosteroid therapy.

The administration of further courses of corticosteroid in women who remain undelivered and still at risk of preterm birth after an initial course of corticosteroids remains controversial. Until further studies are completed and published, repeated doses of corticosteroids should not be prescribed routinely. If they are considered necessary, the protocol described by Crowther et al<sup>(96,97)</sup> should be employed.<sup>(98)</sup>

## 8. RESOLUTION OF PREECLAMPSIA

After delivery, all clinical and laboratory derangements of preeclampsia recover, but there is often a delay of several days, and sometimes longer, in return to normality. On the first day or two after delivery, liver enzyme elevations and thrombocytopenia will often worsen before they reverse. Hypertension may persist for days, weeks or even up to three months and will require monitoring and slow withdrawal of antihypertensive therapy. Resolution is still assured if the diagnosis was pre-eclampsia and there is no other underlying medical disorder. The woman and her family are often overwhelmed and distressed from their experience and appropriate counselling post partum should include psychological and family support.

All women who develop preeclampsia and gestational hypertension are at risk of these disorders in future pregnancies and should receive appropriate counselling before embarking upon another pregnancy.

## 9. MANAGEMENT OF CHRONIC HYPERTENSION IN PREGNANCY

Hypertension affects up to 20% of the Australian adult population, the prevalence increasing with age.<sup>(99)</sup> Many women of child-bearing age are hypertensive, and of the 10 to 12% of pregnancies affected by elevated blood pressure levels, at least one in five is related to chronic hypertension.<sup>(100,101)</sup> The diagnosis can be difficult in women whose blood pressure before pregnancy or early in the first trimester is unknown. Very rarely preeclampsia can present before 20 weeks' gestation and the physiological fall in blood pressure in the second trimester can obscure pre-existing chronic hypertension.

Women with chronic hypertension have an increased risk of accelerated hypertension in the third trimester, superimposed preeclampsia, fetal growth restriction, placental abruption, premature delivery and stillbirth. These events are seen more often in women who develop preeclampsia and are not correlated with actual blood pressure levels.<sup>(55,68,102-107)</sup> The exception to this appears to be uncontrolled hypertension in the first trimester when later fetal and maternal morbidity and mortality are markedly increased.<sup>(108)</sup> Other indicators of poor prognosis include a failure of blood

pressure to normalize in the second trimester, the presence of secondary hypertension, a history of longstanding severe hypertension, and concurrent cardiovascular and/or renal disease.

The woman with chronic hypertension, whether essential or secondary, should be observed frequently during pregnancy by an obstetrician and by a physician familiar with the management of hypertension in pregnancy.

### 9.1 Investigation

A detailed history, physical examination and appropriate laboratory and cardiac testing are essential in seeking a possible cause for hypertension and to ascertain end-organ damage if present.

Investigation of hypertension presenting prior to 20 weeks gestation:

- All patients:
  - Urinalysis for protein, blood and glucose. If proteinuria is evident on dip-stick analysis, a spot urine protein:creatinine ratio
  - Microscopy of centrifuged urinary sediment for white and red blood cells (including red cell morphology) and for casts
  - Mid-stream urine culture
  - Measurement of serum electrolytes, creatinine, uric acid and blood glucose
  - Full blood examination
  - ECG
- Selected patients:
  - Renal Ultrasound should be considered, particularly if the hypertension is severe
  - Fasting free plasma metanephrines or 24-hour urine collection for estimation of catecholamine excretion if there is concern regarding a possible pheochromocytoma. At least two consecutive collections are advised.

### 9.2 Clinical and laboratory monitoring

Because women with chronic hypertension are at high risk of developing preeclampsia, close monitoring for its maternal and fetal manifestations is necessary. In addition to standard antenatal care, the following additional monitoring is indicated:

- Monitoring for signs of superimposed preeclampsia after 20 weeks gestation
- Assessment for proteinuria at every visit
- Laboratory assessment (as above) if worsening hypertension or proteinuria
- Assessment of fetal growth and wellbeing (Table 5)

Admission to hospital or to a day assessment unit is recommended for women with worsening hypertension or proteinuria at any stage of pregnancy. This enables assessment of maternal and fetal welfare and facilitates discussion amongst all involved in the woman's care. When necessary, pharmacological treatment may be commenced under close supervision.

### 9.3 Antihypertensive therapy

The continued administration or initiation of antihypertensive therapy in women with chronic hypertension in pregnancy (except for the acute treatment of severe hypertension) remains controversial. Most women manifest a physiological fall in blood pressure in the first half of



pregnancy that may allow withdrawal or a reduction of antihypertensive medication. Although treatment of chronic hypertension is associated with a significant reduction in severe hypertension, it has not been shown to alter the risk of superimposed preeclampsia, preterm delivery, placental abruption or perinatal death.<sup>(109-111)</sup>

There is insufficient evidence upon which to base a definite recommendation for the levels of blood pressure at which antihypertensive drug treatment should commence. We recommend that such treatment should definitely be started when the blood pressure consistently reaches or exceeds 160 mmHg systolic and/or 100 mmHg diastolic.

Treatment at BP levels between 140 and 160 mmHg systolic and/or 90 - 100 mmHg diastolic is also common practice, with good documented outcomes. It is therefore reasonable to treat with antihypertensive medications at these levels, but not below these levels. In the third trimester of pregnancy an increase in the requirement for antihypertensive therapy should be anticipated. The drugs used for treatment of chronic hypertension are the same as those recommended for preeclampsia and gestational hypertension (Table 4).

Atenolol and other highly selective beta blocker drugs are not recommended for prolonged use in pregnancy as they have been associated with fetal growth restriction.<sup>(57,112-113)</sup> The use of ACE-inhibitors and angiotensin receptor blockers is contraindicated in pregnancy. They have been associated with an increased risk of fetal, particularly cardiovascular, malformations in early pregnancy in one study and are known to cause adverse sequelae for the fetus in late pregnancy.<sup>(114)</sup> Diuretics, although not teratogenic, may restrict the natural plasma volume expansion of pregnancy and are not recommended for the treatment of hypertension.

### 9.4 Post partum management of women with chronic hypertension

In many women with chronic hypertension or superimposed pre-eclampsia, blood pressure is unstable for 1-2 weeks after delivery and may be difficult to control. It may be particularly high on the third to the sixth day after delivery and it is often necessary to increase or commence antihypertensive medication at that time. All of the agents mentioned earlier are compatible with breast feeding, as are the ACE inhibitors enalapril, captopril and quinapril.

### 9.5 Chronic hypertension with superimposed preeclampsia

As already mentioned, the main risk of chronic hypertension in pregnancy is the development of superimposed preeclampsia in the second half of pregnancy which occurs in about 20% of women. This is of considerable concern as the risks to both mother and fetus are greater than those of chronic hypertension alone. Management of superimposed preeclampsia should be as outlined above for pre-eclampsia unless specific diagnostic issues, such as some secondary causes of hypertension, are present.

## 10. ANAESTHETIC CONSIDERATIONS IN HYPERTENSIVE DISORDERS OF PREGNANCY

Whenever possible an anaesthetist should be informed about a woman with severe pre-eclampsia well prior to labour or operative delivery, because appropriate anaesthetic management is associated with reduction in both fetal and maternal morbidity.<sup>(115)</sup> Relevant issues include anaesthetic risk assessment, blood pressure control, fluid management, eclampsia prophylaxis, and planning of analgesia or anaesthesia.<sup>(116-119)</sup>



### 10.1 Fluid management

Fluid management is a challenging area in preeclampsia and there is no clear evidence regarding optimal type or volume of fluid.<sup>(119,120)</sup> Fluid therapy aims to maintain organ perfusion in the setting of vasoconstriction, endothelial dysfunction and in some parturients severe left ventricular diastolic dysfunction. Intravenous fluid should be administered incrementally in small volumes (e.g. crystalloid 250 mL) with monitoring of maternal haemodynamics, urine output and fetal heart rate, because overhydration contributes to maternal mortality from pulmonary oedema and adult respiratory distress syndrome.<sup>(121)</sup> Particular caution is necessary in women with oliguria, renal impairment or pulmonary oedema, in whom the left ventricle may adapt less well to volume load.<sup>(122)</sup> Fluid loading is not mandatory prior to regional analgesia during labour when low-dose local anaesthetic and opioid methods are used.<sup>(123)</sup> Prior to regional anaesthesia intravenous crystalloid loading is ineffective in preventing hypotension but colloid is effective.<sup>(124)</sup> Treatment or prevention of hypotension with drugs such as phenylephrine or metaraminol is effective and appears safe in preeclamptic women.<sup>(125,126)</sup>

### 10.2 Anaesthetic technique

#### 10.2.1 Vaginal delivery

For labour and delivery, epidural analgesia is a useful adjunct to antihypertensive therapy for blood pressure control and improves renal and uteroplacental blood flow. When relatively contraindicated (e.g. severe thrombocytopenia, coagulopathy or sepsis), fentanyl or remifentanyl patient-controlled intravenous analgesia is preferred. Although ephedrine usually does not cause rebound hypertension<sup>(127)</sup> occasionally vasopressors and epidural adrenaline (epinephrine) cause worrisome blood pressure elevation. Other drugs that are best avoided in severe preeclampsia include ergometrine<sup>(128)</sup>, ketamine (hypertension); and the non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors (impaired renal function and hypertension). Oxytocin should be given slowly in small doses to minimise its significant hemodynamic effects.<sup>(101)</sup>

#### 10.2.2 Caesarean section

Unhurried preoperative preparation reduces the risk of anaesthesia in women with preeclampsia.<sup>(128)</sup> Regional anaesthesia is preferred to general anaesthesia (GA) for caesarean section (CS), especially as airway problems including laryngeal oedema may be increased.<sup>(129-131)</sup> However, well-conducted GA is also suitable<sup>(132,133)</sup> and may be indicated in the presence of severe fetal compromise; pulmonary oedema; hemodynamic instability; intraspinal haematoma risk (e.g. placental abruption; severe thrombocytopenia); or after eclampsia where altered consciousness or neurological deficit persists.

Emergency CS confers increased maternal morbidity, so early anaesthetic notification by the obstetrician and in-utero resuscitation provide additional time for assessment, planning and establishment of regional anaesthesia. When a well-functioning epidural catheter is in situ, GA is achieved only marginally more rapidly than conversion to epidural anaesthesia.<sup>(134,135)</sup> Prophylaxis against pulmonary aspiration is recommended using clear antacid and ranitidine, with or without metoclopramide. Skilled anaesthetic assistance is mandatory, as is left lateral tilt on a pelvic displacement wedge or table tilt to minimise aortocaval compression.

### Attenuation of pressor responses at general anaesthesia for caesarean section

Laryngoscopy and tracheal intubation present a particularly dangerous time for the preeclamptic woman, especially if the intracranial pressure is elevated or the blood pressure is inadequately controlled.<sup>(128)</sup> The transient but severe hypertension that usually accompanies intubation can cause myocardial ischemia, cerebral haemorrhage or pulmonary oedema, all being important causes of maternal death.<sup>(121,128)</sup> Attenuation of this pressor response is best achieved with additional induction drugs such as remifentanyl 1 mcg/kg<sup>(136,137)</sup> or magnesium sulphate 40 mg/kg or 30 mg/kg with alfentanil 7.5 mcg/kg.<sup>(138)</sup> Neuromuscular block must always be monitored closely after intravenous magnesium administration.<sup>(139)</sup> Lignocaine (lidocaine) 1.5 mg/kg is less effective<sup>(137)</sup> and fentanyl 2.5-10 mcg/kg or alfentanil 10 mcg/kg of slower onset.<sup>(140)</sup> Other drug options are beta-blockers (e.g. esmolol)<sup>(141)</sup>, hydralazine, glyceryl trinitrate, sodium nitroprusside and diazoxide.

### Regional anaesthesia for caesarean section and preeclampsia

All the regional anaesthetic techniques (spinal, epidural or combined spinal-epidural) appear safe provided meticulous attention is paid to fluid management, preventing aortocaval compression and dealing with hypotension.<sup>(116,119)</sup> Spinal anaesthesia with usual doses is now a recommended technique.<sup>(119,142,143)</sup> Cardiac output is well maintained and it is associated with less hypotension and lower vasopressor requirements than among healthy parturients.<sup>(144)</sup> Combined spinal-epidural anaesthesia appears to offer further advantages in specific cases.<sup>(119)</sup>

Low dose aspirin therapy is not a contraindication to regional techniques, which in the absence of bleeding are considered safe when the platelet count is  $> 75 \times 10^9/L$  (145). Platelet counts of  $< 50 \times 10^9/L$  are generally considered a contraindication. Within the range  $50-75 \times 10^9/L$  an individual assessment (considering patient risks; coagulation tests and thermoelastography or platelet function if available) and risk reduction strategies (experienced operator; single-shot spinal anaesthesia or flexible tip epidural catheter) are encouraged.

## 10.3 Critical Care

### 10.3.1 Admission to an Intensive Therapy Unit

Anaesthetists form an important part of the critical care team. Women who develop organ failure require intensive monitoring and medical management, either within a high dependency or intensive care setting. Indications for admission to an intensive therapy unit include severe pulmonary oedema or sepsis; intractable hypertension; anuria or renal failure; repeated convulsions; massive blood loss with disseminated intravascular coagulation; neurological impairment requiring ventilation (e.g. intracerebral haemorrhage or infarction; cerebral oedema); and critical intra-abdominal pathology (e.g. acute fatty liver; liver or arterial aneurysm rupture; adrenal haemorrhage).

### 10.3.2 Invasive monitoring

Direct intra-arterial blood pressure monitoring is often useful, including during anaesthesia and operative delivery. However, establishing an arterial line should not delay treatment for acute severe hypertension. Central venous pressure correlates poorly with pulmonary capillary wedge pressure and although it may provide trend monitoring it is infrequently used to complement clinical indicators of intravascular volume.<sup>(146)</sup> Some recommend pulmonary artery catheters for assessment of left ventricular preload<sup>(147)</sup> but they can cause serious complications and are not of proven outcome benefit in preeclampsia. The increasing use of echocardiography and pulse contour or pulse power algorithms for cardiac output monitoring appears promising.<sup>(119)</sup>

## 11. PRECONCEPTION MANAGEMENT AND PROPHYLAXIS FOR WOMEN AT RISK OF PREECLAMPSIA

### 11.1 Recurrence and prevention of preeclampsia

It is likely that development of preeclampsia requires a combination of underlying susceptibility and a triggering event. Many susceptibility factors for preeclampsia have been identified (see Table 6) but to date no accurate predictive tool, using either clinical or laboratory markers, has been developed.<sup>(148)</sup> Such a tool applied early in pregnancy would allow intervention that might modify outcomes.

A number of other factors are also associated with an increased risk of preeclampsia including chronic hypertension, pre-existing renal disease, autoimmune disease, > 10 years since previous pregnancy, short sexual relationship prior to conception, other thrombophilias e.g. Factor V Leiden and possibly periodontal disease.<sup>(148)</sup>

**Table 6: Risk factors associated with preeclampsia<sup>(149)</sup>**

Risk Factor	Relative risk [95%CI]
Previous history of preeclampsia	7.19 [5.85, 8.83]
Antiphospholipid antibodies	9.72 [4.34, 21.75]
Pre-existing diabetes	3.56 [2.54, 4.99]
Multiple pregnancy	2.91 [2.04, 4.21]
Nulliparity	2.91 [1.28, 6.61]
Family history of pre-eclampsia	2.90 [1.70, 4.93]
Elevated BMI > 25	2.47 [1.66, 3.67]
Maternal Age ≥ 40	1.96 [1.34, 2.87]
Diastolic BP ≥ 80 mmHg at booking	1.38 [1.01, 1.87]

### 11.2 Recurrence of preeclampsia

Studies of the risk of recurrent preeclampsia in women with a history of a hypertensive pregnancy disorder in a prior pregnancy show variable results. A number of factors appear to influence this risk including severity and gestation at onset of the initial episode and the presence of additional maternal risk factors such as chronic hypertension or diabetes. Recurrence rates vary from 6% to 55% with the greatest risk in women with early onset preeclampsia and chronic hypertension.<sup>(150)</sup> Data from one Australian centre suggest that women with pre-eclampsia have an overall 14% risk of pre-eclampsia and the same risk of developing gestational hypertension in their next pregnancy.<sup>(151)</sup>

### 11.3 Preventing preeclampsia

A number of agents have been studied for their ability to reduce the risk of preeclampsia and improve maternal and fetal outcomes. These include antiplatelet agents, vitamins, calcium and heparin.

#### Antiplatelet agents

Prophylactic therapy with antiplatelet agents has been the subject of a large number of studies and various statistical reassessments. They demonstrate that the use of aspirin in doses between 50-150mg daily is associated with a reduction in the recurrence rate of preeclampsia, delivery prior to 34 weeks as well as preterm birth and perinatal death. There was a reduction in the rate of small-for-gestational age (SGA) infants but this failed to reach statistical significance.

Risk reduction was greater if the antiplatelet agent was started before 20 weeks and if doses > 75mg were taken. Of importance, there was no difference in the rate of bleeding complications such as antepartum and postpartum haemorrhage or placental abruption between treatment and placebo groups.

In translating these results into clinical practice, the underlying risk of preeclampsia in the population being treated must be taken into consideration. If the baseline risk is 8%, treating 114 women will prevent one case of preeclampsia. In a population with a 20% risk of preeclampsia, the number needed to treat to prevent one case of preeclampsia is 50. In view of this potential benefit, and the relative absence of maternal or neonatal complications, low dose aspirin is indicated for the secondary prevention of preeclampsia in women at increased risk. In most cases, aspirin may be ceased at 37 weeks gestation although continuation beyond this period is not unsafe.<sup>(152)</sup>

### Calcium supplements

The use of calcium supplementation has been demonstrated to reduce the risk of preeclampsia, particularly in high risk women and those with low dietary calcium intake. However there was no significant effect on fetal and neonatal outcomes including preterm birth, low birth weight, fetal growth restriction, stillbirth or death before discharge from hospital. Calcium supplementation (1.5g/day) should therefore be offered to women at increased risk of pre-eclampsia, particularly in those women with a low dietary calcium intake.<sup>(153)</sup>

### Other therapies

Randomised, placebo controlled trials of antioxidants Vitamins C and E failed to demonstrate any significant effect on the incidence of preeclampsia. Of concern, a number of adverse effects were seen including an increased risk of stillbirth and of birthweight < 2.5kg but there were fewer fetal deaths due to immaturity. Prophylactic antioxidant therapy with vitamins C and E is therefore not recommended.<sup>(154,155)</sup>

To date, there are no large randomised trials assessing the effect of heparin with or without aspirin in prevention of preeclampsia.<sup>(156)</sup> As discussed above, women with thrombophilias have an increased incidence of preeclampsia and there has been enthusiasm for prophylactic treatment with anticoagulants, particularly low molecular weight heparin, with or without aspirin. Other than in the specific case of antiphospholipid antibody syndrome, there is no randomised study to support this practice.<sup>(157)</sup>

Recent observational studies have suggested that supplementation with multivitamins containing folic acid during pregnancy is associated with a reduced risk of preeclampsia. Folic acid may reduce the risk of preeclampsia by improving placental and systemic endothelial function or by lowering blood homocysteine levels. Randomized, controlled trials are still required to address this potential therapy.<sup>(158,159)</sup>

### Preconception counselling for women with chronic hypertension

Ideally, the woman with pre-existing hypertension and/or renal disease should be seen, investigated and a diagnosis established prior to a planned pregnancy. This also allows discussion of the potential risks and estimation of the prognosis. Women with significant prenatal renal dysfunction (serum creatinine  $\geq 130 \mu\text{mol/L}$ ) should have the risks of perinatal morbidity/mortality and of deterioration of their underlying renal disease fully explained at this time.<sup>(160)</sup>

Antihypertensive drugs contra-indicated in pregnancy such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics may be ceased and more appropriate therapy instituted. In women with mild-moderate chronic hypertension, the

physiological fall in blood pressure that occurs in the first half of pregnancy may allow the discontinuation of antihypertensive therapy, at least temporarily.

### 12. AUDITING OUTCOMES IN WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY

The preceding guidelines aim to optimise the outcome of pregnancies complicated by preeclampsia and other hypertensive disorders of pregnancy. To quantify these outcomes, it is appropriate for all hospitals managing such patients to monitor and review their outcome data. Rigorous data collection is required to ensure the reliability of reported results. Strict diagnostic criteria for the diagnosis of preeclampsia/eclampsia, gestational hypertension and chronic hypertensive disorders should be utilised as defined in this document.

### 13. LONG-TERM CONSEQUENCES OF HYPERTENSIVE DISORDERS OF PREGNANCY

Women who have been diagnosed with either preeclampsia or gestational hypertension are at increased risk of subsequent cardiovascular morbidity including hypertension and coronary heart disease. A recent systematic review and meta-analysis<sup>(162)</sup> determined that the relative risks for hypertension were 3.70 after 14 years follow-up, for ischemic heart disease 2.16 after 12 years, for stroke 1.81 after 10 years, and for venous thromboembolism 1.87 after 5 years. Overall mortality after preeclampsia was increased 1.5 fold after 14 years.

These associations are likely to reflect a common cause for preeclampsia and cardiovascular disease, or an effect of preeclampsia on vascular disease development, or both. It is reasonable to counsel patients who develop hypertension in pregnancy that they will benefit from avoiding smoking, maintaining a healthy weight, exercising regularly and eating a healthy diet. It is recommended that all women with previous preeclampsia or hypertension in pregnancy have an annual blood pressure check and regular (5 yearly or more frequent if indicated) assessment of other cardiovascular risk factors including serum lipids and blood glucose.

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**APPENDIX 1: PRINCIPLES AND METHOD OF ADMINISTRATION OF INTRAVENOUS HYDRALAZINE FOR SEVERE HYPERTENSION IN PREGNANCY**

<b>IV Hydralazine</b>	
<b>AIM:</b> to achieve a gradual reduction in blood pressure to safe levels (90mmHg diastolic), rather than a precipitate drop. <b>NOTE:</b> <i>the risk of sudden hypotension can be greater in women with a contracted plasma volume.</i>	
<b>TRADE NAME: PRESENTATION: INCOMPATIBILITIES:</b>	Apresoline® 20mg ampoule aminophylline, ampicillin, hydrocortisone, sulphadiazine, dextrose diluents
<b>DOSE:</b>	<ul style="list-style-type: none"> <li>Hydralazine 5 mg as an intravenous bolus</li> <li>Repeat if necessary at 20 minute intervals, up to a maximum of 3 doses</li> </ul>
<b>CONCOMITANT ANTIHYPERTENSIVE THERAPY:</b>	<ul style="list-style-type: none"> <li>Continue existing oral antihypertensive therapy and review dose regimen; <b>OR</b></li> <li>If conscious, commence oral antihypertensive therapy (such as clonidine, labetalol or oxprenolol) in addition to the intravenous hydralazine</li> </ul>
<b>Persistent hypertension despite 3 boluses of IV hydralazine 5mg may be due to a compensatory reflex tachycardia:</b>	<p><b>if heart rate &lt; 125bpm:</b></p> <ul style="list-style-type: none"> <li>Commence hydralazine infusion of 10 mg/hr.</li> <li>Load 50 mg of IV hydralazine into 50 ml of normal saline (<b>not</b> glucose sol.);</li> <li>Run the infusion through an infusion pump at a rate of 10 ml/hr;</li> <li>Increase rate by 5ml/hr every 15 minutes until blood pressure is controlled.</li> </ul> <p><b>if heart rate &gt; 125 bpm:</b></p> <ul style="list-style-type: none"> <li>Give oral clonidine, labetalol or oxprenolol in addition to hydralazine infusion</li> </ul>
<b>MATERNAL and FETAL OBSERVATION AND MONITORING</b>	<ul style="list-style-type: none"> <li>Continuous CTG throughout administration of hydralazine and until BP is stable (30 minutes after the last dose);</li> <li>Record BP (Mercury sphygmomanometer, Korotokoff V) and pulse every 5 minutes after each bolus dose;</li> <li>Continue 5 minute BP and pulse until stable, thence measure hourly;</li> <li>Record BP every 15 minutes for the first hour of a continuous infusion, thence measure hourly if stable.</li> </ul>

### APPENDIX 2: MAGNESIUM SULPHATE HEPTAHYDRATE INFUSION NOTES AND EXAMPLE INFUSION PROTOCOLS

#### Indications for magnesium sulphate infusion:

1. seizure prophylaxis in a woman who has already had an eclamptic seizure;
2. seizure prophylaxis in a woman with severe pre-eclampsia who is at risk of eclampsia (although the efficacy for this is less certain)

#### Relative contraindications:

##### **NOTE: Magnesium sulphate can be extremely hazardous in the following circumstances:**

- renal failure, severe renal compromise or if oliguria is present (magnesium concentration can reach toxic levels as elimination is predominantly renal). Half dose magnesium sulphate should be considered if there is renal compromise;
- in association with hypocalcaemic states;
- myasthenia gravis;
- cardiac conditions, in particular conduction problems or myocardial damage.

#### Other considerations:

##### **Magnesium sulphate:**

- may lower blood pressure (secondary to vasodilatation). Dose of any current antihypertensive medication may require adjustment;
- may have some tocolytic effect;
- may decrease fetal heart rate variability;
- may cause loss of reflexes (patellar reflexes will be absent well before toxic serum levels of magnesium are reached);
- should be used with caution in the presence of calcium antagonists or other respiratory depressants (e.g. valium).

#### Common maternal side effects:

- Sensation of pain and warmth in arm
- Flushing of hands, face and neck
- Nausea

#### Signs of maternal toxicity:

- Loss of patellar reflexes
- Respiratory rate < 10
- Slurred speech, weakness, feeling extremely sleepy, double vision
- Muscle paralysis
- Respiratory / cardiac arrest

#### Antidote for magnesium toxicity:

Calcium chloride or calcium gluconate (10ml of 10% solution) by slow intravenous injection over 3 minutes.

#### Protocol for magnesium sulphate heptahydrate (MgSO<sub>4</sub>) infusion:

- Administration of magnesium sulphate heptahydrate should always be via an infusion pump;
- The intravenous line should not be used to inject other drugs;
- Presentation of magnesium sulphate is most commonly a 50% solution in 5mls of H<sub>2</sub>O.
- Undiluted this is 10mmol of magnesium in 5mls, or a 2mmol per ml solution. Magnesium sulfate is administered intravenously or intramuscularly. Intravenous doses should be diluted to a concentration of magnesium 20% or less.



**N.B. Pre-mixed solutions of magnesium sulphate heptahydrate are commercially available for infusion pump use. These preparations are preferred as pre-mixed solutions confer considerable safety benefits over manually prepared solutions. In the event that a maternity service elects not to use pre-mixed solutions, a drug protocol for the manual mixing of the solutions should be developed and approved by the local drug committee. This should then be available and clearly communicated to all staff involved in the use of magnesium sulphate heptahydrate solutions.**

- Recommended loading dose: 4 grams (16 mmol) MgSO<sub>4</sub> heptahydrate over 15-30mins
- Maintenance infusion: 1gram / hour for at least 24 hours

**Care and observations during infusion**

Close observation and assessment (maternal and fetal) is required for the duration of the infusion. Where patient condition is unstable, the frequency of observation will need to be increased.

*Routine observations:*

- 1-2 hourly recording of maternal blood pressure, respiratory rate, heart rate and urine output.
- (Cease infusion if respiratory rate is < 10 per minute or if urine output is < 80mls over four hours);
- Patellar reflexes at completion of loading dose and then 2 hourly. (Cease infusion if unable to elicit reflexes);
- Fetal heart rate monitoring as clinically indicated;
- Serum magnesium levels may be measured 60 minutes after commencing the infusion and thereafter as clinically indicated. Normal therapeutic levels are 1.5-3.5 mmol/L. (Blood for serum levels should not be collected from the limb receiving the infusion)

Example 1: Mixing solution for infusion pump use	
<p><b>1. Loading Dose</b></p> <p><b>4g MgSO<sub>4</sub> (50% solution) diluted in Normal Saline via infusion pump over 20-30 minutes</b></p> <ul style="list-style-type: none"> <li>• Using a 500ml flask of Normal Saline, run <b>100ml</b> into a burette;</li> <li>• Add <b>8ml</b> (4g) of MgSO<sub>4</sub> (50% solution) to the 100ml of Normal Saline in the burette;</li> <li>• Infuse over 20-30 minutes via infusion pump.</li> </ul>	<p><b>2. Maintenance Infusion</b></p> <p><b>1 gram MgSO<sub>4</sub> (50% solution) per hour via infusion pump</b></p> <ul style="list-style-type: none"> <li>• Remove 20ml N/Saline from the N/S remaining in the flask and discard.</li> <li>• Add <b>20ml</b> (10g) of MgSO<sub>4</sub> (50% solution) to the remaining 380ml flask of Normal Saline;</li> <li>• Infuse at 40mls (1g) per hour via infusion pump;</li> <li>• Run maintenance infusion for at least 24hours.</li> </ul>
Example 2: Premixed commercial solution (8 grams Magnesium Sulphate in 100 mls water for injection)	
<p><b>1. Loading Dose</b></p> <p><i>50 mls (4 grams) Magnesium Sulphate premixed solution (8 grams magnesium sulphate heptahydrate in 100 mls water for injection; each 100 mls contains approximately 32 millimoles magnesium and 32 millimoles sulphate)</i></p> <ul style="list-style-type: none"> <li>• Infuse over 15 – 30 minutes</li> </ul>	<p><b>2. Maintenance Infusion</b></p> <p><i>12.5 mls (1 gram) Magnesium Sulphate premixed solution (8 grams magnesium sulphate heptahydrate in 100 mls water for injection; each 100 mls contains approximately 32 millimoles magnesium and 32 millimoles sulphate) per hour</i></p> <ul style="list-style-type: none"> <li>• Infuse at 12.5 mls per hour</li> </ul>

<b>Example 3: Premixed commercial solution (40 grams Magnesium Sulphate in 500 mls water for injection)</b>	
<p><b>1. Loading Dose</b></p> <p><i>50 mls (4 grams) Magnesium Sulphate premixed solution (40 grams magnesium sulphate heptahydrate in 500 mls water for injection; each 500 mls contains approximately 162 millimoles magnesium and 162 millimoles sulphate)</i></p> <ul style="list-style-type: none"><li>• Infuse over 15 – 30 minutes</li></ul>	<p><b>2. Maintenance Infusion</b></p> <p><i>12.5 mls (1 gram) Magnesium Sulphate premixed solution (40 grams magnesium sulphate heptahydrate in 500 mls water for injection; each 500 mls contains approximately 162 millimoles magnesium and 162 millimoles sulphate) per hour</i></p> <ul style="list-style-type: none"><li>• Infuse at 12.5 mls per hour</li></ul>