South Australian Perinatal Practice Guideline

Hypertensive Disorders in Pregnancy

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of Perinatal Practice Guideline (PPG)

The purpose of this guideline is to provide perinatal clinicians with information on the diagnosis, monitoring and treatment of hypertensive disorders in pregnancy including chronic hypertension, gestational hypertension, preeclampsia and eclampsia. It includes the infusion regimens for labetalol, hydralazine and magnesium sulphate.

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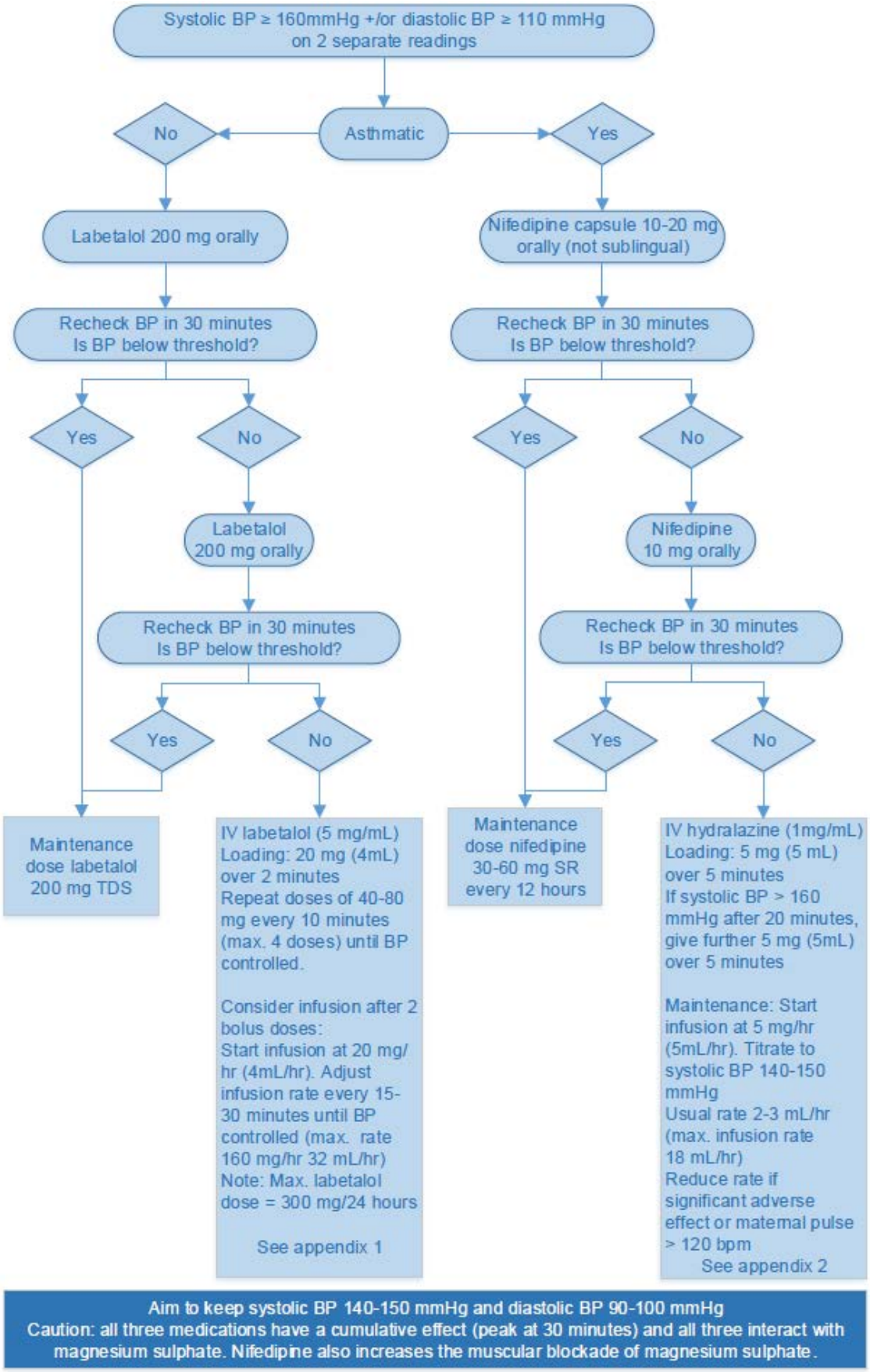
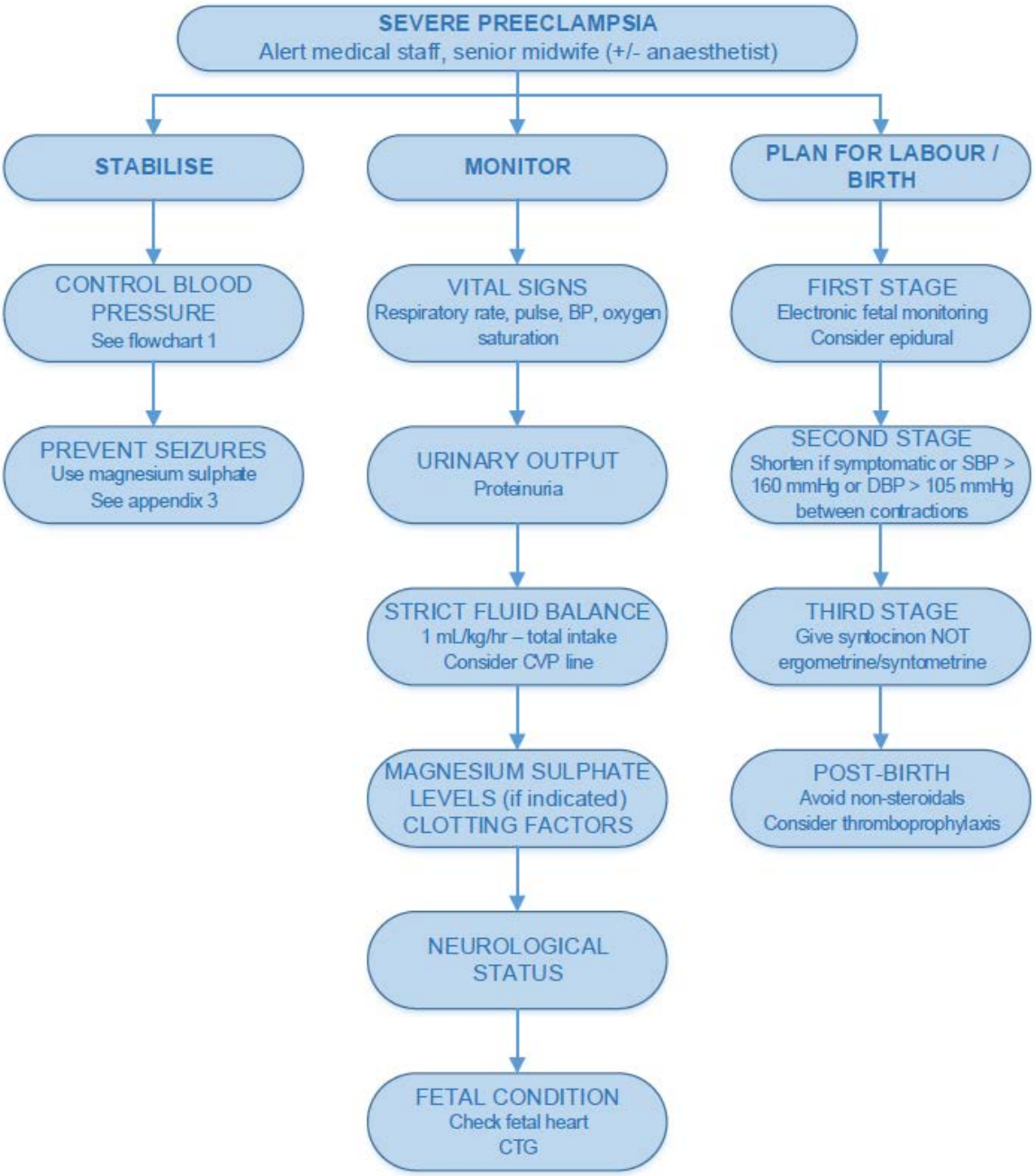
Flowchart 1: Pharmacological Treatment for Severe Hypertension

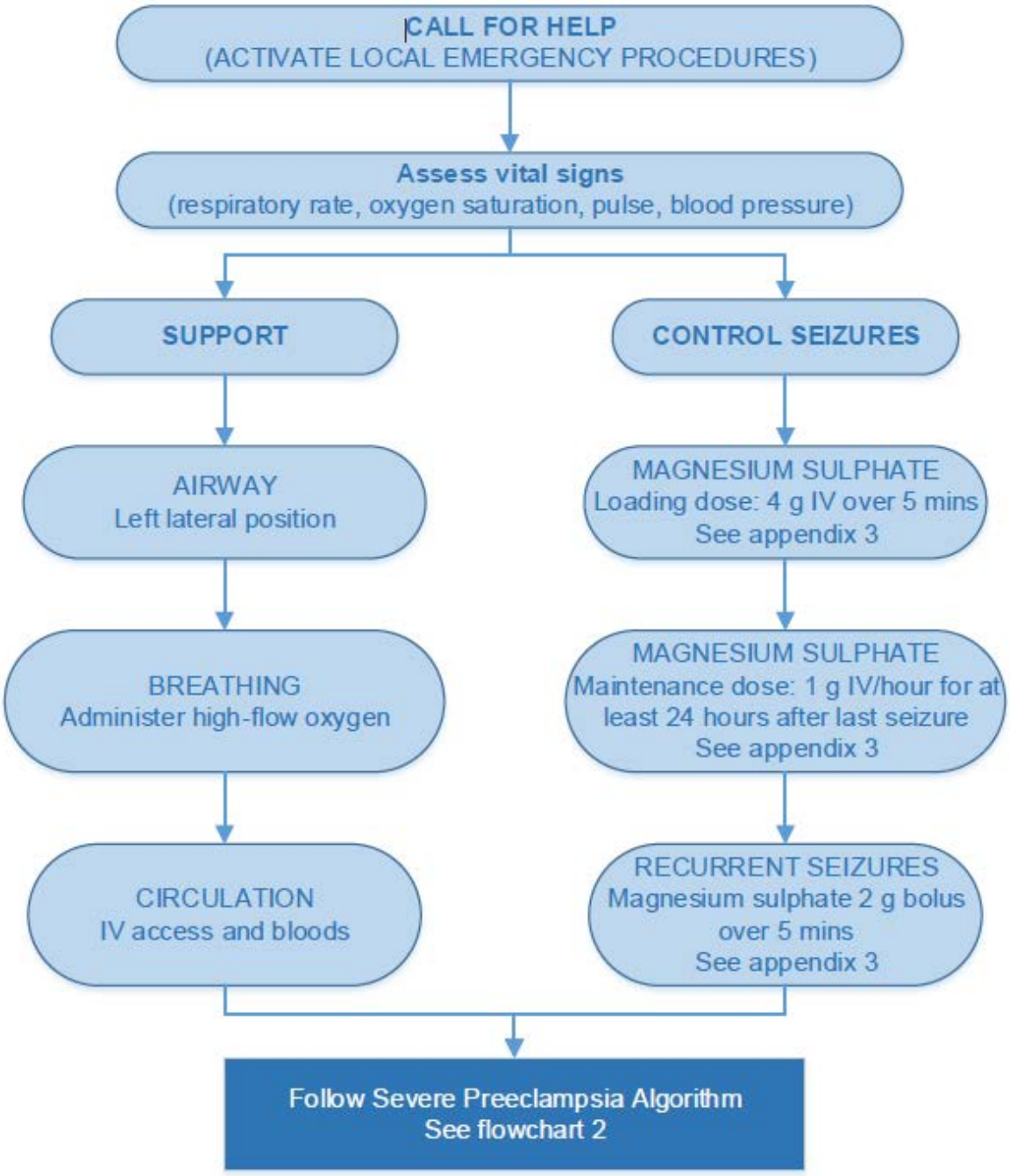


Adapted from SOMANZ guideline[1] and PROMPT manual[2]

Flowchart 2: Management of Severe Preeclampsia[2]



Flowchart 3: Initial Management of Eclampsia[2]



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Summary of Practice Recommendations

Women with an upper arm circumference > 33 cm require an alternate cuff

Women should be assessed for risk factors and commenced on prophylaxis if appropriate

Any woman presenting with new hypertension after 20 weeks gestation should be assessed for signs and symptoms of preeclampsia.

The presence of severe hypertension, headache, epigastric pain, oliguria or nausea and vomiting or any concern re fetal wellbeing should lead to urgent admission and management

A woman with early onset preeclampsia (< 32 weeks) should be transferred to a unit with appropriate maternal and neonatal care facilities as soon as possible

All women with a SBP ≥ 160 mmHg or a DBP ≥ 110 mmHg should be treated because of the risk of intracerebral haemorrhage and eclampsia

If a woman's BP is not controlled with oral antihypertensive medications, advice from an obstetric physician should be sought.

The three main aspects to care of the woman with severe preeclampsia are stabilise, monitor and plan for labour/birth

A strict fluid balance should be maintained in women with severe preeclampsia

Consideration must be given to haematological status in women with severe preeclampsia

It is important to control severe hypertension and stabilise the maternal condition before birth

Eclampsia management involves resuscitation, prevention of further seizures, control of hypertension and plan for birth

Epidural analgesia is helpful for BP control during labour

Avoid non-steroidal anti-inflammatory medication postnatally

BP monitoring and a gradual withdrawal of antihypertensive therapy may be required for up to 3 months postnatally

Consultation with an obstetric provider should be sought for any woman presenting with hypertension and/or headache in the two weeks following birth

Women diagnosed with gestational hypertension and/or pre-eclampsia are at increased risk of cardiovascular disease and require advice re health promotion and increased health checks

Abbreviations

BP	Blood pressure
CI	Confidence interval
cm	centimetres
et al	and others
DBP	Diastolic blood pressure
hr	hour
IV	intravenous
K1 – 5 etc	Korotkoff 1-5
L	litre
mg	Milligram(s)
mg/mmol	Milligrams per millimol
mins	minutes
mL	Millilitre(s)
mmHg	Millimetres of mercury
MSSU	Mid-stream specimen of urine
NSAID	Non-steroidal anti-inflammatory medication
prn	As required
QID	Four times per day
SBP	Systolic blood pressure
TDS	Three times per day

Definitions

Term	Definition
Hypertension	Systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mmHg (K5) Confirmed by repeated readings over several hours
Severe hypertension	Systolic BP ≥160 mm Hg and/or diastolic BP ≥ 110 mmHg
Preeclampsia	A multi-system disorder characterised by hypertension and involvement of one or more other organ systems and/or the fetus Proteinuria is the most commonly recognised additional feature after hypertension (not mandatory for clinical diagnosis)
Gestational hypertension	New onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia Return of BP to normal within 3 months postpartum
Chronic hypertension	Includes essential hypertension as well as hypertension secondary to a range of conditions **Essential hypertension:** A systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg before pregnancy or before 20 weeks gestation without a known cause. It may include women presenting early in pregnancy on antihypertensive medications where no secondary cause for hypertension has been determined. **Secondary hypertension** may be due to: chronic kidney disease, renal artery stenosis, systemic disease with renal involvement, endocrine disorders, coarctation of the aorta, medications **White coat hypertension** refers to raised BP in the presence of a clinical attendant but normal BP otherwise as assessed by ambulatory or home BP monitoring
Preeclampsia superimposed on chronic hypertension	Pre-existing hypertension is a strong risk factor for the development of preeclampsia **Superimposed preeclampsia** is diagnosed when chronic hypertension develops one or more of the systemic features of preeclampsia after 20 weeks of gestation Substantial increases in proteinuria and hypertension should raise suspicion of preeclampsia

Introduction

This PPG is based on the recommendations from a multidisciplinary working party convened by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[1] along with management principles outlined in the Practical Obstetric Multi-Professional Training (PROMPT) course manual[2] .

Recording blood pressure in pregnancy

Technique	Procedure	Rationale
Position of woman	Seated comfortably, legs resting on a flat surface and her arm resting at heart level Measure BP on both arms at initial antenatal visit In labour, measure in lateral recumbency Avoid supine posture	Different arm positions can produce significantly different measurements Avoid supine hypotension
Cuff size	**Upper arm circumference 33-44 cm** Use a large cuff with an inflatable bladder covering 80% of the arm circumference **Upper arm circumference > 44 cm** A thigh cuff or alternative / long adult cuff should be used	Correct cuff size is important for blood pressure recording to minimise over-diagnosis of hypertension The rate of deflation of the cuff should be ≤ 2 mm per second to avoid underestimating SBP
Systolic blood pressure	Accepted as the first sound heard (K 1)	Take readings to the nearest 2 mmHg (not nearest 0 or 5 mmHg)
Diastolic blood pressure	Accepted as the disappearance of sounds completely (K 5) Where K 5 is absent, K 4 (muffling) is accepted	K 5 is detected with greater reliability than K 4

Risk Factors for Preeclampsia

All women should be assessed for risk factors once pregnancy is confirmed.

Relative risk for factors associated with preeclampsia	
Risk Factor	**Unadjusted Relative Risk [95% CI]**
Nulliparity	2.9 [1.3-6.6]
Multiple pregnancy	2.9 [1.3-6.6]
Previous history of preeclampsia	7.2 [5.9-8.8]
Family history of preeclampsia	2.9 [1.7-4.9]
Overweight BMI 25-29.9	1.7 [1.2-2.4]
Obese BMI >30	2.7 [1.7-4.4]
Age ≥ 40	2.0 [1.3-2.9]
Systolic BP>130 mmHg before 20 weeks	2.4 [1.8-3.2]
Diastolic BP >80 mmHg before 20 weeks	1.4 [1.0-1.9]
Antiphospholipid syndrome	9.7 [4.3-21.8]
Pre-existing diabetes	3.6 [2.5-5]
Other risk factors	Underlying renal disease Chronic autoimmune disease Inter-pregnancy interval >10 years

Prophylaxis for women at risk of preeclampsia

Women who have experienced hypertension in a previous pregnancy are at increased risk in any future pregnancies. They should receive appropriate counselling and prophylaxis if the risk is considered significant.

Women with proven antiphospholipid syndrome should receive appropriate counselling and prophylaxis.

Antiplatelet agents

Prophylactic therapy with anti-platelet agents has been the subject of a large number of studies and various systematic reviews, with the majority of trials using aspirin 50-150 mg.

It is important to start aspirin early in pregnancy (as soon as pregnancy is confirmed). Commencement of aspirin is useful at any time in pregnancy but conveys most benefit if started prior to 16 weeks gestation.

In most cases, aspirin may be ceased at 37 weeks gestation although continuation beyond this period is not unsafe.

Calcium supplements

The use of calcium supplementation has been demonstrated to significantly reduce the risk of preeclampsia, particularly in high risk women and those with low dietary calcium intake.

Calcium supplementation (1.5 g / day) should therefore be offered to women with moderate to high risk of preeclampsia, particularly those with a low dietary calcium intake; commenced by 20 weeks gestation and continued for the remainder of pregnancy.

Investigation of new onset hypertension after 20 weeks gestation

Any woman presenting with new hypertension after 20 weeks gestation should be assessed for signs and symptoms of preeclampsia.

Women should be informed about the urgency of seeking advice from a health professional if they experience headache, visual disturbance (such as blurring or flashing before the eyes), epigastric pain, vomiting and/or rapid swelling of the face, hands or feet.

The presence of severe hypertension, headache, epigastric pain, oliguria or nausea and vomiting or any concern re fetal wellbeing should lead to urgent admission and management.

The following investigations should be performed in all women with new onset hypertension after 20 weeks gestation:

Laboratory Investigations

- Protein / creatinine ratio in a ‘spot’ urine sample
- Full blood count
- Creatinine, electrolytes, urate
- Liver function tests
- Coagulation studies (may be indicated depending on severity of clinical presentation)

Ultrasound Assessment

- Fetal growth
- Amniotic fluid volume
- Umbilical artery Doppler assessment

Ongoing investigation of women with hypertension in pregnancy

At each assessment, the clinician should systematically review the woman’s symptoms, examination, laboratory investigations and fetal wellbeing

Further assessment and management should be guided by each woman’s clinical situation.

Diagnosis of 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 signs of organ involvement:

Renal	Significant proteinuria – either 300 mg per 24 hours or a spot urine protein/creatinine ratio of 30 mg/mmol or more Serum or plasma creatinine 90 micromols/L or more Oliguria: less than 80 mL / 4 hours Urate is not included as a diagnostic feature
Haematological	Thrombocytopenia less than100,000 /microlitre Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase more than 600 international units/L, decreased haptoglobin Disseminated intravascular coagulation
Liver	Raised serum transaminases Severe epigastric and / or right upper quadrant pain
Neurological	Convulsions (automatically redefines it as eclampsia) Hyperreflexia with sustained clonus Persistent, new headache Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm) Stroke
Pulmonary	Pulmonary oedema
Uteroplacental	Fetal growth restriction

Management of preeclampsia and gestational hypertension

A woman with early onset preeclampsia (< 32 weeks) should be transferred to a unit with appropriate maternal and neonatal care facilities as soon as possible.

Treatment for hypertension

All women with a SBP ≥ 160 mm Hg or a DBP ≥ 110 mm Hg should be treated because of the risk of intracerebral haemorrhage and eclampsia.

Treatment for mild to moderate hypertension is more controversial.

Antihypertensive therapy

Medications commonly used to treat hypertension in pregnancy include methyldopa, labetalol and nifedipine. If a woman's BP is not controlled with these medications, advice from an obstetric physician should be sought.

Either labetalol or methyldopa can be used in women planning a pregnancy and during pregnancy (including the first trimester). Neither of these agents have been associated with an increased risk of malformations above the background rate of 2-3%. Nifedipine is generally considered a second line agent during pregnancy for the ongoing management of hypertension

Antihypertensive medications in pregnancy				
Drug	**Dose**	**Action**	**Contraindications**	**Practise Points**
Methyldopa	250 mg-750 mg every 8 hours	Central	Depression	Slow onset of action over 24 hours, dry mouth, sedation, depression, blurred vision Withdrawal effect: rebound hypertension
Labetalol	100 mg-400 mg every 8 hours	Beta blocker with mild alpha vasodilator effect	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling which usually resolves within 24 hours
Nifedipine	30 mg or 60 mg slow release every 12 hours	Calcium channel antagonist	Aortic stenosis	Severe headache in first 24 hours, flushing, tachycardia, peripheral oedema, constipation

Treatment of severe hypertension

Blood pressure ≥160 mmHg SBP or 110 mmHg DBP requires urgent treatment. See flowchart 1

Treatment should be administered promptly aiming for a gradual and sustained lowering of blood pressure.

Continuous cardiotocography (CTG) monitoring is advised, particularly when there is evidence of existing fetal compromise.

The concurrent administration of longer acting oral agents will achieve a more sustained blood pressure lowering effect.

Medications for acute blood pressure lowering for severe hypertension				
	Formulations	**Dose and Administration**	**Onset of Action**	**Adverse Effects**
Nifedipine	10 mg & 20 mg immediate release tablet or capsule	10 mg or 20 mg orally. Repeat after 30 minutes if BP not below threshold, maximum 40 mg	30-45 minutes	Headache Flushing
Labetalol	200 mg tablet 5 mg/mL IV vial	200mg orally. Repeat after 30 minutes if BP not below threshold, maximum 400 mg If BP not below threshold after 30 minutes, give 20 mg IV bolus slowly over 2 minutes. Repeat doses of 40-80 mg every 10 minutes until BP controlled (max. 4 doses). Consider infusion after 2 bolus doses. See appendix 1 + flowchart 1	Maximal effect usually occurs within 5 minutes after each dose	Bradycardia Hypotension Fetal bradycardia
Hydralazine	20 mg/mL IV powder vial	If BP not below threshold following administration of nifedipine, give 5 mg IV bolus over 5 minutes. Repeat every 20 minutes until BP controlled, max. 30 mg See appendix 2 + flowchart 1	20 minutes	Flushing Headache Nausea Hypotension Tachycardia

The most important consideration in choice of antihypertensive agent is that the unit has experience and familiarity with that agent.

Treatment of severe preeclampsia

Severe preeclampsia has been defined as BP ≥160/110 mmHg with proteinuria (urinary protein:creatinine ratio > 30mg/mmol or 24 hour urinary protein > 300 mg) **OR**

BP 140/90 – 159/109 mmHg with proteinuria with at least one of the following:

- Severe headache
- Visual disturbances
- Severe pain just below the ribs or vomiting
- Papilloedema
- Signs of clonus (≥ 3 beats)
- Liver tenderness
- HELLP syndrome
- Platelet count < 100 x 109/L
- Abnormal liver enzymes

There are three main aspects to care of the woman with severe preeclampsia (see flowchart 2):

1. Stabilise

- Control BP
- Prevent seizures using Magnesium Sulphate IV (see appendix 3)

2. Monitor

- Vital signs
- Urinary output
- Neurological status
- Clotting factors
- Fetal condition

3. Plan for labour/birth

- The choice for caesarean birth or induction of labour is dependent upon the severity of the maternal disease, gestational age, and the fetal condition
- If the woman is in labour, consider epidural analgesia
- If the woman is in second stage of labour, consider expediting birth

Thromboprophylaxis

Preeclampsia is an independent risk factor for venous thromboembolism (VTE) in pregnancy and postpartum

Pharmacological prophylaxis should be considered (see *Thromboprophylaxis and Thromboembolic Disorders in Pregnancy* PPG at www.sahealth.sa.gov.au/perinatal)

Fluid management

Fluid management in the setting of preeclampsia can be difficult due to:

- The varied pathophysiologic processes which may be contribute to decreased urine output in preeclampsia. These include:
    - glomerular endotheliosis associated with preeclampsia
    - angiogenic factors
    - decreased circulating component of the renin-angiotensin aldosterone system
    - blood loss postpartum exceeding the auto-transfusion associated with uterine contraction following birth
    - decreased circulating volume
    - myocardial dysfunction
- The risk of causing pulmonary oedema associated with the administration of excessive volumes of intravenous fluids due to:
    - micro-albuminaemia
    - increased vascular permeability
    - myocardial dysfunction.

The key management points are[3]:

- Strict fluid balance and care with fluid intake.

- In the immediate postpartum period, oliguria is common, and does not require additional fluid therapy unless the plasma creatinine is rising.
- Diuretics should not be used in the absence of pulmonary oedema or fluid overload[4].
- In severe preeclampsia:
    - measure urine output hourly
    - limit fluids to a maximum of 60-80mL/hr
    - persistent oliguria (<80mL/ four hours) requires medical assessment of the severity of the preeclampsia, any associated complications and current management plan
    - An intravenous fluid bolus of 250mL may be appropriate after careful assessment.
- Obstetric and Obstetric Medicine / Renal / Intensive Care physician review is required where oliguria persists:
    - High dependency or intensive care management may be appropriate.
    - Echocardiography and more dynamic measures of cardiac output, such as devices based on pulse contour analysis or pulse power algorithms may be indicated to evaluate and optimise cardiac function and renal perfusion. Note: central venous pressure correlates poorly with pulmonary capillary wedge pressure and is not an indicator of intravascular volume status[1].

Haematological manifestations

A platelet count of 100 x 10^9/L is considered to be abnormal and requires daily monitoring as the count may fall rapidly

Intravascular haemolysis may occur and should be checked for with appropriate laboratory tests (full blood count, blood film, lactic dehydrogenase and haptoglobins) as this is an indication for expediting birth.

The risk of peripartum bleeding complications is not significantly increased until the platelet count falls below 50 x 10^9/L.

Timing of birth

Timing of birth is dependent upon the severity of the maternal disease, gestational age, and the fetal condition (see table below)

In women with preeclampsia before 34 weeks, aim to delay birth for 24-48 hours if maternal and fetal status permit to allow fetal benefit from antenatal corticosteroids administration.

Consider magnesium sulphate administration for neonatal neuroprotection for women less than 30 weeks gestation (see *Magnesium sulphate for neuroprotection of the fetus in women at risk of preterm birth* PPG available at www.sahealth.sa.gov.au/perinatal)

Indications for birth in women with preeclampsia

Maternal	**Fetal**
Gestational age ≥ 37 weeks	Placental abruption
Inability to control hypertension	Severe fetal growth restriction
Deteriorating platelet count	Non-reassuring fetal status
Intravascular haemolysis	
HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)	
Deteriorating liver function	
Deteriorating renal function	
Persistent neurological symptoms	
Persistent epigastric pain, nausea or vomiting with abnormal liver function	
Pulmonary oedema	

Eclampsia

Eclampsia is characterised by coma and / or convulsions.

Eclampsia may occur at any time up to 24 hours after birth and occasionally later. Hypertension and proteinuria may be absent before the seizure and many seizures occur without previously known neurological symptoms or signs.

Eclampsia is not the commonest cause of seizures in pregnancy (see *Seizures in pregnancy* PPG at www.sahealth.sa.gov.au/perinatal)

Management of eclampsia

There are four main aspects to care of the woman who sustains eclampsia (see flowchart 4)

1. Resuscitation

Assuring a patent airway, high-flow oxygen by mask and institution of intravenous access and administering loading dose of magnesium sulphate – 4 g IV bolus over 5 minutes (see Magnesium sulphate infusion regimen)

2. Prevention of further seizures

Maintenance treatment should continue with magnesium sulphate infused at a rate of 1 g/hour after the original loading dose (see Magnesium sulphate infusion regimen)

Magnesium sulphate is excreted via the kidneys 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%.

3. Control of hypertension

Control of severe hypertension to levels below 160/100 mm Hg is essential. See Treatment of Severe Hypertension

4. Birth

Arrangements for birth should be made once the woman's condition is stable.

Continue fetal monitoring

Anaesthetic considerations in hypertensive disorders of pregnancy

A full anaesthetic assessment should be undertaken in women with severe preeclampsia, preferably well before labour or operative birth[5]:

- There may be an associated thrombocytopaenia. Additional tests to exclude a coagulopathy should be performed in women with severe preeclampsia and platelet counts of <100 $x10^9$
- Fluid management can be complex
- A small proportion of women with preeclampsia will have associated myocardial dysfunction requiring additional consideration and monitoring.

During labour and birth epidural analgesia reduces pain-mediated hypertensive responses.

In the absence of contraindications, regional anaesthetic techniques (spinal, epidural or combined spinal-epidural) are useful for analgesia during labour. They are the preferred method of anaesthesia for caesarean section.

General anaesthesia may be necessary in a small number of cases for a variety of reasons, including coagulopathy, pulmonary oedema or eclampsia. If general anaesthesia is used:

- Particular attention should be taken to blunting the hypertensive response to intubation as this has been identified as a cause of direct maternal mortality. Drugs that have been used for this purpose include alfentanil, fentanyl, remifentanil, $MgSO_4$, lignocaine and esmolol.
- Care is required to avoid complications on emergence from anaesthesia.

Standard post-caesarean analgesia should occur with the initial exclusion of non-steroidal anti-inflammatory drugs (NSAIDs). If tramadol is considered, balance the benefits of its use against its potential to reduce the seizure threshold and the risk of eclampsia.

Resolution of preeclampsia and gestational hypertension

After birth, all clinical and laboratory derangements of preeclampsia recover, but there is often a delay of several days, and sometimes longer.

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 preeclampsia and there is no other underlying medical disorder.

On the first day or two after birth, liver enzyme elevations and thrombocytopenia will often worsen before they improve.

Non-steroidal anti-inflammatory medications (NSAID) are therefore contraindicated as they may adversely affect hypertension, renal function and platelet function.

Consultation with an obstetric provider should be sought for any woman presenting with hypertension and/or headache in the two weeks following birth.

Recurrence

Women who have experienced hypertension in a previous pregnancy are at increased risk in any future pregnancies. They should receive appropriate counselling and prophylaxis in subsequent pregnancies if the risk is considered significant.

Long-term consequences

Women who have been diagnosed with either preeclampsia or gestational hypertension are at increased risk of developing hypertension, cardiovascular disease and cerebrovascular disease (Hyperlink to table below). It has also been linked with increased risks of developing deep vein thrombosis, end stage renal disease, type II diabetes.

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. Women who have had preeclampsia will benefit from avoiding smoking, maintaining a healthy weight, exercising regularly and eating a healthy diet.

Risk of developing subsequent disease after preeclampsia	
Medical Condition	**Relative Risk [95% CI]**
Chronic Hypertension	3.70 [2.70-5.05]
Ischaemic Heart Disease	2.16 [1.86-2.52]
Cerebrovascular Disease	1.81 [1.45-2.27]
Peripheral Vascular Disease	1.87 [0.94-3.73]
Deep Vein Thrombosis	1.79 [1.37-2.33]
End Stage Renal Disease	4.3 [3.3-5.6]
Type II Diabetes	1.86 [1.22-2.84]
Elevated TSH	1.7 [1.1-1.7]
All Cancer	0.96 [0.73-1.27]

References

1. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA et al. Guideline for the management of hypertensive disorders of pregnancy 2014. Society of Obstetric Medicine of Australia and New Zealand (SOMANZ); 2014. Available from URL: https://somanz.org/guidelines.asp
2. Sowter M, Weaver E and Beaves M (Eds) PROMPT. PRactical Obstetric Multi-Professional Training Course Manual,Australia and New Zealand Edition, Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), 2013
3. Druzin ML, Shields LE, Peterson NL et al. Improving Health Care Response to Preeclampsia: A California Quality Improvement Toolkit. California Maternal Quality Care Collaborative. 2014
4. Queensland Clinical Guidelines. Hypertensive disorders of pregnancy. 2015. Available From URL: https://www.health.qld.gov.au/__data/assets/pdf_file/0034/139948/g-hdp.pdf
5. Dennis AT. Management of pre-eclampsia. Anaesthesia 2012:67: 1009-1020
6. Australian Medicines Handbook https://amhonline.amh.net.au/
7. MIMS https://www.mimsonline.com.au/Search/Search.aspx
8. Australian Injectable Drugs Handbook https://aidh.hcn.com.au/browse/about_aidh

Appendices

Appendix 1: Labetalol – Intermittent IV Bolus and IV Infusion Regimen

Labetalol intermittent bolus IV administration	
The aim is to reduce diastolic blood pressure by 10 mm Hg and to below 105 mm Hg in the first instance (over 20-40 minutes), and to maintain the blood pressure at or below that level **Co-administration of oral labetalol 200 mg OR 20 mg nifedipine (NOT controlled release) is recommended while gaining intravenous access**	
Administration precautions	> Give intravenous fluid preload of 250 mL of either sodium chloride 0.9 % or Hartmann's immediately before use > The maximum labetalol dose is 300 mg / 24 hours > Extravasation of labetalol solution may cause ischaemia and necrosis (pH 3.5-4.2). > Ensure line is patent before administration, and flush with sodium chloride 0.9 % > Incompatible with bicarbonate or alkaline solutions
Intermittent bolus dose	> Labetalol comes as 50 mg in 10 mL vials (5 mg / mL) > Draw up labetalol 100 mg (20 mL) undiluted > Use medication added sticker and label syringe "labetalol 100 mg in 20 mL" > Inject 20 mg (4 mL) over 2 minutes
Observations	> Record blood pressure and heart rate every 5 minutes until stable > The maximal effect usually occurs within 5 minutes of each injection > If no change in blood pressure, repeat labetalol 40 mg – 80 mg (8 mL – 16mL) every 10 minutes (titrated to blood pressure) to a maximum of 4 doses (max = 300 mg [60 mL] / 24 hours)

Labetalol intravenous infusion

If the blood pressure is not adequately controlled after 2 bolus doses, consider a continuous labetalol infusion, either via a syringe driver or an infusion pump. Max. dose = 300 mg/24 hrs

Syringe driver

Set up

- Draw up labetalol 200 mg (40 mL) undiluted
- Using medication added sticker write "labetalol 5 mg in 1 mL" and attach label to syringe

Syringe driver infusion dose

- Start infusion at 4 mL / hour (20 mg / hour). Titrate to stabilise blood pressure by maintaining or adjusting (e.g. doubling, halving) the infusion as required every 15-30 minutes to a maximum dose of 32 mL / hour (160 mg / hour)
- Discontinue by weaning over 1-2 hours when blood pressure is consistently less than155/95 mmHg

Infusion pump

Set up

- Withdraw 40 mL from a 100 mL bag of sodium chloride 0.9 %
- Draw up 200 mg labetalol (40 mL) and add to remaining 60 mL in the bag of sodium chloride 0.9 %
- Using medication added sticker write "labetalol 2 mg in 1 mL in sodium chloride 0.9 % (labetalol 200 mg made up to 100 mL with sodium chloride 0.9 %)" and attach label to bag

Infusion pump dose

- Start infusion at 10 mL / hour (20 mg / hour). Titrate to stabilise blood pressure by maintaining or adjusting (e.g. doubling, halving) the infusion as required every 15-30 minutes to a maximum dose of 80 mL / hour (160 mg / hour)
- Discontinue by weaning over 1-2 hours when blood pressure is consistently less than155/95 mmHg

Observations

- Measure blood pressure and pulse every 15-30 minutes until stabilised, then record every hour as required
  - If blood pressure decreases precipitously, halve the infusion rate or cease (depending on severity)
  - Blood pressure should not be lowered below 140/85 mmHg
- Continuous electronic fetal monitoring during intravenous administration

Relative contraindications

- Bronchial asthma or chronic obstructive airways disease
- For more contraindications refer to the Product Information or the Australian Medicines Handbook[3]

Side effects

- Hypotension: cease if blood pressure < 140 mm Hg systolic
- Bradycardia: cease if heart rate < 60/minute
- Fetal bradycardia
- Wheezing and bronchospasm: cease if severe
- Headache and nausea
- Extravasation of labetalol solution may cause tissue damage. Stop and seek urgent assistance to re-site the IV
- Blurred vision and/or retention of urine may occasionally be seen, as may scalp tingling that may last up to 24-48 hours
- Prolonged maternal high doses of labetalol may cause hypotension in the preterm growth restricted newborn

Appendix 2: Hydralazine – Intermittent IV Bolus and IV Infusion Regimen

Hydralazine intermittent bolus IV administration	
Administration precautions	> **A precipitous fall in blood pressure can occur after intravenous hydralazine which may impair placental perfusion resulting in fetal distress.** > If there is a risk of hypovolaemia, give intravenous fluid preload of 250 mL of either sodium chloride 0.9 % or Hartmann's immediately before use – see Fluid Management > May be administered by a midwife under the supervision of a medical officer
Intermittent bolus dose	> Hydralazine (Apresoline®) is available as a 20 mg vial in powder form > Reconstitute the hydralazine 20 mg vial with 1 mL of water for injection to make a 20 mg / mL solution > Dilute hydralazine 1 mL (20 mg) up to 20 mL with sodium chloride 0.9 %. Label: hydralazine 1 mg per mL > The initial dose is 5 mg as ordered, given by slow intravenous injection over 5 minutes
Observations	> Blood pressure is taken at 5 minute intervals for at least 20 minutes following each bolus > After 20 minutes, depending upon response, a second dose of 5 mg may be given. Repeat every 20 minutes until BP controlled, maximum 30 mg. **Note that the maximal effect occurs 15-20 minutes after each bolus** > Consider infusion if the total intermittent bolus dosage is 20 mg or more > Continuous electronic fetal monitoring is required (Hydralazine is known to cross the placenta following IV administration and has been associated with fetal distress and fetal cardiac arrhythmia in the last trimester[3])

Hydralazine IV infusion administration	
Administration precautions	> **A precipitous fall in blood pressure can occur after intravenous hydralazine which may impair placental perfusion resulting in fetal distress.** > If there is a risk of hypovolaemia, give intravenous fluid preload of 250 mL of either sodium chloride 0.9 % or Hartmann's immediately before use – see Fluid Management > May be administered by a midwife under the supervision of a medical officer
Intravenous Infusion (syringe pump)	> **Administer via syringe pump** > Hydralazine (Apresoline®) is available as a 20 mg vial in powder form > Reconstitute the hydralazine 20 mg vial with 1 mL of water for injection to make a 20 mg / mL solution > Mix 2 ampoules (40 mg) of hydralazine up to a volume of 40 mL with sodium chloride 0.9 % (to obtain 1 mg per mL in a 50 mL syringe) > Commence infusion at the rate of 10 to 20 mg per hour, reducing rate when adequate response is achieved. > Maintenance: 2 to 10 mg per hour depending on blood pressure.
Observations	> Monitor blood pressure and pulse every 15 - 30 minutes as required > Blood pressure should not be lowered below 140 / 85 mm Hg > Continuous electronic fetal monitoring is required (Hydralazine is known to cross the placenta following IV administration and has been associated with fetal distress and fetal cardiac arrhythmia in the last trimester[3])

Contraindications[4]

> Known hypersensitivity to hydralazine or dihydralazine
> Idiopathic systemic lupus erythematosus (SLE)
> Severe tachycardia and heart failure with a high cardiac output (e.g. thyrotoxicosis)
> Myocardial insufficiency due to mechanical obstruction (e.g. aortic or mitral stenosis or constrictive pericarditis)
> Isolated right ventricular heart failure due to pulmonary hypertension (cor pulmonale)
> Dissecting aortic aneurysm

For more contraindications refer to the Product Information or the Australian Medicines Handbook[3]

Appendix 3: Magnesium Sulphate Infusion Regimen & Intramuscular Dose

Magnesium sulphate syringe driver infusion regimen

Administration precautions

- ***Magnesium sulphate is a High Risk Medicine***
- ***Use a dedicated intravenous line for magnesium sulphate.*** The magnesium line should be labelled clearly
- The undiluted syringe driver infusion may be connected into a mainline of sodium chloride 0.9% or Hartmann's 1000 mL. ***Never inject other drugs into this line***
- The total adult daily dose should not exceed 30 to 40 g of magnesium sulphate
- No more than 8 g of magnesium sulphate should be administered over 1 hour
- Continue for up to 24 hours after the last seizure activity and for 24 hours after birth
- Administration may cause pain and phlebitis.

Magnesium sulphate undiluted 50 %

Loading dose set up	Maintenance dose set up
> Draw up 5 g (10 mL) magnesium sulphate > Discard 2 mL magnesium sulphate to give 4 g in 8 mL > Using medication added label write "magnesium sulphate 4 g in 8 mL" and attach label to syringe	> **NB: To avoid mixing up the syringes, do not draw up the maintenance dose until after the loading dose has been commenced** > Draw up 10 g (20 mL) magnesium sulphate > Using medication added label write "magnesium sulphate 10 g in 20 mL" and attach label to syringe

Prevent eclampsia (prophylaxis)*

- Use loading dose syringe
- Set syringe driver at 24 mL / hour to infuse 4 g (8 mL) over 20 minutes
- After 20 minutes, use maintenance dose syringe to commence maintenance at 1 g / hour (2 mL / hour)

For eclamptic seizures*

- Use loading dose syringe
- Set syringe driver at 96 mL / hour to infuse 4 g (8 mL) over 5 minutes
- After 5 minutes, use maintenance dose syringe to commence maintenance at 1 to 2 g / hour (2 to 4 mL / hour)

Recurrence of seizure during maintenance treatment*

- Set syringe driver at 48 mL / hour to infuse 2 g (4 mL) IV over 5 minutes
- Once the condition is stable, reset syringe driver to maintenance dose of 1 to 2 g / hour
- (2 to 4 mL / hour)

*Please check 'Care during intravenous infusion' below for monitoring

Ensure calcium gluconate is available

Magnesium sulphate volumetric infusion pump regimen

Note: A volumetric infusion pump should only be utilised for the administration of magnesium sulphate where there is no access to a syringe driver

Administration precautions

- ***Magnesium sulphate is a High Risk Medicine***
- ***Use a dedicated intravenous line for magnesium sulphate.*** The magnesium line should be labelled clearly
- ***Never inject other drugs into this line***
- The total adult daily dose should not exceed 30 to 40 g of magnesium sulphate
- No more than 8 g of magnesium sulphate should be administered over 1 hour
- Continue for up to 24 hours after the last seizure activity and for 24 hours after birth
- Administration may cause pain and phlebitis.

Magnesium sulphate diluted

Loading dose set up

- Draw up 5 g (10 mL) magnesium sulphate
- Discard 2 mL magnesium sulphate to give 4 g in 8 mL
- Withdraw 8 mL from a 100 mL bag of sodium chloride 0.9 % and discard
- Add the 8 mL magnesium sulphate (4 g) to the remaining 92 mL bag of sodium chloride 0.9 % to make 100 mL
- Using medication added label write "magnesium sulphate 4 g (8 mL) in sodium chloride 0.9 % to a total volume of 100 mL" and attach label to bag

Maintenance dose set up

- **NB: To avoid mixing up the infusion bags, do not draw up the maintenance dose until after the loading dose infusion has been commenced**
- Draw up 20 g (40 mL) magnesium sulphate
- Withdraw 40 mL from a 100 mL bag of sodium chloride 0.9 % and discard
- Add the 40 mL magnesium sulphate (20 g) to the remaining 60 mL bag of sodium chloride 0.9 % to make 100 mL
- Using medication added label write "magnesium sulphate 20 g (40 mL) in sodium chloride 0.9 % to a total volume of 100 mL" and attach label to bag

Prevent eclampsia (prophylaxis)*

- Use loading dose bag
- 4 g (set at 300 mL / hour) over 20 minutes
- After 20 minutes, use maintenance dose infusion bag to commence maintenance at 1 g / hour (5 mL / hour)

For eclamptic seizures*

- Use loading dose bag
- 4 g (set at 1200 mL / hour) over 5 minutes
- After 5 minutes, use maintenance dose infusion bag to commence maintenance at 1 to 2 g / hour (5 to 10 mL / hour)

Recurrence of seizure during maintenance treatment*

- 2 g (set at 120 mL / hour) IV over 5 minutes
- Once the condition is stable, reset volumetric infusion pump to maintenance dose of 1 to 2 g / hour (5 to 10 mL / hour)

*Please check 'Care during intravenous infusion' below for monitoring

Ensure calcium gluconate is available

Relative contraindications

The use of this drug can be hazardous in association with:

- Renal failure or severe renal compromise
- Hypocalcaemic states
- Other drugs, especially vasoactive drugs
- Acute haemolytic states
- Some forms of neurological disease

Drug interactions

- Nifedipine increases the effects of magnesium sulphate and risk of hypotension; use cautiously, consider reducing magnesium sulphate dosage; monitor blood pressure, deep tendon reflexes and respiratory function[1]

Adverse effects

- Common adverse effects include feeling of warmth, flushing, nausea and vomiting
- More serious adverse effects which indicate hypermagnesaemia are:
    - Loss of deep tendon reflexes
    - Respiratory depression
    - Respiratory arrest
    - Cardiac arrest
- Other effects may include: thirst, muscle weakness, headache, dizziness, hypotension, bradycardia

Levels of magnesium sulphate at which adverse effects occur[2]

Symptoms	MgSO4 levels (mmol/L)
Feeling of warmth, flushing, double vision, slurred speech	3.8 to 5.0
Loss of tendon reflexes	Greater than 5.0
Respiratory depression	Greater than 6.0
Respiratory arrest	6.3 to 7.0
Cardiac arrest	Greater than 12.0

Care during intravenous infusion

- Monitor observations (pulse, blood pressure, respiratory rate, SpO_2 and [deep tendon] patellar reflexes)
- Ensure the woman is aware that a feeling of warm flushing may occur during the loading dose
- Recheck observations including patellar reflexes ten minutes after the loading dose was started and at the end of the loading dose (20 minutes)
- Continuous fetal monitoring from 26^{+0} weeks gestation until clinical review / discussion by medical staff. Between 24 to 26 weeks gestation, individualised management with regard to fetal monitoring will be considered

Maintenance

- Monitor blood pressure, respiratory rate, pulse oximeter (SpO_2), patellar reflexes and urine output 4 hourly (insert urine catheter)
    - NB: If the urine output is less than 100 mL over 4 hours, check magnesium levels (see below) and consider reducing magnesium sulphate infusion to 0.5 g/hour

- **Patellar reflexes should be documented as one of the following:**
  - A = Absent
  - N = Normal
  - B = Brisk

  (NB: Patellar reflexes are always suppressed before respiratory depression occurs)
- Monitoring magnesium levels is usually not necessary. Where serum creatinine is > 100 mmol/L or urine output is < 100 mL over 4 hours, check serum magnesium levels and adjust infusion levels. In these circumstances check serum magnesium levels every 6 hours after commencing infusion
  - Blood for magnesium estimation must NOT be taken from the arm receiving the infusion
  - Levels will vary according to serum albumin concentrations

Symptoms of overdose

Stop the infusion and seek medical review if:

- patellar reflexes are absent
- the respiratory rate is less than 12 per minute
- the diastolic BP drops more than 15 mm Hg below baseline
- or the urine output drops below 100 mL in 4 hours

Magnesium sulphate toxicity

If signs of toxicity occur (hypoventilation, arrhythmia, hypotonia):

- Call for medical assistance
- Administer oxygen at 8-12 litres/minute
- Stop infusion
- Monitor vital signs
- Administer calcium gluconate (10 % solution), 10 mL, slowly intravenously
- Electrocardiogram (ECG) to identify heart block
- Check electrolytes, creatinine, magnesium sulphate levels

Neonatal considerations

For the neonate, hypermagnesaemia can lead to hyporeflexia, poor sucking and rarely, respiratory depression needing mechanical ventilation

Intramuscular dose (suitable for retrieval and transfer)

- In situations where an infusion pump is not available, an intravenous bolus dose of magnesium sulphate 20 % in combination with intramuscular magnesium sulphate 50 % may be preferable for treating women in actual preterm labour before transferring to a tertiary centre
- The preferred regimen in such circumstances is:
  - Magnesium sulphate 20 % solution, 4 g by slow intravenous injection over a period of 5 minutes, followed by
  - Two deep intramuscular injections of 4 to 5 g magnesium sulphate 50 % solution into each buttock (the total dose of up to 10 g injected into one site is highly irritating)
  - If no infusion pumps are available, maintenance treatment is 5 g magnesium sulphate 50 %, given by deep intramuscular injection, every 4 hours. Alternate the buttocks in which the injection is administered[3]
  - A maintenance infusion (see above) can be commenced at any time after the initial bolus dose

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Fluid Management and Monitoring in Severe Preeclampsia
Labetalol Infusion Regimen
Hydralazine Infusion Regimen
Magnesium Sulphate Infusion Regimen

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