South Australian Perinatal Practice Guidelines
Hypertensive disorders in pregnancy

Definitions

> Normal pregnancy is characterised 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 [1]

> 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 [2]

>> Readings above this level were beyond two standard deviations of mean blood pressure in a New Zealand cohort of normal pregnant women [3]

>> 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 [4,5]

>> Nevertheless such a rise may be significant in some women, particularly in the presence of hyperuricemia and proteinuria. Further data are required and in the meantime, closer monitoring of pregnant women with an increment in blood pressure of ≥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 6

> 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 160mm Hg. 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 Section 5).

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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 7

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)8-10

> 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 11

> For further information link to chapter 63 monitoring blood pressure in pregnancy

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 12

> 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 13,14

> 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

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Twenty four hour Ambulatory Blood Pressure Monitoring (ABPM)

> Normal blood pressure values recorded by ABPM have been established for different stages of pregnancy 15,16

> ABPM is useful in the evaluation of early (< 20 weeks gestation) hypertension where approximately one third of these women will be shown to have "white coat" or "office" hypertension7

> 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 17

> 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 18

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) 19. 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 20 as well as earlier published criteria.

The classification is as follows:

> Preeclampsia – eclampsia

> Gestational hypertension

> Chronic hypertension

>> essential
>> secondary
>> white coat

> Preeclampsia superimposed on chronic hypertension

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 ≥ 30mg/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 µmol/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 [22.] 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 [23,] 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 [24.] 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. Hyperuricemia is a common but not diagnostic feature of preeclampsia; the degree of hyperuricemia may correlate with fetal risk [25, 26] although some studies have questioned this [27-29.] 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 (Hemolysis, 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. For further information refer to references [72-76.]
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,[30] 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

We endorse the ISSHP research definition of preeclampsia [19] as follows:

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> De novo hypertension after 20 weeks gestation, returning to normal postpartum and

> properly documented proteinuria

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 31. 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 32 or an adverse pregnancy outcome 33. Severe hypertension (≥170/110mmHg) is associated with increased risk of adverse outcomes in pregnancy 33

Chronic Hypertension

> Essential hypertension is defined by a blood pressure > 140 mmHg systolic and/or > 90mm 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 7

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. phaeochromocytoma, 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

Preeclampsia superimposed on chronic hypertension.

> Pre-existing hypertension is a strong risk factor for the development of preeclampsia 34. 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

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 management35,36, 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 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 phaeochromcytoma in pregnancy is potentially fatal and may present as preeclampsia [37,38]. 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

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

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 39-42 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 monitoring43. 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

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

Maternal	Fetal
Gestational age ≥ 37^{+0} 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 oedema	

> 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)

> The only controlled studies of bed rest for preeclampsia have shown no significant maternal or fetal benefit 44

> > 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.

Hypertension

Acute treatment of severe hypertension

> Antihypertensive treatment should be commenced in all women with a systolic blood pressure ≥170 mm Hg or a diastolic blood pressure ≥110 mm Hg because of the risk of intracerebral hemorrhage and eclampsia 45.

> 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 46. Several rapidly acting agents are available to control severe hypertension (Table 3).

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 minutes, repeat after 15-30 minutes
Nifedipine	10-20 mg tablet	Oral	30-45 mins, repeat after 45 mins
Hydralazine	5-10 mg	IV bolus	20 mins, repeat after 30 mins
Diazoxide	15-45 mg, maximum 300 mg	IV rapid bolus	3-5 mins, repeat after 5 mins

> 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. sodium chloride 250 mL at the time of administration of antihypertensive therapy 52.
> > 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.

> 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. Because of the 3 day half-life of the thiocyanate metabolite, caution is advised if the woman has received nitroprusside for more than 24 hours.

> 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.

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 vasodilation 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 53. One small Australian placebo-controlled randomised study examined the role of antihypertensive therapy in the management of mild hypertension 54. 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 55-57. Second line agents are hydralazine, nifedipine and prazosin 58-61.

> 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 62.

Table 4. Guidelines for selecting antihypertensive drug treatment in pregnancy

Drug	Dose	Action	Contraindications	Practice points
Methyldopa	250 to 750 mg tds	Central	Depression	Slow onset of action over 24 hours. Dry mouth, sedation, depression, blurred vision
Clonidine	75 to 300 micrograms tds			Withdrawal effect with clonidine
Labetalol	100 to 400 mg tds	ß blocker with mild alpha vasodilator effect	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling, which usually resolves within 24 to 48 hours (labetalol only)
Oxprenolol	20 to 160 mg tds	ß blocker with ISA	Heart block	
Nifedipine	20 mg bd 60 mg SR bd	Ca channel antagonist	Aortic stenosis	Severe headache associated with flushing, tachycardia
				Periperal oedema, constipation
Prazosin	0.5 to 5 mg tds	α blocker		First dose effect -orthostatic hypotension
Hydralazine	25 to 50 mg tds	Vasodilator		Flushing, headache, nausea, lupus-like syndrome

Hypertensive disorders in pregnancy

> 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.

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.

Treatment of other manifestations

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 63.

> 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 guidelines to deal with the timing of LMWH administration in regard to the insertion and withdrawal of epidural and spinal canulae 64.

Intravenous Fluids

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

1. Women with severe preeclampsia immediately prior to parenteral hydalazine, 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 67 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 hypoalbuminemia. 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.

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 68.

> 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 69.

> 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 guidelines for the management of eclampsia (and severe hypertension) should be available in all appropriate areas. Follow link to chapter 14c seizures in pregnancy for further information

> 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. Magnesium sulphate is the drug of choice for first line treatment.

2. *Prevention of further seizures*

> Following appropriate resuscitation, treatment should be commenced with magnesium sulphate (4 g over 10-15 minutes) followed by an infusion (1-2 g / hour). In the event of a further seizure, a further 2-4 g of magnesium sulphate 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 by infusion should continue for 24 hours after the last fit 70, 71.

> 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 % 72.

3. Control of hypertension

> Control of severe hypertension to levels below 160/100 mm Hg 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 71. 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 Hematological 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.

> Thrombocytopenia is the commonest haematologic abnormality seen in preeclampsia; the lower limit of the normal platelet count in pregnancy is approximately 140 x 109 / L but the risk of spontaneous bleeding is not significantly increased until the count falls below 50 x 109 / L. Even so, there are concerns with central neuraxial anaesthesic and analgesic techniques at higher levels (50-75 x 109 / 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 haematoma 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 73. These abnormalities recover spontaneously postpartum within a few days of delivery, without specific treatment 74-77. 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.

Fetal surveillance

> Adverse perinatal outcome is increased in women with all subcategories of hypertensive disease in pregnancy as compared to normotensive women 78.

> 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 78-80.

> Although fetal surveillance is commonly recommended and performed in women with hypertensive disease in pregnancy 6,81 there is no established consensus on how this should be performed 82,83.

> Frequency, intensity, and modality of fetal evaluation will depend on individual pregnancy (maternal and fetal) characteristics. Individual obstetric units should devise their own guidelines for monitoring the fetus in pregnancies complicated by hypertension.

> In compiling such guidelines, 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) [84]. 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. 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 [85, 86]. 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.
3. 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 [87-89], none of these has shown significant benefit in systematic reviews [90,91].
4. No fetal testing can predict an acute obstetric event such as placental abruption or cord accident.
5. 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].
6. 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 guidelines for fetal surveillance in women with hypertensive disease in pregnancy where immediate delivery is deferred. None of these guidelines 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 Fetal surveillance in women with hypertensive disease

Hypertension	Modality	Frequency
Chronic hypertension	Early dating ultrasound	1st trimester
	Ultrasound for fetal growth / AFV / Doppler	3rd 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

Antenatal Corticosteroid administration

> Contrary to popular belief, accelerated fetal lung maturation does not occur in preeclampsia 93.

> 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 94. 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 94. A recent randomised trial demonstrated a small benefit of antenatal corticosteroids to mothers undergoing a term (37 to 39 weeks gestation) elective Caesarean section 95. 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. 96, 97 should be employed 98.

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.

Management of chronic hypertension in pregnancy

> Hypertension affects up to 20 % of the Australian adult population, the prevalence increasing with age 99.

> 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 100,101. 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, preterm delivery and stillbirth. These events are seen more often in women who develop preeclampsia and are not correlated with actual blood pressure levels 55, 68,102-107. The exception to this appears to be uncontrolled hypertension in the first trimester when later fetal and maternal morbidity and mortality are markedly increased 108. 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.

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 phaeochromocytoma. At least two consecutive collections are advised.

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.

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 [109-111].

> 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 mm Hg diastolic. Treatment at BP levels between 140 and 160 mm Hg systolic and / or 90 - 100 mm Hg 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 57,112-113. 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 114.

> Diuretics, although not teratogenic, may restrict the natural plasma volume expansion of pregnancy and are not recommended for the treatment of hypertension.

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.

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.

Anaesthetic considerations in hypertensive disorders of pregnancy

> Whenever possible an anaesthetist should be informed about a woman with severe preeclampsia well prior to labour or operative delivery, because appropriate anaesthetic management is associated with reduction in both fetal and maternal morbidity 115.

> Relevant issues include anaesthetic risk assessment, blood pressure control, fluid management, eclampsia prophylaxis, and planning of analgesia or anaesthesia 116-119.

Hypertensive disorders in pregnancy

Fluid management

> Fluid management is a challenging area in preeclampsia and there is no clear evidence regarding optimal type or volume of fluid 119,120.

> 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 121.

> Particular caution is necessary in women with oliguria, renal impairment or pulmonary edema, in whom the left ventricle may adapt less well to volume load 122.

> Fluid loading is not mandatory prior to regional analgesia during labour when low-dose local anaesthetic and opioid methods are used 123. Prior to regional anaesthesia intravenous crystalloid loading is ineffective in preventing hypotension but colloid is effective 124.

> Treatment or prevention of hypotension with drugs such as phenylephrine or metaraminol is effective and appears safe in preeclamptic women 125,126.

Anaesthetic technique

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 remifentanil patient-controlled intravenous analgesia is preferred.

> Although ephedrine usually does not cause rebound hypertension 127 occasionally vasopressors and epidural adrenaline (epinephrine) cause worrisome blood pressure elevation. Other drugs that are best avoided in severe preeclampsia include ergometrine 128, 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 haemodynamic effects 101.

Caesarean section

> Unhurried preoperative preparation reduces the risk of anaesthesia in women with preeclampsia 128.

> Regional anaesthesia is preferred to general anaesthesia (GA) for caesarean section (CS), especially as airway problems including laryngeal oedema may be increased 129-131. However, well-conducted GA is also suitable 132,133 and may be indicated in the presence of severe fetal compromise; pulmonary oedema; haemodynamic 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 134,135.

> 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 128. The transient but severe hypertension that usually accompanies intubation can cause myocardial ischaemia, cerebral haemorrhage or pulmonary oedema, all being important causes of maternal death 121,128.

> Attenuation of this pressor response is best achieved with additional induction drugs such as remifentanil 1 microgram / kg 136,137 or magnesium sulphate 40 mg / kg or 30 mg / kg with alfentanil 7.5 micrograms / kg 138. Neuromuscular block must always be monitored closely after intravenous magnesium administration 139. Lignocaine (lidocaine) 1.5 mg / kg is less effective 137 and fentanyl 2.5-10 micrograms / kg or alfentanil 10 micrograms / kg of slower onset 140. Other drug options are beta-blockers (e.g. esmolol) 141, 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 116,119. Spinal anaesthesia with usual doses is now a recommended technique 119,142,143. Cardiac output is well maintained and it is associated with less hypotension and lower vasopressor requirements than among healthy parturients 144. Combined spinal-epidural anaesthesia appears to offer further advantages in specific cases 119.

> 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 x109 / L 145. Platelet counts of < 50 x109 / L are generally considered a contraindication. Within the range 50-75 x109 / 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.

Critical Care

Hypertensive disorders in pregnancy

Admission to an Intensive Therapy Unit

> Anesthetists 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).

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 146. Some recommend pulmonary artery catheters for assessment of left ventricular preload 147 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 119.

Preconception management and prophylaxis for women at risk of preeclampsia

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 148. Such a tool applied early in pregnancy would allow intervention that might modify outcomes.

Table 6. Risk factors associated with preeclampsia [149]

Risk factors	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 preeclampsia	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 mm Hg at booking	1.38 (1.01, 1.87)

> 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 148.

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 150. Data from one Australian centre suggest that women with preeclampsia have an overall 14 % risk of preeclampsia and the same risk of developing gestational hypertension in their next pregnancy 151.

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 50-150 mg 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 > 75 mg 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 152.

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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 (1.5 g / day) should therefore be offered to women at increased risk of pre-eclampsia, particularly in those women with a low dietary calcium intake 153.

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 birth weight < 2.5kg but there were fewer fetal deaths due to immaturity. Prophylactic antioxidant therapy with vitamins C and E is therefore not recommended 154,155.

> To date, there are no large randomised trials assessing the effect of heparin with or without aspirin in prevention of preeclampsia 156. 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 157.

> 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. Randomised, controlled trials are still required to address this potential therapy 158,159.

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 ≥ 130 µmol/L) should have the risks of perinatal morbidity / mortality and of deterioration of their underlying renal disease fully explained at this time 160.

> 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.

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. The indicators listed below are those that may be useful to assess various management strategies within and between hospitals. 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.

Table 7. Selected maternal and fetal/neonatal clinical indicators for women with hypertensive disorders of pregnancy [161]

1. Maternal mortality: death during pregnancy or within 42 days of delivery.
2. Composite severe adverse maternal outcome: One or more of the following morbidities
    > Cardiovascular: positive inotrope support or myocardial infarction
    > Hepatic: failure or haematoma / rupture
    > Renal: Dialysis or transplantation
    > Neurological: Glascow coma score <13 or stroke or cortical blindness or 2 or more seizures
    > Respiratory: requirement of ≥ 50 % FI02 for >1 hr or intubation or pulmonary oedema
    > Haematological: transfusion of ≥10 units blood products
    > Death
3. Perinatal mortality: death during the perinatal period i.e. 20 completed weeks of gestation to 28 days after birth.
4. Rate of admission of term babies to neonatal intensive care units

It is recommended that measurement and analysis of these and other appropriate clinical indicators should form the basis of regular audits and quality improvement strategies.

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 [162] determined that the relative risks for hypertension were 3.70 after 14 years follow-up, for ischaemic 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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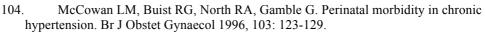
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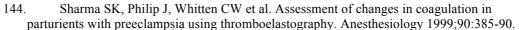
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Abbreviations

ABPM	Ambulatory Blood pressure monitoring
ACE	Angiotensin converting enzyme
AFV	Amniotic fluid volume
ALT	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
ASSHP	Australian Society for the Study of Hypertension in Pregnancy
AST	Aspartate Aminotransferase
bd	Twice per day
BMI	Body mass index
BP	Blood pressure
CS	Caesarean section
CTG	Cardiotocograph
dL	Decilitre
ECG	Electrocardiograph
FGR	Fetal growth restriction
e.g.	For example
GA	General anaesthesia
g	Gram(s)
HELLP	Haemolysis, elevated liver enzymes, low platelets
INR	International normalised ratio
ISA	intrinsic sympathomimetic activity
ISSHP	International Society for the Study of Hypertension in Pregnancy
IV	Intravenous
K	Korotkoff
LDH	Lactate dehydrogenase
L	Litre(s)
LMWH	low molecular weight heparin
µmol	Micromole(s)
mg	Milligram(s)
mL	Millilitre(s)
min	minute
mm Hg	Millimetres of mercury
NHBPEP	National High Blood Pressure Education Programme
RDS	Respiratory distress syndrome
SR	Slow release
SGA	Small for gestational age
tds	Three times per day

Hypertensive disorders in pregnancy

Version control and change history

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Version	Date from	Date to	Amendment
1.0	28 June 04	28 Feb 05	Original version
2.0	28 Feb 05	26 Oct 09	Review
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