NSW HEALTH DEPARTMENT

CIRCULAR

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Contact	Administrative Contact: Quality Unit: 02 9424 5703 Clinical Contact: NSW Pregnancy & New Born Services Network 02 9351 7318

Hypertension in Pregnancy

1. This Circular supercedes Circular 97/106.

2. The NSW Maternal and Perinatal Committee endorsed the revised guidelines of *The Australasian Society for the Study of Hypertension in Pregnancy (ASSHP): Consensus Statement - The detection, investigation and management of hypertension in pregnancy: executive summary and full consensus statement, 2000* and it is now issued as NSW Health policy.

3. Hypertension in pregnancy is common and may reflect a number of underlying disorders that have different clinical outcomes. Hypertension complicates approximately 7% of pregnancies1 and is associated with increased maternal morbidity and mortality.

4. The definition of hypertension in pregnancy is 2:

   Systolic blood pressure is equal or greater than 140 mmHg

   and/or

   Diastolic blood pressure (Korotkoff V) is equal or greater than 90 mmHg.

   These blood pressures should be confirmed by repeated readings using mercury sphygmomanometry over several hours in a clinic or day assessment unit or after rest in hospital. Both systolic and diastolic blood pressures have been closely associated with fetal outcome and both are important.

1 Centre for Epidemiology and Research, NSW Department of Health. NSW Mothers and Babies Report 2001.NSW Public Health Bulletin 2002:13(S-4).
2 The Australasian Society for the Study of Hypertension in Pregnancy (ASSHP), *2000,*Consensus Statement for the detection, investigation and management of hypertension in pregnancy: Executive Summary and Full Consensus Statement .

Distributed in accordance with circular list(s):

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73 Miller Street North Sydney NSW 2060
Locked Mail Bag 961 North Sydney NSW 2059
Telephone (02) 9391 9000 Facsimile (02) 9391 9101

5. As complications of hypertension may develop rapidly in pregnancy, any mother who has a blood pressure meeting these criteria at any time during pregnancy should be managed by a multidisciplinary team approach and advice should be sought from appropriate specialists eg anaesthetists and neonatalogists, where indicated.

6. In addition, clinicians should be aware of the side effects of non-steroidal anti-inflammatory drugs (NSAIDs) and particular care should be given to prescribing NSAIDS to postpartum women with pre-existing renal disease and/or a hypertensive disease of pregnancy (HDP) eg preeclampsia3.

7. The ASSHP Consensus Statement provides a framework for a multidisciplinary team approach to the detection, investigation and management of women with hypertension in pregnancy.

8. All maternity facilities should develop local protocols based on the full ASSHP Consensus Statement. This can be down loaded from the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) web address: http://www.racp.edu.au/asshp/asshp.pdf

9. The intended users of this policy are medical staff, midwives, registered nurses and other health professionals involved in maternity care.

10. This Circular is due for revision two years from the date by the NSW Health Department.

11. This Circular is to be read in conjunction with:
    Circular No. 99/86 *Maternity Emergencies* (Patient Matters Manual Part 1 S.6.18)
    Circular No. 99/71 *Policy for Emergency obstetric and neonatal referrals* (Patient Matters Manual Part 1 S6.16)
    Circular No. 02/27 *Magnesium sulphate infusion protocol for eclamptic seizure prophylaxis*
    Circular No. 02/29 *Protocol for administration of intravenous hydralazine for severe hypertension in pregnancy* .

Robyn Kruk
Director-General

3 Makris A, Thornton C, Hennessy A, 2004, *Post-partum hypertension and non-steroidal analgesia,* American Journal of Obstetrics and Gynaecology (in press).

CONSENSUS STATEMENT

The detection, investigation and management of hypertension in pregnancy: executive summary

Recommendations from the Council of the Australasian Society for the Study of Hypertension in Pregnancy

MA Brown
WM Hague
J Higgins
S Lowe
L McCowan
J Oats
MJ Peek
JA Rowan
BNJ Walters

The Council acknowledges the valuable contributions of Prof S Brennecke, Dr B Duffy, Prof DJ Henderson-Smart and Dr RA North in the preparation of these recommendations. They are also grateful for constructive criticism from Dr A Hennessey (of the Australian and New Zealand Society of Nephrology), from Dr M Paech and Dr RG Walsh (of the Australian and New Zealand College of Anaesthetists), and from A/Prof L Arnolda (of the Cardiac Society of Australia and New Zealand).

These recommendations have been endorsed by The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Australian & New Zealand Society of Nephrology and the Cardiac Society of Australia and New Zealand, and developed in consultation and agreement with the Australian and New Zealand College of Anaesthetists.

EXECUTIVE SUMMARY

INTRODUCTION

These are the recommendations of a multidisciplinary working party set up by the Australasian Society for the Study of Hypertension in Pregnancy to review and revise its previous guidelines for the detection, investigation and management of hypertension in pregnancy. They are based on definitions and a classification system that reflect current knowledge. It is recommended that each obstetric unit develop its own management protocols.

The following summarises the contents of the consensus Report. This may prove a useful "office guide" for clinicians but should still be interpreted in light of the full discussion within the body of this report.

DEFINITION OF HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is diagnosed when:

- Systolic blood pressure is $\geq$140 mmHg
  and/or
- Diastolic blood pressure (Korotkoff V) is $\geq$90 mmHg.

These blood pressures should be confirmed by repeated readings over several hours in a clinic or day assessment unit or after rest in hospital.

RECORDING BLOOD PRESSURE IN PREGNANCY

- The pregnant woman should be seated, with feet supported, for 2-3 minutes.
- An appropriate sized cuff should be used [standard cuff for arms $\leq$33 cm circumference, large cuff (15 x 33 cm bladder) for larger arms].
- Systolic blood pressure should be palpated at the brachial artery and the cuff inflated to 20 mmHg above this level.
- The cuff should be deflated slowly, at approximately 2 mmHg per second.
- Blood pressure should be recorded with a mercury sphygmomanometer.

- Systolic and diastolic blood pressure should be recorded. Diastolic blood pressure recorded as the phase V Korotkoff sound, ie. when sounds disappear. If phase V is not present, Korotkoff IV, ie. when sounds muffle, should be recorded.

- Blood pressure should be taken using both arms at the first antenatal visit and thereafter using the right arm if, as anticipated, there is little difference in blood pressure between arms. If a significant difference in pressure is found, an opinion should be sought from a consultant physician.

- Automated devices and ambulatory blood pressure monitoring should not yet be used in routine clinical practice until more detailed information becomes available about their accuracy and effectiveness.

The debate as to whether Korotkoff phase IV (K4) (ie. point of muffling) or phase V (K5) (ie. point of disappearance) should be used to record diastolic blood pressure in pregnancy has now been largely resolved. It is apparent that K5 is detected more reliably than K4 during pregnancy. K5 more closely reflects true diastolic pressure in pregnancy than K4. Changing from use of K4 to K5 in hypertensive pregnant women does not increase morbidity for mother or baby.

Blood pressures obtained using automated blood pressure recording devices may differ significantly from those using mercury sphygmomanometry in pregnancy which should remain the gold standard for now. Ambulatory or other automated blood pressure monitoring has no established place in the management of women with established pre-eclampsia or gestational hypertension but is promising as an adjunct to the management of women with chronic or 'white-coat' hypertension in pregnancy. Further studies in this area are required.

CLASSIFICATION OF HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertension during pregnancy may develop as a result of the pregnancy or follow pre-existing hypertension (either essential or secondary). Hypertension arising for the first time after 20 weeks gestation may be an isolated finding, ie gestational hypertension, or part of a multisystem disorder, ie pre-eclampsia.

The classification is as follows:

- **GESTATIONAL HYPERTENSION**

- **PRE-ECLAMPSIA**

- **CHRONIC HYPERTENSION**

    - **essential**
    - **secondary**

- **PRE-ECLAMPSIA superimposed on CHRONIC HYPERTENSION**

Gestational hypertension

Gestational hypertension is hypertension arising in pregnancy after 20 weeks gestation without any other feature of the multisystem disorder pre-eclampsia (see below) and which resolves within 3 months postpartum.

Pre-eclampsia

Pre-eclampsia is usually first detected by the measurement of high blood pressure but features other than hypertension are required to make the diagnosis. It is now recognised that pre-eclampsia is a disorder which affects other organ systems including the feto-placental unit:. Proteinuria is the most commonly recognised feature of pre-eclampsia after hypertension but should not be considered mandatory to make the clinical diagnosis.

A clinical diagnosis of pre-eclampsia can be made when the following criteria are fulfilled:

Hypertension arising after 20 weeks gestation and the new onset after 20 weeks gestation of one or more of:

- Proteinuria - ≥300 mg/24h or spot urine protein/creatinine ratio ≥30 mg/mmol
- Renal insufficiency – serum/plasma creatinine ≥ 0.09 mmol/L or oliguria
- Liver disease – raised serum transaminases and/or severe epigastric/right upper quadrant pain
- Neurological problems – convulsions (eclampsia); hyperreflexia with clonus; severe headaches with hyperreflexia; persistent visual disturbances (scotomata)
- Haematological disturbances – thrombocytopenia; disseminated intravascular coagulation; haemolysis
- Fetal growth restriction

The hypertension of pre-eclampsia will have returned to normal within 3 months post partum.

NOTES:

1. Many disorders may present with similar features, eg acute fatty liver of pregnancy, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, cholecystitis. Clinical judgement is necessary in every case to exclude such disorders before a diagnosis of pre-eclampsia is made.

2. Oedema is not included in the diagnostic features of pre-eclampsia. It occurs equally in normal pregnant women and those with pre-eclampsia, although the rapid development of generalised oedema is usually abnormal.

3. Proteinuria: dipstick testing for proteinuria is a screening test only, with very high false positive rates. While all hypertensive pregnant women with any level of positive dipstick

proteinuria should be treated initially as though they have pre-eclampsia, dipstick proteinuria should always be confirmed with either:

- a 24 hour urine collection $\geq$300 mg/day, or:
- a spot urine protein/creatinine ratio $\geq$30 mg protein/mmol creatinine.

Urinary tract infection should also be excluded.

True proteinuria is present in most women with pre-eclampsia, but some women will have other evidence of this multisystem disease, even convulsions (eclampsia), without proteinuria.

4. Hyperuricaemia is a useful antenatal marker of pre-eclampsia, both as a guide to potential fetal risks and as an aid in diagnosis.

5. Fetal growth restriction indicates probable placental involvement and warrants close observation of the pregnancy.

The above definition requires clinical judgement to classify accurately a woman with pre-eclampsia. Researchers may choose to keep a definition of pre-eclampsia which includes both hypertension and proteinuria as this is less open to clinical interpretation and error. While it is likely that restricting the diagnosis of pre-eclampsia to 'proteinuric pre-eclampsia' will exclude some women with this multisystem disorder, it will leave a well-defined group for the purposes of research.

Chronic hypertension

- Essential hypertension: blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic (K5) pre-conception or in the first half of pregnancy without an apparent underlying cause. It may also be diagnosed in those women presenting in pregnancy taking antihypertensive medications, again with no apparent underlying cause.

- Secondary hypertension: hypertension associated with renal, renovascular and endocrine disorders and aortic coarctation.

‘White-coat’ hypertension, a diagnosis of raised blood pressure in the presence of a clinical attendant but normal blood pressure in the normal environment (as assessed by ambulatory blood pressure monitoring), is not chronic hypertension. The prevalence of this disorder in pregnant women may be lower than that found in the non-pregnant population, and pregnancy outcomes are similar to those in women not displaying this phenomenon.

Pre-eclampsia superimposed on chronic hypertension

In women with chronic hypertension, superimposed pre-eclampsia is diagnosed when one or more of the systemic features of pre-eclampsia (see above) develop after 20 weeks gestation. In women with chronic renal disease a diagnosis of superimposed pre-eclampsia is often difficult. In such women, sudden increases in proteinuria and hypertension should lead to increased surveillance for pre-

eclampsia but the diagnosis is not secure without the development of other features, eg abnormal liver function, thrombocytopenia or neurological abnormalities.

GESTATIONAL HYPERTENSION

Women whose pregnancies are complicated by gestational hypertension alone have a very good pregnancy outcome compared with women who develop pre-eclampsia.

Assessment: usually in a day stay assessment unit; some women may require a short admission to hospital especially if severe hypertension is present ($\geq$170/110 mmHg). Maternal and fetal investigations must be performed to exclude pre-eclampsia.

Treatment: antihypertensive agents as for the ongoing treatment of pre-eclampsia (see below) to maintain blood pressure between 110 and 140 mmHg systolic and 80 to 90 mmHg diastolic without inducing undue side effects.

Close monitoring is required to detect the development of pre-eclampsia.

PRE-ECLAMPSIA

a) ASSESSMENT

The "at risk" woman:

- Primigravid state
- Multigravida pregnant by a different partner
- Prior pre-eclampsia in a pregnancy by the same partner
- Family history of pre-eclampsia
- Multiple pregnancy
- Obesity
- Renal disease
- Essential hypertension
- Diabetes
- Autoimmune disease, especially SLE and antiphospholipid syndrome
- Thrombophilic state
- Severe alloimmunisation

It is not practical to increase the frequency of antenatal visits for all primigravidae when only 10% will develop gestational hypertension and only up to 7% will develop pre-eclampsia. The other “at risk” groups, who form a smaller total number, can be seen more frequently during pregnancy to detect the development of pre-eclampsia.

Two clinical features should alert clinicians to the impending appearance of pre-eclampsia:

- failure of blood pressure to fall in mid-pregnancy

- the *de novo* appearance of proteinuria in the second half of pregnancy (see above)

Pre-eclampsia is diagnosed if the above criteria are fulfilled. It may rarely occur before the 20th week of pregnancy associated with hydatidiform mole, with multiple pregnancy or with fetal triploidy, and very rarely with other prothrombotic disorders such as antiphospholipid syndrome, or with severe renal disease. Hypertension before 20 weeks gestation is usually due to chronic hypertension or to 'white-coat' hypertension.

The stage of gestation, adequacy of fetal growth and the extent of maternal organ dysfunction should be the three areas which need to be addressed by the clinician managing a woman with pre-eclampsia.

b) MANAGEMENT

- **Maternal - general**

Admission to hospital is usually required once the diagnosis of pre-eclampsia has been made. Bed rest, however, is not usually required and no specific dietary restrictions are necessary in the management of women with pre-eclampsia.

A) Antihypertensive medications

i.) **Acute treatment** (for severe hypertension: BP >170 mmHg systolic and/or >110 mmHg diastolic)

- oral **nifedipine** tablets (NB nifedipine capsules no longer available in Australia)
- iv or im **hydralazine**
- iv **labetalol** (NB not available in Australia) or **diazoxide**

Acute lowering of blood pressure can be achieved with any of the above drugs. Oral therapy should be used initially unless the woman is symptomatic (eg headache or abdominal pain) or has features of impending eclampsia (eg hyperreflexia). Reducing systolic BP initially by only 20-30 mmHg and diastolic by 10-15 mmHg should protect the mother from cerebral haemorrhage without jeopardising the fetus. Continuous **CTG monitoring** should be used to ensure that lowering the blood pressure does not cause fetal distress.

All obstetric units should develop protocols for the use of these agents. The risk of sudden hypotension with vasodilators such as nifedipine and hydralazine can be minimised by the use of concomitant plasma expansion.

ii.) **Ongoing treatment**

- methyldopa
- oxprenolol
- nifedipine

- labetalol
- clonidine
- prazosin

There is controversy over the use of oral antihypertensives for women with pre-eclampsia who do not have severe hypertension. These agents have been used with safety in the third trimester of pregnancy and have demonstrated efficacy in lowering maternal blood pressure. The major benefit of such treatment is to protect the mother from complications of hypertension and benefits to the fetus are secondary by reducing the incidence of severe hypertension as an indication for early delivery. Instituting therapy at diastolic blood pressure >90 mmHg and maintaining blood pressure as 120-140 mmHg systolic and 80-90 mmHg diastolic should achieve both aims. There are no conclusive data allowing clinicians to know at what systolic blood pressure antihypertensives should be commenced. Units should develop their own protocols.

AVOID angiotensin-converting enzyme (ACE) inhibitors (unless in puerperium), angiotensin II receptor antagonists, diuretics

ACE inhibitors used throughout pregnancy have been associated with fetal growth retardation, oligohydramnios, neonatal renal failure and fetal death. Diuretics may reduce an already low plasma volume.

B) Volume manipulation

Because of the risk of inducing pulmonary oedema, intravascular volume loading (up to 500 ml initially) may be considered for only a few indications:

- prefilling those women with severe pre-eclampsia about to have parenteral antihypertensive therapy, epidural anaesthesia or immediate delivery (ie in whom vasodilation will be induced)
- initial management of those who develop oliguria

Subsequent fluid therapy in the persistently oliguric woman should not be given without careful monitoring in a high dependency unit, especially in those whose gestation is at the limits of viability (24-26 weeks).

C) Invasive monitoring

Monitoring the central venous pressure (CVP) in women with pre-eclampsia may not be helpful as there is a poor correlation between CVP and pulmonary capillary wedge pressure. The (rare) indications for consideration of a pulmonary artery catheter are (a) the development of pulmonary oedema resistant to standard diuretic therapy and other anti-failure therapy, (b) persistent oliguria and deteriorating creatinine despite volume expansion. If either of these situations arise antenatally, then delivery is necessary as soon as the woman is stabilised.

- **Maternal - specific organ dysfunction**

A) Neurological

- terminate ongoing convulsions with **iv diazepam** (5-20mg)
- treat blood pressure
- prophylaxis of further convulsions with **magnesium sulphate,** initially 4 g iv loading dose followed by 1-3 g/hr for 24 hrs after delivery.

Such treatment can also be considered for women with premonitory signs of eclampsia (hyperreflexia with clonus, repeated visual scotomata, persistent severe headaches with hyperreflexia), although the use of magnesium in this situation remains controversial and cannot be recommended on the basis of available literature. Clinicians should make the decision to use convulsion prophylaxis on the basis of available literature and their clinical experience. Withholding convulsion prophylaxis in women without the premonitory signs listed above will not result in a high frequency of eclampsia. These premonitory signs are also indicators for delivery.

All obstetric units should hold protocols for the use of magnesium sulphate and anticonvulsants.

B) Hepatic

- delivery for worsening liver function tests
- ultrasound or contrast CT scanning of liver if pain persists after delivery, to exclude subcapsular haematoma

C) Haematological

Delivery is usually indicated for:

- progressive thrombocytopenia
- microangiopathic haemolysis

D) Renal

- delivery for developing renal failure, ie progressive increases in serum creatinine $\geq$0.09 mmol/L, not responsive to volume restoration
- volume expansion as initial therapy for oliguria
- proteinuria per se is **not** an indication for delivery

- **Fetal**

A) General

- corticosteroids should be administered for promotion of fetal lung maturity if pre-eclampsia is established at <34 weeks gestation and delivery is anticipated within one week
- early transfer to a tertiary centre for the woman with early onset pre-eclampsia

B) Ultrasound and umbilical artery Doppler velocimetry

- Ultrasound estimation of fetal growth rate every 2 weeks
- Umbilical artery Doppler studies if available as well as estimation of amniotic fluid volume
- Consider fetal karyotyping for severe fetal growth restriction with normal or excess liquor volume and severe pre-eclampsia

C) Cardiotocography

- In the very preterm fetus the CTG should be read by clinicians experienced in its interpretation
- In the preterm fetus a non-reactive CTG tracing indicates the need for more detailed biophysical monitoring
- In the mature fetus a non-reactive CTG tracing may be an indication for delivery
- Late fetal heart-rate decelerations associated with reduced baseline variability is usually an indication for delivery if the fetus is viable

a) DELIVERY

i) Timing

General indications for delivery are:

- pre-eclampsia occurring at term (>37 weeks)
- inability to control blood pressure despite adequate hypertensive therapy

- deteriorating liver function
- deteriorating renal function
- progressive thrombocytopenia
- neurological complications or imminent eclampsia
- placental abruption
- concern regarding fetal welfare

In pre-eclampsia close to term the fetus will usually tolerate labour and vaginal delivery. Continuous electronic monitoring of the fetal heart rate is recommended during labour to enable appropriate intervention should fetal distress develop.
When delivery is indicated pre-term because of severe pre-eclampsia, particularly when the indication for delivery is fetal, delivery by caesarean section will usually be in the best interests of both fetus and mother.

ii) Management of hypertension during labour

- Blood pressures ≥170 mmHg systolic or ≥110 mmHg diastolic should be lowered with parenteral therapy to prevent maternal complications
- Continue oral antihypertensive medications unless blood pressure is <120/70 mmHg (NB do not withhold clonidine, to avoid rebound hypertension).
- Consider epidural anaesthesia with volume expansion
- Check blood pressure at least half hourly

Do NOT give ergometrine (either on its own or in Syntometrine) to the woman with pre-eclampsia. Oxytocin should be used in its place.

iii) Anaesthetic considerations in pre-eclampsia

- Women with pre-eclampsia should ideally have a pre-labour/delivery assessment by an obstetric anaesthetist
- Analgesia by the lumbar epidural route provides good control of hypertension and improves uteroplacental blood flow
- For operative delivery, lumbar epidural anaesthesia (LEA) gives reliable blood pressure control and good operating conditions
- Subarachnoid or spinal anaesthesia (SAB) with appropriate attention to IV fluid administration, posture and judicious administration of vasopressors for hypotension, is also suitable in most cases of pre-eclampsia
- Regional anaesthesia (LEA or SAB) is contraindicated in the presence of coagulopathy and in most cases of fetal distress requiring immediate delivery

- Low dose aspirin is generally not a contraindication to LEA or SAB if the platelet count is normal
- General anaesthesia (GA) will be required for severe fetal distress requiring immediate delivery, haemodynamic compromise from placental abruption, difficult surgical access
- Pulmonary acid aspiration (Mendelson's syndrome) should be avoided by administration of clear antacid with or without ranitidine and metoclopramide, avoidance of the supine hypotensive syndrome, eg by employing left lateral tilt on a right pelvic displacement wedge, and several minutes preoxygenation
- GA may be associated with severe hypertension following laryngoscopy and intubation. This can be attenuated by combinations of antihypertensives, induction agents, narcotics and magnesium sulphate

d) POSTPARTUM

- All of the features of pre-eclampsia will eventually resolve postpartum
- New maternal complications may occur up to a week after delivery
- Women who require delivery for maternal indications usually need monitoring in a high dependency area and laboratory tests may need repeating 4-6 hourly
- Careful monitoring of fluid balance is mandatory
- Oliguria should alert concern for developing post partum renal failure
- In the woman who is showing clinical improvement, blood tests are not routinely indicated post partum
- Antihypertensive drugs are usually continued but can be weaned as the blood pressure continues to settle

CHRONIC HYPERTENSION

In all women with chronic hypertension an underlying cause for hypertension should be considered, as essential hypertension is at present a diagnosis of exclusion. Secondary hypertension may have implications for the pregnancy unrelated to the level of blood pressure.

- Renal disease
  Assessment of the underlying prognosis of the renal disease and the degree of renal impairment is important in determining risk in relation to pregnancy which may be much higher than that associated with the degree of hypertension

- Systemic disease with renal manifestations (such as diabetes mellitus, systemic lupus erythematosus).

The extent of other organ involvement will also determine the degree of risk associated with pregnancy.

- Endocrine disorders
  Phaeochromocytoma, though rare, has grave prognostic implications for both maternal and fetal welfare and must be considered in all cases of hypertension in pregnancy.

a) Significance of chronic hypertension in pregnancy

The risks of chronic hypertension are:

- exacerbation of **maternal hypertension**
- **superimposed pre-eclampsia** (diagnosed by *de novo* proteinuria or other *de novo* features as listed above for pre-eclampsia)
- uteroplacental insufficiency; IUGR; abruption

All of these risks are magnified if the pregnant woman, in addition to hypertension, suffers from renal disease with impairment of renal function. The incidence of these complications in women with severe disease may be reduced by control of hypertension.

b) Laboratory testing

Initial tests should include:

- Urinalysis for protein, blood and glucose
- Microscopy of centrifuged urinary sediment for white and red blood cells (including red cell morphology) and for casts
- Mid stream urine culture
- 24 hour urine protein or spot urine protein/creatinine ratio, if proteinuria is detected on dipstick testing
- measurement of serum electrolytes, creatinine, uric acid and blood glucose
- full blood examination
- 24 hour urine for estimation of catecholamine excretion if phaeochromocytoma is considered possible

c) Clinical and laboratory monitoring

- Record any symptoms and enquire about fetal movements at each visit
- Measurement of blood pressure, urinalysis, assessment of fundal height at each visit

The role of ambulatory blood pressure measurement in the diagnosis and management of women with chronic hypertension in pregnancy is not established

- Early obstetric ultrasound for confirmation of gestational age
- Careful monitoring of fetal growth; this may require regular scans.
- Repeat full blood count, serum uric acid, creatinine and liver function tests, together with assessment of urinary protein at 20-24 weeks, at 25-28 weeks and at 33-36 weeks gestation (or more frequently if clinically indicated)
- Admission to hospital or a day assessment unit if systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg, or for those with less severe hypertension (systolic blood pressure 140-160 mmHg, diastolic blood pressure 90-100 mmHg) if accompanied by newly developed proteinuria or other signs of pre-eclampsia, at any stage of pregnancy
- Pre-labour/delivery assessment by an obstetric anaesthetist

d) Drug therapy

- As for pre-eclampsia (see above)
- Avoid atenolol prior to the third trimester

e) Delivery

i) Timing

- If blood pressure remains well controlled and no fetal or maternal problem mandating delivery arises, aim for vaginal delivery at term.
- In other cases (almost always in the setting of superimposed pre-eclampsia), early delivery may be necessary (see above)
- In women whose blood pressure becomes impossible to control despite maximal doses of usual medications, delivery may be necessary to protect against maternal cerebral haemorrhage.

ii) Mode of delivery

As for pre-eclampsia (see above).

f) Post partum

In many women with chronic hypertension, a period of instability follows delivery for 7-14 days, during which it may be extremely difficult to achieve adequate control of blood pressure. It is often necessary to increase medication, or commence new antihypertensive therapy at that time.

CHRONIC HYPERTENSION WITH SUPERIMPOSED PRE-ECLAMPSIA

Superimposed pre-eclampsia occurs in about 20% of women with chronic hypertension. The risks to mother and fetus are greater than those of chronic hypertension alone.

Management of superimposed pre-eclampsia should be as outlined above.

FOLLOW UP POSTPARTUM

- Continue to watch for maternal complications first **3-5 days** as pre-eclamptic women may continue to deteriorate during this time.
- Taper oral antihypertensives as blood pressure settles.
- Monitor laboratory tests and urinalysis to ensure all abnormalities resolve after delivery.
- Review three months post partum: check blood pressure, urinalysis and microscopy.
- Further investigations may be necessary if elevated blood pressure, proteinuria or abnormal urine sediment at that stage.
- Advise recurrence is likely in up to half of women with pre-eclampsia or gestational hypertension, especially if this occurred early in pregnancy, though often milder disease. Recurrent gestational hypertension may herald future essential hypertension.
- Investigations for an underlying thrombophilic state, renal disease or auto-immune disease are not routinely indicated but should be undertaken in women with recurrent or early onset severe pre-eclampsia or if there is evidence of significant placental vasculopathy.
- There is no well-established therapy that will effectively prevent the recurrence of pre-eclampsia. Further clinical trials are required.

CONSENSUS STATEMENT

The detection, investigation and management of hypertension in pregnancy: full consensus statement

Recommendations from the Council of the Australasian Society for the Study of Hypertension in Pregnancy

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INTRODUCTION

Hypertension in pregnancy is associated with increased maternal and fetal morbidity and mortality. It is a common sign, reflecting a number of underlying disorders that may have different clinical outcomes. It is important that a woman with hypertension be diagnosed accurately so that the cause of the hypertension can be identified. She can then be informed about her likely clinical course and be managed appropriately.

Hypertensive disorders in pregnancy are best managed with a multidisciplinary approach; the obstetrician should remain the doctor in charge and seek advice from other appropriate specialists (eg anaesthetists, neonatologists, physicians) where indicated. This document offers a framework for a team approach to the diagnosis, investigation and management of women with hypertension in pregnancy. The recommendations are those of a multidisciplinary working party set up by the Australasian Society for the Study of Hypertension in Pregnancy to review and revise its previous guidelines for the detection, investigation and management of hypertension in pregnancy. They are based on definitions and a classification system that reflect current knowledge. It is recommended that each obstetric unit develop its own management protocols.

DEFINITION OF HYPERTENSION IN PREGNANCY

In normal pregnancy there is a well-recognised fall in both systolic and diastolic blood pressures, most marked early in the second trimester, the blood pressure rising towards pre-conception values in the third trimester.

Hypertension in pregnancy is diagnosed when:

- **Systolic blood pressure is $\geq$140 mmHg**
  and/or
- **Diastolic blood pressure (Korotkoff V) is $\geq$90 mmHg.**

These blood pressures should be confirmed by repeated readings over several hours in a clinic or day assessment unit or after rest in hospital.

Both systolic and diastolic blood pressures have been closely associated with fetal outcome and both are important (1).

Blood pressure of $\geq$140 mmHg systolic and/or $\geq$90 mmHg diastolic is widely used to diagnose hypertension in pregnancy as blood pressure above these values, particularly diastolic blood pressure, has been shown to be associated with a sharp rise in perinatal mortality (2). A study of almost 4000 pregnant women in New Zealand concluded that a blood pressure $\geq$140/90 mmHg was outside two standard deviations of the blood pressure mean in the normal pregnant population, and that on this basis 140/90 mmHg was a reasonable cut-off to define hypertension in pregnancy (3).

Detecting a rise in blood pressure, rather than relying on an absolute value, has also been considered useful for identifying women who develop severe complications of pre-eclampsia without reaching a blood pressure of 140/90 mmHg. A rise in systolic blood pressure $\geq$30 mmHg and/or a rise in diastolic blood pressure $\geq$15 mmHg from blood pressure measurements taken pre-conception or in the first trimester has been included in previous definitions (4, 5). The use of this rise, however, was never based on proper scientific evidence, and to date there are no data which adequately support or refute this as a method of defining hypertension in pregnancy. It is recognised that such a rise *may* be significant in some women. Further data are required.

RECORDING BLOOD PRESSURE IN PREGNANCY

There are major differences in the ways clinicians record blood pressure in pregnant women (6-8). The key issues are:

- whether the pregnant woman should be seated or recumbent
- which Korotkoff sound should be recorded as the diastolic blood pressure
- appropriate choice in cuff size

The following factors must be considered.

a) Position

The pregnant woman be seated comfortably. Blood pressure measurements so obtained vary little from those acquired in lateral recumbency provided the arm is at the level of the heart (9). Thus, blood pressure may be measured in the left arm in lateral recumbency during labour. If, however, the blood pressure is taken with the right arm held high whilst the pregnant woman is in the left lateral position, then a falsely low level of blood pressure will be recorded. Supine posture should be avoided. Measuring blood pressure on the same arm throughout pregnancy is very important in reducing inter-observer error. The right arm has been chosen by convention and not for important physiological reasons. Measurement of the blood pressure at the initial visit allows for the consideration, if a significant difference is found, of the rare diagnoses of aortic coarctation, subclavian stenosis and aortic dissection.

b) Korotkoff sounds

The debate as to whether Korotkoff phase IV (K4) (ie. point of muffling) or phase V (K5) (ie. point of disappearance) should be used to record diastolic blood pressure in pregnancy has now been largely resolved.

- It is apparent that K5 is detected more reliably than K4 during pregnancy (10, 11)
- K5 more closely reflects true diastolic pressure in pregnancy than K4 (12).
- Changing from use of K4 to K5 in hypertensive pregnant women does not increase morbidity for mother or baby (13).

Studies have challenged the traditional view that there are large differences between phase IV and V diastolic blood pressures (14-16), particularly in hypertensive pregnant women (16). Contrary to some long-held views, K5 is close to zero in only a very small proportion of pregnancies (17). Thus, it is now recommended that K5 be used to record the diastolic blood pressure in pregnancy (18, 19). Diastolic blood pressure should be recorded as K4 in those cases where K5 is absent.

c) Cuff size

Correct cuff size is mandatory for accurate blood pressure recording. A large cuff (15 x 33 cm bladder) should be used if the upper arm circumference is greater than 33 cm (20). This helps to minimise over-diagnosis of hypertension during pregnancy (21). Ideally, the inflatable balloon should cover 80% of the arm circumference.

d) Measurement devices

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 (22). Few studies have evaluated these self-initiated devices against 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 (23) and their accuracy may be further altered in pre-eclamptic women (24). Anaeroid sphygmomanometers are also prone to error. Mercury sphygmomanometry should remain the gold standard for now.

Non-invasive ambulatory blood pressure monitoring (ABPM) has been used in pregnant women but its role is still being defined (25). Normal blood pressure values recorded by ABPM have been established for different stages of pregnancy (26). ABPM devices may prove to be very useful in the future but cannot be recommended for use in pregnancy until more detailed evaluation of their potential use has been obtained in pregnant women.

Recommendations:

1. **The pregnant woman should be seated, with feet supported, for 2-3 minutes.**

2. **An appropriate sized cuff should be used [standard cuff for arms <33 cm circumference, large cuff (15 x 33 cm bladder) for larger arms].**

3. **Systolic blood pressure should be palpated at the brachial artery and the cuff inflated to 20 mmHg above this level.**

4. **The cuff should be deflated slowly, at approximately 2 mmHg per second.**

5. **Blood pressure should be recorded with a mercury sphygmomanometer.**

6. **Systolic blood pressure is recorded and diastolic blood pressure recorded as the phase V Korotkoff sound, ie. when sounds disappear. If phase V is not present, Korotkoff IV, ie. when sounds muffle, should be recorded.**

7. **Blood pressure should be taken using both arms at the first antenatal visit and thereafter using the right arm if, as anticipated, there is little difference in blood pressure between arms. If a significant difference in pressure is found, an opinion should be sought from a consultant physician.**

8. **Automated devices and ambulatory blood pressure monitoring should not yet be used in routine clinical practice until more detailed information becomes available about their accuracy and effectiveness.**

CLASSIFICATION OF HYPERTENSIVE DISORDERS OF PREGNANCY

Various classifications of the hypertensive disorders have been proposed (4, 5, 27). Hypertension during pregnancy may develop as a result of the pregnancy or follow pre-existing hypertension (either essential or secondary). Hypertension arising for the first time after 20 weeks gestation may be an isolated finding, ie gestational hypertension, or part of a multisystem disorder, ie pre-eclampsia.

The classification is as follows:

- **GESTATIONAL HYPERTENSION**
- **PRE-ECLAMPSIA**
- **CHRONIC HYPERTENSION**
  - **essential**
  - **secondary**
- **PRE-ECLAMPSIA superimposed on CHRONIC HYPERTENSION**

Gestational hypertension

Gestational hypertension is hypertension arising in pregnancy after 20 weeks gestation without any other feature of the multisystem disorder pre-eclampsia (see below) and which resolves within 3 months postpartum.

Other classifications include a group labelled ‘transient hypertension’, considered to be fairly benign and carrying a good maternal and fetal prognosis (5). We include such women here in the category of ‘gestational hypertension’.

Pre-eclampsia

Pre-eclampsia is usually first detected by the measurement of high blood pressure but features other than hypertension are required to make the diagnosis. It is now recognised that pre-eclampsia is a disorder which affects other organ systems including the feto-placental unit. Proteinuria is the most commonly recognised feature of pre-eclampsia after hypertension but should not be considered mandatory to make the clinical diagnosis.

A clinical diagnosis of pre-eclampsia can be made when the following criteria are fulfilled:

Hypertension arising after 20 weeks gestation

AND THE NEW ONSET AFTER 20 WEEKS GESTATION OF ONE OR MORE OF:

- **Proteinuria** - ≥300 mg/24h or spot urine protein/creatinine ratio ≥30 mg/mmol
- **Renal insufficiency** – serum/plasma creatinine ≥ 0.09 mmol/L or oliguria
- **Liver disease** – raised serum transaminases and/or severe epigastric/right upper quadrant pain
- **Neurological problems** – convulsions (eclampsia); hyperreflexia with clonus; severe headaches with hyperreflexia; persistent visual disturbances (scotomata)
- **Haematological disturbances** – thrombocytopenia; disseminated intravascular coagulation; haemolysis
- **Fetal growth restriction**

The hypertension of pre-eclampsia will have returned to normal within 3 months post partum.

NOTES:

1. Many disorders may present with similar features, eg acute fatty liver of pregnancy, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura or cholecystitis. Clinical judgement is necessary in every case to exclude such disorders before a diagnosis of pre-eclampsia is made.

2. Oedema is not included in the diagnostic features of pre-eclampsia. The appearance of oedema, whilst of concern to the mother, is probably of little clinical importance. It occurs equally in normal pregnant women and those with pre-eclampsia, although the rapid development of generalised oedema is usually abnormal.

3. Proteinuria: dipstick testing for proteinuria is a screening test only, with very high false positive rates. While all hypertensive pregnant women with any level of positive dipstick proteinuria should be treated initially as though they have pre-eclampsia, dipstick proteinuria should always be confirmed with either:
    - a 24 hour urine collection ≥300 mg/day, or:
    - a spot urine protein/creatinine ratio ≥30 mg protein/mmol creatinine.

Urinary tract infection should also be excluded. The spot urine protein/creatinine ratio has been shown to be as reliable as a 24 hour urine protein estimation for detecting significant proteinuria (28).

True proteinuria is present in most women with pre-eclampsia, but some women will have other evidence of this multisystem disease, even convulsions (eclampsia), without proteinuria.

4. Hyperuricaemia is a useful antenatal marker of pre-eclampsia, both as a guide to potential fetal risks (29) and as an aid in diagnosis, although some groups have questioned the utility of serum uric acid concentrations in distinguishing between various forms of hypertensive disease in pregnancy (30). Serial measurements of uric acid are useful as a rapid rise in uric acid concentration over a few days usually heralds progressive pre-eclampsia. Normal ranges at different gestations and in different ethnic groups need to be recognised.

5. Fetal growth restriction indicates probable placental involvement and warrants close observation of the pregnancy. Further data are required to determine the degree of surveillance of the mother required when there is predominantly fetal involvement.

The above classification system for a *clinical diagnosis* of pre-eclampsia has been compared with the more traditional system of defining pre-eclampsia as 'proteinuric *de novo* hypertension' in a study of 1183 hypertensive pregnant women (31). About half of these women with multisystem disease did not have proteinuria. A clinical diagnosis of pre-eclampsia based on this system, which accounts for the known pathophysiology of the disorder without **insisting** upon the presence of proteinuria, stratified a group of pregnancies of just as high a risk as did the traditional 'proteinuric hypertension' system.

For including women in basic science research, it is important to have a clearly defined group of women with pre-eclampsia. It is recognised that the above definition requires clinical judgement to classify accurately a woman with pre-eclampsia. Researchers may choose to keep a definition of pre-eclampsia which includes both hypertension and proteinuria as this is less open to clinical interpretation and error. Using such a definition may be less sensitive than using the above criteria for a clinical diagnosis of pre-eclampsia but will be more specific. While it is likely that restricting the diagnosis of pre-eclampsia to 'proteinuric hypertension' will exclude some women with this multisystem disorder, it will leave a well-defined group for the purposes of research.

Chronic hypertension

- Essential hypertension: blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic (K5) pre-conception or in the first half of pregnancy without an apparent underlying cause. It may also be diagnosed in those women presenting in pregnancy taking antihypertensive medications, again with no apparent underlying cause.

- Secondary hypertension: hypertension associated with renal, renovascular and endocrine disorders and aortic coarctation.

'White-coat' hypertension, a diagnosis of raised blood pressure in the presence of a clinical attendant but normal blood pressure in the normal environment (as assessed by ambulatory blood pressure monitoring), is not chronic hypertension. The prevalence of this disorder in pregnant women may be lower than that found in the non-pregnant population, and pregnancy outcomes are similar to those in women not displaying this phenomenon (32). Further data are required.

Pre-eclampsia superimposed on chronic hypertension

In women with chronic hypertension, superimposed pre-eclampsia is diagnosed when one or more of the systemic features of pre-eclampsia (see above) develop after 20 weeks gestation. In women with chronic renal disease a diagnosis of superimposed pre-eclampsia is often difficult, eg proteinuria may increase due to the primary renal disease alone. In such women, sudden dramatic increases in proteinuria and hypertension should lead to increased surveillance for pre-eclampsia but the diagnosis is not secure without the development of other features, eg abnormal liver function, thrombocytopenia or neurological abnormalities.

GESTATIONAL HYPERTENSION

It is important to distinguish gestational hypertension from pre-eclampsia as women whose pregnancies are complicated by gestational hypertension alone have a very good pregnancy outcome. The risks of maternal and fetal morbidity are very low compared with those of pre-eclampsia (33). The likelihood of a woman with gestational hypertension progressing to develop pre-eclampsia is much higher with early presentation, ranging from a 40% risk if presenting before 30 weeks to a less than 10% risk if presenting after 37 weeks (34).

a) Diagnosis

It is important to arrange adequate assessment of a woman who presents with gestational hypertension. This is usually done over several hours in a day stay assessment unit though some women may require a short admission to hospital especially if severe hypertension is present ($\geq$170/110 mmHg). Maternal and fetal investigations must be performed to exclude pre-eclampsia (see below).

b) Antihypertensive treatment

The level of blood pressure which requires treatment in pregnancy is not clear (see pre-eclampsia/chronic hypertension sections). The rationale for treatment is to prevent severe hypertension which may lead to concern about maternal wellbeing and delivery. Medication choices are similar to those used in ongoing treatment of pre-eclampsia (see below). A suggested aim of treatment is to maintain blood pressure between 110 and 140 mmHg systolic and 80 to 90 mmHg diastolic without inducing undue side effects.

c) Monitoring

A woman needs to be monitored to detect superimposed pre-eclampsia, usually two or three times per week. The woman needs education about the symptoms and signs of pre-eclampsia and about the need to present for assessment if they occur. Laboratory tests are indicated weekly or sooner if the woman develops worsening hypertension, or symptoms or signs of pre-eclampsia. Admission to hospital is always indicated if severe hypertension or pre-eclampsia develops.

PRE-ECLAMPSIA

Pre-eclampsia is diagnosed if the above criteria are fulfilled. It may rarely occur before the 20th week of pregnancy associated with hydatidiform mole, with multiple pregnancy or with fetal triploidy, and very rarely with other prothrombotic disorders such as antiphospholipid syndrome, or with severe renal disease. Hypertension before 20 weeks gestation is usually due to chronic hypertension or to 'white-coat' hypertension.

a) AWARENESS

Careful history and physical examination when the pregnant woman presents for her first antenatal visit can provide clues that she is "at risk" of developing this disorder in the second half of her pregnancy.

<u>The "at risk" woman:</u>

- Primigravid state
- Multigravida pregnant by a different partner
- Prior pre-eclampsia in a pregnancy by the same partner
- Family history of pre-eclampsia
- Multiple pregnancy
- Obesity
- Renal disease
- Essential hypertension
- Diabetes
- Autoimmune disease, especially SLE and antiphospholipid syndrome
- Thrombophilic state
- Severe alloimmunisation

Most of these conditions will be apparent from the history but careful measurement of blood pressure, examination of optic fundi, urinalysis and urine microscopy will provide most other clues. It is not practical to increase the frequency of antenatal visits for all primigravidae when only 10% will develop gestational hypertension and only up to 7% will develop pre-eclampsia. The other "at risk" groups, who form a smaller total number, can be seen more frequently during pregnancy to detect the development of pre-eclampsia.

Two clinical features should alert clinicians to the impending appearance of pre-eclampsia:

- failure of blood pressure to fall in mid-pregnancy (35)
- the *de novo* appearance of proteinuria in the second half of pregnancy (see above)

b) ASSESSMENT

- **Clinical features**

The widespread potential manifestations of pre-eclampsia are presented in Figure 1. Some women exhibit many or all of these features while others have only elevated blood pressure and little evidence of other maternal organ dysfunction

In some women maternal features predominate with little or no effect on the fetus whilst in others fetal survival may be compromised in the presence of few maternal features of pre-eclampsia. The timing of presentation is important - those presenting at early gestation not only pose problems for fetal viability but also tend to exhibit more maternal features of pre-eclampsia than those who present later in pregnancy. Thus, the stage of gestation, adequacy of fetal growth and the extent of maternal organ dysfunction should be the three areas which need to be addressed by the clinician managing a woman with pre-eclampsia.

- **Laboratory testing**

  This should include:

  - haemoglobin, haematocrit, platelet count, blood film
  - coagulation studies only if thrombocytopenia or evidence of haemolysis is present
  - serum uric acid
  - serum creatinine
  - liver function tests – serum transaminase, albumin
  - urinalysis and microscopy on a carefully collected midstream sample
  - quantitation of proteinuria - 24 hr collection, or spot urine protein/creatinine ratio

c) MANAGEMENT

The aim of management is to maximise perinatal outcome without endangering maternal health. A team approach, involving obstetrician, midwife, neonatologist, anaesthetist and physician, provides the best chance of achieving this aim. Once the diagnosis of pre-eclampsia is established, the woman needs close observation. In general she should be admitted to hospital.

- **Maternal - general**

A) Bed rest

This used to be accepted initial management of pre-eclampsia but the only controlled studies of bed rest for pre-eclampsia have shown no significant maternal or fetal benefit (36). Bed rest should no longer be considered necessary in the management of pre-eclampsia.

B) Diets

All sorts of diets have been employed over the years to treat pre-eclampsia but none has been successful, including salt-restriction (37) and the use of fish oils (38).

C) Antihypertensive medications

i.) Acute treatment

There is general agreement that blood pressure should be lowered if blood pressure rises above 170 mmHg systolic and/or 110 mmHg diastolic, in order to prevent intracerebral haemorrhage. Several agents have been used for this purpose including parenteral hydralazine (39), labetalol (39), clonidine (40) and diazoxide (41), and oral (42-44) or sublingual nifedipine (45, 46). All have been effective and generally safe, although nifedipine capsules have now been withdrawn from the Australian market. Oral therapy should be used initially unless the woman is symptomatic (eg headache or abdominal pain) or has features of impending eclampsia (eg hyperreflexia). Controlled reduction of the blood pressure without overshoot should protect the mother against cerebral haemorrhage whilst not jeopardising the fetus. Continuous CTG monitoring should be used to ensure any reduction in blood pressure does not cause fetal distress. In the studies cited above fetal death did not occur with blood pressure reductions of the order of 20-30 mmHg systolic and/or 10-15 mmHg diastolic. Greater reductions will be necessary in women with higher blood pressures. The risk of sudden hypotension with vasodilators such as nifedipine can be minimised by the use of concomitant plasma expansion.

Infusion of sodium nitroprusside or glyceryl trinitrate or trimetaphan can produce controlled blood pressure reduction but are recommended only in exceptional circumstances. Sodium nitroprusside may cause fetal cyanide and thiocyanate toxicity and transient fetal bradycardia. Such infusions can be used with intra-arterial blood pressure monitoring while preparing the woman for delivery if the above medications have failed to control the blood pressure.

The most important considerations in choice of antihypertensive agent are that it is effective and safe and that the unit has experience and familiarity with that agent. It is recommended that protocols for the management of severe hypertension should be in place in all obstetric units.

ii.) Ongoing treatment

There is considerable controversy as to whether antihypertensive agents should be used in women with pre-eclampsia if blood pressure remains below 170/110 mmHg. Proponents of such treatment

offer rationales such as (a) blood pressure is extremely labile in pre-eclampsia and treatment at lower blood pressure levels may help to prevent or reduce acute and severe rises in blood pressure, or (b) blood pressure control is effected through arteriolar vasodilation, which may help to improve organ perfusion. Others believe (a) 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), or (b) that fetal perfusion is dependent upon adequate systemic blood pressure and that lowering this will compromise the fetus, or (c) that lowering blood pressure suppresses an important sign of the severity or progression of pre-eclampsia.

There is no study or series of studies which allow clinicians to resolve this debate definitively. One small Australian placebo-controlled randomised study examined the role of antihypertensive therapy in the management of mild hypertension (47). Significantly more placebo-treated women were delivered early, mainly as a result of severe hypertension or premonitory signs of eclampsia, and there was more neonatal morbidity secondary to prematurity.

Safety and efficacy, at least in terms of lowering blood pressure in pre-eclampsia, has been demonstrated for oxprenolol (48), methyldopa (49), clonidine (47), labetalol (50), prazosin (51) and nifedipine tablets (52). Atenolol has also been shown to be useful but, because of its association with fetal growth restriction in chronic hypertension (discussed later), doubts remain over its role in the treatment of pre-eclampsia. Felodipine and amlodipine may also prove as useful as nifedipine but data establishing the safety of these drugs in pregnancy are lacking. Angiotensin converting enzyme (ACE) inhibitors should be avoided antepartum as they have been associated with fetal death and neonatal renal failure (53), although they may be used postpartum: captopril and enalapril only appear in breast milk in minute amounts.

iii) Summary

In view of the relative safety of the medications outlined above and the opportunity to reduce premature delivery by their use, there is an argument for using antihypertensive agents in mild to moderate pre-eclamptic hypertension. Although blood pressures which rise above 90 mmHg diastolic have been associated with an increase in perinatal mortality, there are no firm data from which to determine the optimum blood pressure during treatment. If the rationale of treatment is to prevent severe maternal hypertension while not compromising fetal perfusion, then instituting therapy at diastolic blood pressure >90 mmHg and maintaining blood pressure as 120-140 mmHg systolic and 80-90 mmHg diastolic should achieve both aims. There are no conclusive data allowing clinicians to know at what systolic blood pressure antihypertensives should be commenced. Units should develop their own protocols for antihypertensive management and are encouraged to publish their outcomes.

Most importantly, antihypertensive agents should not be initiated in the newly diagnosed hypertensive pregnant woman after 20 weeks gestation without full clinical and laboratory assessment.

D) Volume manipulation

In general, maternal plasma volume is reduced in women with pre-eclampsia (54) and direct re-expansion of this volume has been associated with a fall in blood pressure in women with pre-eclampsia (55). Not all women with pre-eclampsia, however, have low plasma volume and it is difficult to predict this without direct measurement (56). Importantly, capillary permeability is increased in women with pre-eclampsia (57) and administration of large volumes of intravenous fluid may cause pulmonary oedema.

The mean reduction in plasma volume is around 500-600 ml, and administration of this volume rarely poses a risk. Clinical trials to provide guidance in this area are limited. Accordingly, intravascular volume loading (up to 500 ml initially) may be considered for only a few indications:

- prefilling those women with severe or proteinuric pre-eclampsia about to have parenteral antihypertensive therapy, epidural anaesthesia or immediate delivery (ie in whom vasodilation will be induced)
- initial management of those who develop oliguria

Subsequent fluid therapy in the persistently oliguric woman should not be given without careful monitoring in a high dependency unit, especially in those whose gestation is at the limits of viability (24-26 weeks). Rarely, invasive monitoring may be considered (see below).

In view of the reduced plasma volume in most women with pre-eclampsia, diuretics or salt restriction should NOT be used in the absence of pulmonary oedema.

E) Invasive monitoring

Invasive monitoring (with pulmonary artery (PA) catheterisation) is rarely necessary and should be reserved for those few selected cases not responding to standard treatment. Left ventricular failure is an uncommon feature of pre-eclampsia, and insertion and subsequent management of a PA catheter is associated with hazards to the woman. Monitoring the central venous pressure (CVP) in women with pre-eclampsia may not be helpful as there is a poor correlation between CVP and pulmonary capillary wedge pressure (PCWP) (58).

The (rare) indications for consideration of a PA catheter are (a) the development of pulmonary oedema resistant to standard diuretic therapy and other anti-failure therapy, (b) persistent oliguria and deteriorating creatinine despite volume expansion. If either of these situations arise antenatally, then delivery is necessary as soon as the woman is stabilised.

Direct intra-arterial blood pressure monitoring may be useful in a high-risk situation if appropriate facilities and trained staff are available.

- **Maternal - specific organ dysfunction**

As previously emphasised, the management of pre-eclampsia centres around appropriately timed delivery. A number of abnormalities may occur in the mother which require specific management before, during and after labour.

A) Neurological

Eclampsia may occur at only moderate levels of blood pressure and can arise post partum (59). Convulsions, if prolonged, should be terminated with intravenous diazepam, blood pressure should be controlled, as indicated above, with parenteral therapy if the woman remains unconscious and severely hypertensive, and prophylaxis of further convulsions commenced with magnesium sulphate. Delivery can then be effected (if the woman is still pregnant) when the situation has been stabilised.

Magnesium sulphate is usually given as an intravenous loading dose (which some units combine with a deep intramuscular injection) followed by regular maintenance doses. Care needs to be taken to monitor the clinical response. Serum magnesium concentration should be monitored in women with renal impairment. All obstetric units should have a readily available protocol for the use of magnesium sulphate in women with eclampsia.

Diazepam, whilst effective for terminating convulsions, has been shown to be less effective than magnesium sulphate in the prophylaxis of further seizures with increased maternal morbidity (60). Phenytoin is also less effective than magnesium sulphate in the prophylaxis of further seizures (60) and its use should be confined to the treatment of those women who have recurrent seizures despite magnesium sulphate therapy. Chlormethiazole may cause profound respiratory depression and should no longer be used.

Careful clinical monitoring should detect premonitory signs of convulsions (eclampsia) such as hyperreflexia with clonus, retinal vasospasm, visual obscurations and persistent headaches. Women with such symptoms and signs may be considered for convulsion prophylaxis with magnesium sulphate, although its use in this setting still awaits the outcome of a major international clinical trial to determine the risks and benefits.

B) Hepatic

Routine monitoring of liver function tests in women with pre-eclampsia will often detect early abnormalities of liver function. If these changes progress, then delivery is indicated. Epigastric or right upper quadrant pain, often described as a tightness or atypical indigestion, in a woman with pre-eclampsia often reflects hepatic involvement, and may be associated with progressive thrombocytopenia and coagulopathy. (The term HELLP syndrome – Haemolysis, Elevated Liver enzymes, Low Platelets – should be abandoned as it is just one pattern of presentation of severe pre-eclampsia. Its use may detract attention from other systems which may be involved.) Women with persistent epigastric pain, abnormal liver function and pre-eclampsia need delivery. Occasionally subcapsular haematoma or even liver rupture may occur. Coagulation studies should be checked and appropriate treatment given if necessary. Transient epigastric or right upper quadrant pain may occur in association with severe hypertension and will often respond to acute blood pressure lowering with vasodilator therapy. If the diagnosis of epigastric or right upper quadrant pain is not clear, close assessment over a few hours will usually clarify the situation.

The combination of abnormal liver function, marked hyperuricaemia and *de novo* vomiting in the third trimester, particularly in a woman carrying a multiple pregnancy, raises the possibility of acute fatty liver of pregnancy (AFLP) (61). Marked polyuria consistent with a (transient) diabetes

insipidus syndrome may also be a feature (62). Such women may progress to liver failure and delivery is indicated. It may be impossible to distinguish between AFLP and pre-eclampsia as the two conditions often overlap. Whatever the precise diagnosis, progressive deterioration in liver function dictates the need for delivery.

C) Haematological

Thrombocytopenia usually indicates the presence of low-grade disseminated intravascular coagulation (DIC). This may co-exist with liver dysfunction (see above).

Coagulation studies, including prothrombin time and activated partial thromboplastin time (APTT) are appropriate investigations in the pre-eclamptic woman with thrombocytopenia. Delivery is usually indicated for progressive thrombocytopenia to avoid fulminant DIC which may develop over hours.

Antiphospholipid syndrome can be associated with thrombocytopenia and prolongation of APTT secondary to the presence of a lupus anticoagulant. Careful clinical judgment is required to interpret results when superimposed pre-eclampsia develops.

Intravascular haemolysis is a rarer feature of severe pre-eclampsia; this is usually microangiopathic and is a feature of accompanying DIC. It is another indication for delivery. Consideration may be given to alkalinising the urine, and a high urine flow rate maintained to avoid acute renal failure.

D) Renal

The most common manifestations of renal involvement in pre-eclampsia are hyperuricaemia and proteinuria. Although these are hallmarks of pre-eclampsia, they are not indications for delivery by themselves (63). Progressive deteriorating renal impairment (creatinine >0.09 mmol/L) warrants consideration of delivery, with careful management of fluids and blood pressure to prevent acute renal failure. This may be due to a combination of glomerular pathology and acute tubular necrosis, the result of renal vasoconstriction, volume depletion, intravascular coagulation, low cardiac output and perhaps other factors. If hypertension is severe enough (malignant), then it may cause acute renal failure *per se*.

- **Fetal**

A) General

Definitions of fetal viability vary in different tertiary centres in Australia and New Zealand. Neonatal survival at discharge for babies with birthweights 500-599 g born in level 3 neonatal intensive care units in Australia and New Zealand during 1995 was 47% and for babies with birthweights 600-699 g was 64% (64). Corresponding figures for babies born at 24 and 25 weeks gestation were 53% and 70% respectively. Long term follow-up of this cohort is not available. It is currently unknown whether long term neurodevelopmental outcome is worse in these extremely

preterm babies compared with those delivered beyond 26 weeks. If inpatient monitoring is necessary from 23 to 24 weeks onwards, it is best performed in a tertiary centre with on-site neonatal intensive care facilities. *Early transfer to a tertiary centre is recommended for the woman with early onset pre-eclampsia to avoid the adverse outcomes associated with the transfer of a critically ill pre-term neonate* (65).

Stabilisation of the maternal condition and close surveillance of fetal wellbeing can result in a significant improvement in fetal outcome, without an increase in maternal morbidity, for pregnancies complicated by severe early onset pre-eclampsia (66).

The first large randomised controlled trial of corticosteroid use in women with pre-eclampsia has recently been published (67). 218 women with severe pre-eclampsia and gestational age between 26 and 34 weeks were randomised to betamethasone or placebo injections. Corticosteroid treatment halved the risk of respiratory distress syndrome, intraventricular haemorrhage and neonatal death. There was no increase in the stillbirth rate. As pre-eclampsia is an unpredictable condition, corticosteroid treatment for fetal lung maturation is recommended for women who present at <34 weeks. Treatment should commence when delivery is anticipated within one week.

Assessment of fetal wellbeing must be included as part of the management of hypertensive pregnancies which have reached the stage of fetal viability. Different institutions have different approaches to fetal monitoring. It is not possible to recommend an optimum regimen for monitoring fetal wellbeing as there is a lack of good evidence on which to base a recommendation. In most units, however, the initial assessment of the fetus of a woman with pre-eclampsia will include an ultrasound scan to assess growth liquor volume and umbilical artery Doppler waveforms. Many clinicians will also perform a cardiotocograph.

B) Ultrasound and umbilical artery Doppler velocimetry

About 25% of women with pre-eclampsia deliver small for gestational age babies (68). Ultrasound estimation of fetal growth rate should be performed every 2 weeks in pre-eclampsia. Umbilical artery Doppler studies should be performed (if facilities are available) as well as estimation of amniotic fluid volume. The presence of diminished amniotic fluid volume (usually associated with intrauterine growth restriction) is associated with increased fetal risk. Severe fetal growth restriction with normal or excess liquor volume and severe pre-eclampsia should raise the possibility of fetal aneuploidy. Amniocentesis or cordocentesis should then be considered.

Abnormal umbilical artery Doppler waveforms are associated with adverse perinatal outcomes in pre-eclampsia and are an indication for frequent fetal monitoring (69). The use of umbilical artery Doppler studies in high risk pregnancies (pre-eclampsia or intrauterine growth restriction) is associated with a reduction in perinatal mortality (70). Absence or reversal of umbilical artery end-diastolic velocities has been associated with high perinatal morbidity and mortality. Currently it is unknown whether absent or reversed end-diastolic velocities should be considered an indication for delivery of a very preterm fetus.

C) Cardiotocography

Antenatal cardiotocography (CTG), although not proven to reduce perinatal morbidity or mortality (71), is commonly used in high risk pregnancies. Between 24 and 26 weeks the healthy very preterm fetus has a higher baseline fetal heart rate, may not demonstrate accelerations in response to fetal movements, and accelerations which do occur are often of amplitude <15 beats/minute (72, 73). In addition, fetuses which are growth restricted but not acidotic at birth can have reduced fetal heart rate variability (74). The CTG can therefore be difficult to interpret in the very preterm fetus especially if the fetus is also growth restricted. In this context, therefore, the CTG should be read by clinicians experienced in its interpretation.

The presence of non reactivity after a CTG tracing of at least 40 minutes duration may indicate the need for more detailed biophysical monitoring in the preterm fetus, or may be an indication for delivery in the mature fetus. The presence of late fetal heart-rate decelerations which are usually associated with reduced baseline variability will usually constitute an indication for delivery if the fetus is viable (75).

The frequency of CTG assessments will be determined by the clinical situation with more intensive monitoring usually recommended if the fetus is growth restricted or has abnormal umbilical artery Doppler waveforms.

d) DELIVERY

i) Timing

Pre-eclampsia occurring at term (>37 weeks) is an indication for delivery. When the fetus is pre-term, especially when the gestation is <32 weeks, conservative management with careful monitoring of maternal and fetal well being is usually recommended. The decisions regarding timing, mode, location of and indications for delivery are complex and require careful consideration of the merits of each case, involving consultation between obstetric, medical, paediatric, midwifery and anaesthetic members of the team caring for the woman. While every case must be considered individually, general indications for delivery are:

- inability to control blood pressure despite adequate hypertensive therapy
- deteriorating liver function
- deteriorating renal function
- progressive thrombocytopenia
- placental abruption
- neurological complications or imminent eclampsia
- concern regarding fetal welfare

Note

Delivery of the growth-restricted fetus prior to the development of major acidosis may improve long-term neurodevelopmental outcome (76). It can, however, be difficult to detect imminent acidosis. Longitudinal studies in preterm growth-restricted pregnancies have identified a sequence of changes in tests of fetal welfare prior to delivery carried out for suspected fetal compromise (75). An abnormal umbilical artery Doppler waveform with or without ultrasound evidence of poor fetal growth, is usually the first abnormality. This is followed by a reduction in fetal heart rate variability which is usually gradual, and subsequently the appearance of late fetal heart rate decelerations and reduced fetal activity (75). The median time from first appearance of absent end diastolic velocity to delivery (performed on the basis of late decelerations) is 14 days for fetuses of less than 28 weeks gestation and 5 days for more mature fetuses (77).

In studies utilising computerised assessment of the fetal heart rate, abnormal fetal heart rate variability (<30 ms) occurs at about the same time as the onset of late decelerations. If delivery occurs at this point most fetuses are hypoxaemic but major acidosis is uncommon (78). Some investigators have therefore recommended delaying delivery until the first appearance of late decelerations in the fetus of borderline viability (75). Others advocate intervening earlier (77).

The mode of delivery will largely be determined by the clinical situation. When there is pre-eclampsia close to term the fetus will usually tolerate labour and vaginal delivery. Continuous electronic monitoring of the fetal heart rate is recommended during labour to enable appropriate intervention should fetal distress develop.

Vaginal delivery will often be impractical when delivery is indicated pre-term because of severe pre-eclampsia, particularly when the indication for delivery is fetal. In such situations delivery by caesarean section will usually be in the best interests of both fetus and mother.

ii) Management of hypertension during labour

Blood pressure rises during normal labour. Blood pressures ≥170 mmHg systolic or ≥110 mmHg diastolic should be lowered with parenteral therapy to prevent maternal complications. Oral antihypertensive medications may be continued unless blood pressure is <120/70 mmHg. (NB clonidine should *always* be continued during labour to prevent "rebound" hypertension.) The effects of blood loss, analgesia or anaesthesia should be considered in the assessment of blood pressure in labour.

Epidural anaesthesia also lowers blood pressure during labour and can be useful. It has no effect on cardiac index and pulmonary vascular resistance, at the same time stopping the release of endogenous catecholamines and reducing systemic vascular resistance (see below).

Blood pressure should be checked at least half hourly during labour and immediately upon delivery of the placenta as sudden falls in blood pressure may occur at this stage, responsive to volume expansion. Ergometrine (either on its own or in Syntometrine) should NOT be given to the woman with pre-eclampsia, even if the blood pressure is normal at delivery, as this may precipitate a hypertensive crisis. Oxytocin should be used in its place.

iii) Anaesthetic considerations in pre-eclampsia

The obstetric anaesthetist plays a key role in the management of the woman with severe pre-eclampsia and close collaboration with the obstetrician is essential. Ideally, anaesthetic assessment of the pre-eclamptic patient should be undertaken prior to labour/delivery. Anaesthesia for caesarean section (CS) for should be undertaken only after carefully considering the following:

- Where the procedure is to be performed, by whom and the quality of the facilities available to provide the expert postoperative care required for such cases.
- Type of anaesthesia, that is general (GA) or central neural blockade (lumbar epidural - LEA, subarachnoid - SAB or combined spinal/epidural - CSE).
- The presence of laryngeal and upper airway oedema may make intubation difficult or impossible. Personnel and equipment must be available to pre-empt and deal with such eventualities.
- Attenuation of the pressor responses to laryngoscopy and intubation if GA is to be performed.
- Modifications to the anaesthetic in the presence of liver damage.
- How the presence of a coagulopathy will influence the performance of neural blockade.
- Stabilisation of the woman in terms of blood pressure control, eclampsia prophylaxis, intravenous fluid management and urine output.
- The level of invasive haemodynamic monitoring required.
- The agent to be used in the event of hypertensive crises.

(Some of these issues have been considered in the previous discussion).

"Best" anaesthetic for severe pre-eclampsia

Lumbar epidural anaesthesia (LEA), carefully administered, generally provides reliable blood pressure control and good operating conditions. Appropriate fluid preloading with crystalloid or occasionally, colloid, using haemodynamic monitoring where indicated, and attention to avoidance of aorto-caval compression should prevent the development of maternal hypotension. Under these conditions LEA has no detrimental effects on uteroplacental or fetal circulations (79). Adrenaline-containing solutions should be used with caution because these women are sensitive to exogenous pressors. Vasopressors such as ephedrine should also be used with care to avoid an excessive hypertensive response.

Subarachnoid anaesthesia is rapidly becoming the most widely used anaesthetic for CS, either alone or as a combined spinal/epidural technique. Provided meticulous attention is paid to fluid management, aorto-caval compression and prevention or rapid treatment of maternal hypotension these techniques would appear to be equally safe for women with pre-eclampsia. While regional blockade may be the anaesthetic technique of choice for Caesarean section, there are situations where intraspinal anaesthesia may be contraindicated (eg. severe thrombocytopenia, severe fetal distress

requiring immediate delivery, haemodynamic compromise from placental abruption, etc) and a GA will be required.

Preparation of a woman with severe pre-eclampsia immediately prior to GA for Caesarean section should include blood grouping and antibody screening, prophylaxis against pulmonary acid aspiration (Mendelson's syndrome) by administration of clear antacid with or without ranitidine and metoclopramide, avoidance of the supine hypotensive syndrome, eg by employing left lateral tilt on a right pelvic displacement wedge, and several minutes preoxygenation. A vasodilator infusion may be necessary to avoid spikes of blood pressure. Skilled assistance for the anaesthetist is vital in these high-risk women.

Ketamine should not be used as part of the rapid sequence induction regimen as it causes further increases in blood pressure. In those with liver and kidney impairment the use of agents with low biotransformation (eg isoflurane), minimal renal excretion (eg atracurium), short half life (eg propofol) and absence of active metabolites is theoretically preferable. All muscle relaxants potentially interact with magnesium sulphate.

Attenuation of Pressor Responses to Intubation & Laryngoscopy

Airway manipulation and endotracheal intubation present a particularly dangerous time for the woman with pre-eclampsia especially if the intracranial pressure is already elevated or the blood pressure is inadequately controlled. Such pressor responses may cause intracerebral haemorrhage and/or pulmonary oedema. Agents used to modify or abolish the pressor responses to tracheal intubation and laryngoscopy include a combination of parenteral vasodilator timed to take effect at the time of intubation (eg glyceryl trinitrate, sodium nitroprusside), increased doses of induction agent, intravenous narcotics, magnesium sulphate, parenteral lignocaine and β-adrenoreceptor antagonists such as esmolol (80, 81). A combination of alfentanil and magnesium sulphate may prove to be the best prophylaxis against hypertensive reflexes.

Coagulation Disorder and Anaesthesia

Investigation of coagulation disorders in severe pre-eclampsia can be expensive and time-consuming, and even in those women receiving LEA it seems likely that initial screening with a platelet count is all that is required. In order to avoid unnecessary delays in provision of adequate analgesia in labour, coagulation screening should be restricted to those with pre-eclampsia who have thrombocytopenia.

Because (i) the epidural vessel puncture rate (“blood” tap) may be as high as 18% (82), (ii) pre-eclampsia may be associated with thrombocytopenia, or platelet function defect (83), and (iii) the antiplatelet activity of aspirin may increase the potential for formation of extradural haematoma, it is important to know if LEA can be safely administered in a woman with pre-eclampsia on aspirin. The CLASP Study (Collaborative Low-dose Aspirin Study in Pregnancy) in data from 9,364 pregnant women reported no increase in the incidence of LEA bleeding complications in those women who were randomised to aspirin 60 mg daily and who subsequently were managed with LEA at delivery (84). These investigators did not recommend the routine use of bleeding times for women on low-dose aspirin.

It is not clear what level of thrombocytopenia is associated with increased risk of complications with LEA in women with pre-eclampsia. In women with a platelet count below 100 x 10^9/L and/or with prolonged clotting tests, LEA should only be instituted with extreme caution on a case-by-case basis weighing the risk-benefit outcome. In selected borderline cases (eg in a woman anticipated to be difficult to intubate), fine gauge needle spinal anaesthesia or continuous microcatheter subarachnoid block may be the technique of choice but both still carry risks in those with platelet function defects or thrombocytopenia (83).

The requirement for platelet and other blood component transfusions will be determined according to the various test results, the presence of obstetric bleeding and the need for surgery. Early consultation with a obstetric physician or haematologist is recommended.

e) POSTPARTUM

All of the features of pre-eclampsia will resolve postpartum but clinicians should remain alert for new maternal complications for at least a week after delivery. In particular, women who require delivery for maternal indications are not immediately "cured" by delivery. They usually need monitoring in a high dependency area and laboratory tests may need repeating 4-6 hourly. Careful monitoring of fluid balance is mandatory as most cases of pulmonary oedema have been associated with injudicious volume overload, while oliguria should alert concern for developing post partum renal failure, often associated with haemolysis, which may require treatment with fresh frozen plasma or plasmapheresis and occasionally dialysis. Eclampsia is a well recognised complication of the puerperium (59), especially when the guard of regular observations has been dropped. Some abnormalities, particularly thrombocytopenia and platelet function defects, will often get worse during the first 2-3 days after delivery, while there is often a rise in serum gamma-glutamyl transpeptidase (GGT) up to two weeks after delivery (85).

In the woman who is showing clinical improvement, blood tests are not routinely indicated post partum unless pre-existing abnormalities were present (eg thrombocytopenia, elevated serum transaminases or serum creatinine) in which case these should be checked to ensure they have returned to normal. Hypertension often seems to settle in the first 24-48 hours after delivery, especially if ongoing epidural analgesia is used. It may, however, worsen over subsequent days, so antihypertensive drugs are usually continued unless hypotension is a concern. Medications can be weaned as the blood pressure continues to settle, often over several weeks, occasionally taking up to three months. Methyldopa and clonidine are often changed to an alternative if they cannot be weaned over a few days.

Women who have had pre-eclampsia need assessment at three months to ensure they are normotensive and there is no residual proteinuria or abnormal urine microscopy. Even heavy proteinuria in pre-eclamptic women will have disappeared by three months post partum if there is no underlying primary renal abnormality (86). Persistent abnormalities indicate the need for further investigation. Also, women who have had early onset pre-eclampsia will usually require investigation for underlying renal problems or thrombophilia as they are more likely to have underlying disease (87). In addition, they will need counselling about their risks and management in a future pregnancy.

f) NEONATAL OUTCOME

The risk of intrauterine growth restriction (IUGR) is significantly increased in hypertensive pregnancies compared with normotensive pregnancies. The relative risk has been estimated to be 2.7 (95% confidence interval 1.8-4.0) for chronic hypertension and 14.6 (95% confidence interval 5.8-36.5) for pre-eclampsia (88).

Acute neonatal morbidity can be more common following hypertensive pregnancies. Haematological abnormalities including neutropenia (89), and thrombocytopenia (90) are commonly observed within the early postnatal days. The risk of developing respiratory distress syndrome is almost double that of gestationally-matched peers from non-hypertensive pregnancies (60% versus 33%) for infants delivered before 33 weeks gestation (91). The risk of intraventricular haemorrhage may, however, be reduced in preterm (<33 weeks) babies of pre-eclamptic women compared with gestation-matched controls (92). The acute morbidity does not, however, appear to include neonatal hypotension or rebound hypertension (93).

Hypertensive pregnancies also have a higher perinatal mortality rate than normotensive pregnancies, with the infants' chances of survival being largely related to their degree of prematurity. Those infants with severe IUGR have a perinatal mortality rate which is intermediate between that of their appropriately grown peers by gestational age and their appropriately grown peers by weight (91).

Controlled long-term follow-up studies up to the age of seven years have generally not suggested any adverse long-term physical or developmental outcomes for children born following pre-eclamptic pregnancies when compared with children born to mothers with hypertension alone during pregnancy (94). There may, however, be some decrease in intellectual performance in infants with severe IUGR associated with pre-eclampsia (95). Data concerning outcome with respect to blood pressure in childhood have been conflicting. One large study has suggested no difference in blood pressure compared with controls at the age of seven years (96). Another smaller study in mid-late childhood, however, found children resulting from hypertensive pregnancies to have higher blood pressure than controls (97).

CHRONIC HYPERTENSION

Hypertension is a common finding, affecting up to 20% of the adult population, the prevalence increasing with age (98). Almost 2% of Australian women of child-bearing age have hypertension. Most of these women have essential hypertension. In all women with chronic hypertension an underlying cause for hypertension should be considered, as essential hypertension is at present a diagnosis of exclusion. Secondary hypertension may have implications for the pregnancy unrelated to the level of blood pressure. Causes of chronic hypertension in pregnancy include:

- Renal disease

  The most important disorders to be considered are glomerulonephritis, reflux nephropathy, and adult polycystic kidney disease. Assessment of the underlying prognosis of the renal disease and

the degree of renal impairment is important in determining risk in relation to pregnancy which may be much higher than that associated with the degree of hypertension (99, 100).

- Renal artery stenosis (usually fibromuscular dysplasia in young women)(101).

- Systemic disease with renal manifestations (such as diabetes mellitus, systemic lupus erythematosus). The extent of other organ involvement will also determine the degree of risk associated with pregnancy.

- Endocrine disorders including phaeochromocytoma and primary hyperaldosteronism. Phaeochromocytoma, though rare, has grave prognostic implications for both maternal and fetal welfare (102) and must be considered in all cases of hypertension in pregnancy.

- Coarctation of the aorta.

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

a) Significance of chronic hypertension in pregnancy

Many authors have shown a correlation between the severity of chronic hypertension and the eventual outcome of pregnancy (103-105). More severe underlying disease is known to be associated with an increased risk of episodes of severe hypertension, of superimposed pre-eclampsia (determined by the *de novo* development of proteinuria), of intrauterine fetal growth restriction and death, and of premature delivery. All of these risks are magnified if the pregnant woman, in addition to hypertension, suffers from renal disease with impairment of renal function. The incidence of these complications in women with severe disease may be reduced by control of hypertension (106-109).

b) Clinical features

A detailed history and physical examination are essential in seeking a possible cause for hypertension. A history of urinary infection, renal colic, haematuria, and/or proteinuria should be sought, and women questioned about their drug ingestion (including hormonal preparations) prior to the pregnancy. A history of rash, arthritis or diabetes may be pointers towards a systemic disease, while episodic palpitations, headache or flushing may point towards a phaeochromocytoma. Details of any family history of hypertension or renal disease should be ascertained.

Physical examination should include measurement of the blood pressure in both arms with the woman sitting. The femoral pulses should be palpated, and auscultation in the epigastrium and over the renal angles posteriorly may be of value in a search for renovascular disease. Evidence of any systemic disease should be recorded. Examination should also search for evidence of end-organ damage from hypertension. This will require examination of the praecordium for left ventricular hypertrophy, and optic fundoscopy.

c) Laboratory testing

Initial tests should be performed in all women with chronic hypertension. These are to assess the severity of the hypertension and seek possible causes. These should include:

- Urinalysis for protein, blood and glucose
- Microscopy of centrifuged urinary sediment for white and red blood cells (including red cell morphology) and for casts
- Mid stream urine culture
- 24 hour urine protein or spot urine protein/creatinine ratio, if proteinuria is detected on dipstick testing
- measurement of serum electrolytes, creatinine, uric acid and blood glucose
- full blood examination
- 24 hour urine for estimation of catecholamine excretion if phaeochromocytoma is considered possible

d) Preconception counselling

It is ideal for the woman with hypertension and/or renal disease to be seen and investigated, a diagnosis established and her underlying condition stabilised prior to planned pregnancy. This also allows discussion of the potential risks and estimation of the prognosis for a successful outcome.

Women with significant pre-pregnancy renal dysfunction (serum creatinine >0.12 mmol/L) should have the risks of perinatal morbidity/mortality and of deterioration of their underlying renal disease fully explained at this time (110).

The woman with chronic hypertension, whether essential or secondary, should be observed frequently during pregnancy by an obstetrician, and preferably also by a physician familiar with the physiological changes of pregnancy as well as with the management of hypertension in pregnancy and of pre-eclampsia which may supervene. Review by an obstetric anaesthetist prior to labour and delivery is also recommended, particularly where the woman is obese.

e) Clinical and laboratory monitoring

Statistically, the most likely event to complicate the pregnancy of a woman with chronic hypertension is pre-eclampsia, with or without intrauterine growth restriction. Early detection and appropriate management of these complications assume the highest priority from 20-24 weeks onwards. The following are the elements of a standard monitoring program:

- Record any symptoms and enquire about fetal movements at each visit.

- Physical examination at each visit should include measurement of blood pressure, urinalysis, assessment of uterine size. Ambulatory blood pressure measurement may have application in the diagnosis and management of women with chronic hypertension in pregnancy but its exact role remains to be defined.
- Obstetric ultrasound should be performed early for confirmation of gestational age, and repeated if there is a clinical indication thereafter.
- Biochemical and haematological tests as outlined above should be performed at the initial visit if not assessed recently and repeated if there is a clinical indication thereafter. In particular, women with underlying renal functional impairment should have these tests performed regularly . In other women, repeat estimation at 20-24 weeks, at 25-28 weeks and at 33-36 weeks gestation may be of value for the detection of superimposed pre-eclampsia.
- If urinalysis for protein is positive at any visit, a 24 hour urine protein estimation or measurement of spot urine protein/creatinine ratio should be performed.

Admission to hospital or a day assessment unit is recommended for women with systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg, or for those with less severe hypertension (systolic blood pressure 140-160 mmHg, diastolic blood pressure 90-100 mmHg) if accompanied by newly developed proteinuria, at any stage of pregnancy. This allows assessment of maternal and fetal welfare and facilitates discussion amongst all involved parties and permits the institution of pharmacological treatment under close supervision.

f) Drug therapy

The objectives of antihypertensive therapy are (i) to protect the mother from extreme hypertension, and (ii) to allow continuation of pregnancy, fetal growth and maturation. There is no absolute level of blood pressure above which treatment is mandatory, and below which it is unnecessary. Many clinicians use a diastolic blood pressure of 90 mmHg as a cut-off at which to recommend treatment. The therapeutic aim should be a blood pressure below this level, with avoidance of frank hypotension (i.e. to maintain systolic blood pressure 110-140 mmHg and diastolic blood pressure 80-90 mmHg). The benefits of antihypertensive medication are less clear for women with mild hypertension, and in this group antihypertensive medication has not been shown to reduce the incidence of superimposed pre-eclampsia (109).

Drugs which have been used for many years with safety include methyldopa, labetalol, clonidine, hydralazine, atenolol and oxprenolol. Amongst the beta blockers, there is evidence of differential effects. Maternal therapy with atenolol (a cardioselective drug with no intrinsic sympathomimetic activity) was associated with impairment of fetal growth in two studies (111, 112), especially when used prior to the third trimester, in distinction to the beneficial effect on fetal growth found with oxprenolol (a non-selective agent which does possess intrinsic sympathomimetic activity) (48). This highlights that drugs within a pharmacological class may not have identical effects and that the findings for one drug may not always be extrapolated to others within that group.

Of the calcium-channel blocking drugs nifedipine has been used extensively for acute lowering of blood pressure in later pregnancy (113) but, in large doses, it may inhibit uterine contractions (114).

Although use of nifedipine has not been recommended in early pregnancy, more recent data found no evidence of a major teratogenic risk of calcium channel blockers in early pregnancy (115).

g) Delivery

The decisions regarding timing, mode, location of and indications for delivery are complex and require careful consideration of the merits of each case, involving consultation between obstetric, medical, paediatric, midwifery and anaesthetic members of the team caring for the woman. Such decisions are determined by fetal and/or maternal factors.

i) Timing

The general principle is that pregnancy should be allowed to proceed as far as possible provided there is ongoing reassurance of maternal and fetal wellbeing. In many women with chronic hypertension blood pressure remains well controlled and no fetal or maternal problem mandating delivery arises. In these cases it is usual for the pregnancy to be allowed to continue with close supervision, aiming for vaginal delivery at term.

In other cases, and almost always in the setting of superimposed pre-eclampsia, early delivery is made necessary by the occurrence of one or more of a number of "endpoints" representing fetal or maternal compromise (see above).

In some cases, there is no proteinuria, no deficit in fetal growth or wellbeing, no maternal feature diagnostic of pre-eclampsia, and yet the blood pressure becomes impossible to control despite maximal doses of usual medications. In these cases, delivery may be necessary to protect against maternal cerebral haemorrhage, the indication being "failed blood pressure control".

ii) Mode of delivery

The vaginal route of delivery is favoured unless delivery is required urgently, eg for fetal distress, antepartum haemorrhage or severe pre-eclampsia.

Regional anaesthesia is extremely helpful in most cases and caesarean section should be performed under regional block unless there is maternal coagulopathy or other unusual factors. Despite the undoubted utility of epidural block, it does not provide complete blood pressure control and all usual monitoring and therapy of hypertension should be continued.

iii) Location

Delivery should be conducted in a centre with adequate facilities to care for the mother with severe hypertension or other features of severe pre-eclampsia, and for preterm infants.

h) Post partum

In many women with chronic hypertension, a period of instability follows delivery for 7-14 days, during which it may be extremely difficult to achieve adequate control of blood pressure. This is more pronounced in those who have sustained superimposed pre-eclampsia, but is also seen in those without. Typically the blood pressure will be exaggerated on the second to third day after delivery and be sustained for several days thereafter. It is often necessary to increase medication, or commence new antihypertensive therapy at that time. The risk of eclampsia remains up to about five days post partum after which it is extremely rare.

CHRONIC HYPERTENSION WITH SUPERIMPOSED PRE-ECLAMPSIA

As mentioned above, the chief risk of chronic hypertension in pregnancy is the development of superimposed pre-eclampsia in the second half of pregnancy which occurs in about 20% of women (104). This is of considerable concern as the risks to mother and fetus are greater than those of chronic hypertension alone.

Management of superimposed pre-eclampsia should be as outlined above.

FOLLOW UP POSTPARTUM

All women with hypertension during pregnancy, whether initially diagnosed as chronic hypertension or pre-eclampsia, should be reviewed postpartum. Early visits are necessary for reduction and/or cessation of antihypertensive drugs. Assessment of at least blood pressure, urinalysis and microscopy at 3-4 months postpartum allows any investigations necessary for arrival at a final diagnosis, and assessment of the impact which the index pregnancy has made on the underlying maternal disease process. It is also the time to discuss the woman's long-term prognosis and any potential problems for future pregnancies.

If hypertension persists postpartum, then further investigation is required (eg. IVP or renal ultrasound, catecholamines, plasma renin and aldosterone) if any secondary cause for hypertension is suspected. Persistent urine abnormalities at this stage should also be fully investigated, even in the absence of hypertension, as they usually reflect underlying renal disorders such as glomerulonephritis or reflux nephropathy.

Women who have experienced early-onset pre-eclampsia (especially 32 weeks gestation or earlier) should be assessed for the possibility of an underlying thrombophilic disorder such as antiphospholipid syndrome, activated protein C resistance or hyperhomocysteinaemia (87).

It is now clear that pre-eclampsia recurs in up to one half of affected women, depending on the gestation at delivery in the first pregnancy and the presence of predisposing factors. These women need specialist care in subsequent pregnancy. The clinical course in subsequent pregnancies tends to be milder with recurrence of pre-eclampsia at a later gestation (116).

Recurrent pre-eclampsia may be a forerunner of essential hypertension but pre-eclampsia in a first pregnancy followed by a normotensive pregnancy is not associated with an increase in the risk of cardiovascular disease in later life.

Pre-eclampsia cannot yet be prevented. Initial enthusiasm for low-dose aspirin has not been supported by the large randomised clinical trials (117). In the main, these tested very low doses of aspirin (60-80 mg daily) and controversy remains as to whether higher doses of aspirin (100-150 mg daily started early in pregnancy) might be beneficial in high risk women. Initial results of calcium supplementation in the prevention of pre-eclampsia from South American countries were encouraging (118), although the subsequent large prospective study from the United States did not show a benefit (119). The results of a more recent Australian study, however, did show a benefit (120) and the status of calcium supplementation in the prevention of pre-eclampsia remains uncertain (121). Other dietary manipulations likewise remain unproven. Education of both women and their carers is still vitally important in the early recognition of this serious disorder of pregnancy.

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