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SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

Guideline for the Management of Hypertensive Disorders of Pregnancy

2014

Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, Paech M. Said JM.

These are the recommendations of a multidisciplinary working party convened by the Society of Obstetric Medicine of Australia and New Zealand. They reflect current medical literature and the clinical experience of members of the working party.

CONTENTS

ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
AFV	Amniotic fluid volume
ALT	Alanine transaminase
AOR	Adjusted odds ratio
APPT	Activated partial thromboplastin time
AST	Aspartate transaminase
BW	Birth weight
CI	Confidence Interval
ECG	Electrocardiogram
FBC	Full blood count
FGR	Fetal growth restriction
HELLP	Haemolysis, elevated liver enzymes and low platelet syndrome
Hr	Hour(s)
INR	International normalised ratio
ISSHP	International Society for the Study of Hypertension in Pregnancy
IU	International units
IV	Intravenous
K1	Korotkoff sound 1
K2	Korotkoff sound 2
Kg	kilogram
LDA	Low dose aspirin
LDH	Lactate dehydrogenase
LFT	Liver function tests
mcg	microgram
mg	milligram
min	minute
mL	millilitre
NICU	Neonatal intensive care
NPV	Negative predictive value
PCR	Protein/creatinine ratio
PlGF	Placental growth factor
RDS	Respiratory distress syndrome
RR	Relative risk
SFlt1	soluble fms like tyrosine kinase-1
SGA	Small for gestational age
UEC	Urea, electrolytes and creatinine
umol/L	Micromole/litre
U/S	Ultrasound
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism

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1. Definition of hypertension in pregnancy

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

Hypertension in pregnancy is defined as:

Systolic blood pressure greater than or equal to 140 mmHg and/or

Diastolic blood pressure greater than or equal to 90 mmHg (Korotkoff 5)

These measurements should be confirmed by repeated readings over several hours. Elevations of both systolic and diastolic blood pressures have been associated with adverse maternal and fetal outcome and therefore both are important (1).There are several reasons to support the blood pressure readings above as diagnostic of hypertension in pregnancy:

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

Detecting a rise in blood pressure from ‘booking’ or preconception blood pressure (> 30/15 mmHg), rather than relying on an absolute value has in the past been considered useful in diagnosing preeclampsia in women who do not reach blood pressures of 140 or 90 mmHg. Available evidence does not support the notion that these women have an increased risk of adverse outcomes (4, 5). Nevertheless such a rise may be significant in some pregnant women, particularly in the presence of hyperuricaemia, proteinuria or a small for gestational age (SGA) infant and these women warrant closer monitoring.

Severe hypertension in pregnancy

This guideline recommends antihypertensive treatment for all pregnant women with blood pressure greater than or equal to 160mm Hg systolic or 110 mm Hg diastolic. Severe hypertension requiring urgent treatment is defined as a systolic blood pressure greater than or equal to 170 mmHg with or without diastolic blood pressure greater than or equal to 110 mmHg. This represents a level of blood pressure above which the risk of maternal morbidity and mortality is increased (6, 7). This degree of hypertension requires urgent assessment and management. Increasing evidence exists that cerebral perfusion pressure is altered in pregnant women making them more susceptible to cerebral haemorrhage, posterior reversible encephalopathy syndrome and hypertensive encephalopathy (8, 9). It is universally agreed that severe hypertension should be lowered promptly, albeit carefully, to prevent such complications (7, 10-13). [See Section 5]

2. Recording blood pressure in pregnancy

Accurate blood pressure measurement is important as the level of blood pressure may result in changes in clinical management (14). The woman should be seated comfortably with her legs resting on a flat surface and her arm resting at the level of her heart. In labour, the blood pressure may be measured in lateral recumbency. Supine posture should be avoided because of the supine hypotension syndrome. The variation in blood pressure between arms is usually less than 10 mmHg, with 8% and 2% of pregnant women having an inter-arm difference of at least 10 mm Hg for systolic and diastolic blood pressure, respectively (15).

The systolic blood pressure is accepted as the first sound heard (K1) and the diastolic blood pressure the disappearance of sounds completely (K5) (16). Where K5 is absent, K4 (muffling) should be accepted. Correct cuff size is important for accurate blood pressure recording. A large cuff with an inflatable bladder covering 80% of the arm circumference should be used if the upper arm circumference is greater than 33 cm but less than 44 cm and a thigh cuff used if the upper arm circumference is greater than 44 cm (14, 17). This helps to minimise over-diagnosis of hypertension during pregnancy. The rate of deflation of the cuff should be $\leq$2 mm per second to avoid underestimating systolic blood pressure (18).

Measurement Devices

Mercury sphygmomanometers remain the gold standard for measurement of blood pressure in pregnancy, however, occupational health concerns are limiting their availability. Self initiated home blood pressure monitors have provided major advantages for treatment and diagnosis of hypertension in the general community and are now widely used by both pregnant women and their clinicians. While automated devices may give similar mean blood pressure values to those obtained with mercury sphygmomanometry, there is wide intra-individual error and their accuracy may be further compromised in preeclamptic women (19-21). Only a few automated blood pressure monitors (Microlife WatchBP Home, Microlife 3BTO-A and Omron T9P have been validated for use in normotensive or mildly hypertensive pregnant women (22-24). In women with preeclampsia, especially those with severe hypertension, the accuracy of both Microlife 3BTO-A and Omron M7 declined and these devices cannot be recommended for use in preeclampsia (25). Nonmercury auditory sphygmomanometers present an option with appropriately trained observers (26). Aneroid sphygmomanometers may be used but are also prone to error. Each unit should maintain a mercury sphygmomanometer for validation of automated and aneroid devices. Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions as recommended by the British Hypertension Society Society (27) To establish the role of automated blood pressure monitors in hypertensive complications in pregnancy requires further studies comparing the impact

of blood pressure measurement with automated devices to mercury sphygmomanometers on important clinical outcomes (28, 29).

Twenty four hour Ambulatory Blood Pressure Monitoring (ABPM)

Normal blood pressure ranges for values recorded by ABPM have been established for different stages of pregnancy (30). The major role of ABPM is in identifying women with white coat hypertension, thereby avoiding inappropriate intervention (31). ABPM is useful in the evaluation of early hypertension (before 20 weeks gestation) where approximately one third of these women will be shown to have "white coat" or "office" hypertension (32). About half of these women with white coat hypertension will not require antihypertensive medication in pregnancy, while the other half will develop true hypertension (ABPM confirmed). ABPM is less useful in screening for white coat hypertension in the second half of pregnancy (33).

Twenty four hour ABPM has poor sensitivity and specificity when used to identify women at risk of developing hypertension later in pregnancy (33). In women with hypertensive disorders in pregnancy, ABPM has modest prognostic value in predicting adverse outcomes but further research is necessary to define its role in clinical management of hypertensive disorders in pregnancy.

3. Classification of hypertensive disorders in pregnancy

This classification of the hypertensive disorders in pregnancy reflects the pathophysiology of the constituent conditions as well as the risks and potential outcomes for both mother and baby. The following (or very similar) clinical classification has been adopted by numerous National and International bodies, differing predominantly in whether they require proteinuria or not for the diagnosis of preeclampsia (11, 13, 34, 35). Internationally, the latest ISSHP guideline no longer requires proteinuria for the diagnosis of preeclampsia, leaving only the British NICE guideline with this requirement (13, 35).

The classification is as follows:

- Preeclampsia – eclampsia
- Gestational hypertension
- Chronic hypertension
  - -essential
  - -secondary
  - -white coat
- Preeclampsia superimposed on chronic hypertension

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

A diagnosis of preeclampsia can be made when hypertension arises after 20 weeks gestation [Note b] and is accompanied by one or more of the following signs of organ involvement:

Renal involvement

Significant proteinuria – a spot urine protein/creatinine ratio ≥ 30mg/mmol [Note c]
Serum or plasma creatinine > 90 μmol/L [Note d]
Oliguria: <80mL/4 hr [Note e]
(Urate is not included as a diagnostic feature [Note f])

Haematological involvement

Thrombocytopenia <100,000 /μL [Note g]
Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600mIU/L, decreased haptoglobin
Disseminated intravascular coagulation [Note h]

Liver involvement

Raised serum transaminases [Note i]
Severe epigastric and/or right upper quadrant pain.

Neurological involvement

Convulsions (eclampsia)
Hypereflexia with sustained clonus
Persistent, new headache
Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm)
Stroke

Pulmonary oedema

Fetal growth restriction (FGR) [Note j]

Controversies in classifying the severity of preeclampsia

A number of features of preeclampsia are recognised to significantly increase the risk of adverse maternal and fetal outcomes and are sometimes used to classify severe preeclampsia.(12, 13, 34, 36). The natural history of preeclampsia is to progress at an unpredictable rate, at least until delivery, and therefore all women with preeclampsia should be closely monitored.

The classification of severe preeclampsia would ideally allow the identification of those women and babies at increased risk of adverse maternal/fetal outcomes and/or requiring more intensive monitoring and/or treatment. A number of classification systems and surveys have attempted to identify which features are predictive. One study reported that features that had previously been recommended as indicators of severe disease were neither sensitive nor specific in identifying women and/or babies at particular risk (37). The recent ISSHP statement suggested there was general consensus that factors determining severity include difficulty in controlling blood pressure and deteriorating clinical condition including HELLP syndrome, impending eclampsia, worsening thrombocytopenia or worsening fetal growth restriction while there is less concern regarding increasing proteinuria (12).

Alterations in circulating angiogenic factors [increased soluble fms like tyrosine kinase-1 (sFlt1) or soluble endoglin and reduced placental growth factor (PlGF)] are pathophysiologically important in the development of preeclampsia and may have a potential role in diagnosis (38). Changes in these angiogenic factors are detectable both prior to and at the time of onset of hypertension in women with preeclampsia. Measurement of PlGF alone, or in combination with sFlt1, are currently not part of the classification of hypertensive disorders of pregnancy (see Section 3).

NOTES

a. Other rare disorders may present with some of the features of preeclampsia (22). Disorders such as acute fatty liver of pregnancy, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, exacerbation of systemic lupus erythaematosus or cholecystitis may need to be excluded.

b. Rarely preeclampsia presents before 20 weeks gestation; usually in the presence of a predisposing factor such as hydatidiform mole, multiple pregnancy, fetal triploidy, severe renal disease or antiphospholipid antibody syndrome.

c. The measurement and interpretation of proteinuria in hypertensive disorders of pregnancy has been recently reviewed (39, 40). Dipstick testing is not accurate to confirm or exclude significant proteinuria (≥300mg/24 hours): sensitivities of 22-82% have been reported (41-44). This is improved slightly with automated dipstick testing but even this will miss more than half the patients with significant proteinuria (45, 46). The presence of 2+ or 3+ proteinuria or repeated +1 dipstick testing increases both sensitivity and specificity and, therefore, should be assumed to represent significant proteinuria until proven otherwise by confirmatory tests.
Twenty four hour urine protein has been the historic gold standard for quantifying proteinuria in pregnancy although its accuracy is affected by numerous factors such as adequacy and accuracy of collection and variations in protein excretion.

A spot urine protein/creatinine cut-off level of 30 mg/mmol equates to a 24-h urine protein >300 mg per day and at this level has adequate sensitivity and specificity to be used as a 'rule out' value below which true proteinuria is unlikely to be present (47). This is the recommended method and cut-off for diagnosing proteinuria in pregnancy.

In practise, dipstick testing is simple, cheap and an appropriate screening test but spot urine PCR is recommended for confirmation or exclusion of proteinuria when preeclampsia is suspected (47).

In women with underlying renal disease, particularly with pre-existing hypertension, the interpretation of proteinuria is difficult and preeclampsia should not be diagnosed until other features are present.

d. Serum/plasma creatinine usually falls in normal pregnancy and levels even at the upper end of the normal range (70-100 umol/L) may indicate impaired renal function. Other guidelines have used cut-offs up to >100-110umol/L to indicate renal impairment in preeclampsia. (10, 11, 13, 39). Serum/plasma creatinine (along with other parameters) is an indicator of adverse maternal outcome in preeclampsia particularly in the presence of proteinuria (36).

e. Oliguria is generally defined as urine output <500mL/24 hrs. By the time the pregnant preeclamptic women has been observed for 24 hrs, significant renal impairment may have occurred; hence this guideline recommends observation of urinary output over 4 hrs.

Intrapartum and in the immediate postpartum period, oliguria is common and physiological and does not require fluid therapy unless the serum/plasma creatinine is rising.

f. Hyperuricemia is a common but not diagnostic feature of preeclampsia. The literature regarding uric acid as a predictor of maternal and/or fetal complications in preeclampsia is conflicting although a recent meta-analysis did suggest its usefulness in the management of preeclampsia (48). It is important to use gestational corrected normal ranges which may correlate better with adverse events (49).

Table 1. Upper limits for uric acid (based on mean+2SD) at different gestational ages

Gestation (wks)	24	32	36	38
Uric acid (mmol/L)	0.28	0.32	0.34	0.38

g. The platelet count normally decreases in pregnancy. A platelet count of <100,000/μL is seen in 4.5% of women with proteinuric preeclampsia and 9.9% with non-proteinuric preeclampsia and only 1% of normal pregnant women (50, 51).

h. Coagulation studies are not indicated if the platelet count is normal (52).

i. HELLP syndrome represents a subset of women with severe preeclampsia characterised by **ha**emolysis, raised **l**iver enzymes (transaminases) and **l**ow **p**latelets with or without other preeclamptic features. Often only two of the three components are recognisable (53).

j. FGR is diagnosed when a fetus fails to achieve its growth potential *in utero.* It is usually (although not always) associated with a small for gestational age (SGA) fetus and is often associated with features suggestive of placental disease including abnormal umbilical artery Dopplers or oligohydramnios (in the absence of alternate diagnoses for such changes).
In women with chronic hypertension, the incidence of SGA is increased (see Section 9). In these women, evidence of fetal effects of pre-eclampsia requires the presence of oligohydramnios or abnormal uterine artery Doppler flows. SGA alone should not be considered as a criteria for superimposed preeclampsia.

Gestational Hypertension

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

Gestational hypertension near term is associated with little increase in the risk of adverse pregnancy outcomes (54). The earlier the gestation at presentation and the more severe the hypertension, the higher is the likelihood that the woman with gestational hypertension will progress to develop preeclampsia or an adverse pregnancy outcome (55, 56). Severe hypertension (≥170/110mmHg) is associated with increased risk of adverse outcomes in pregnancy (6, 7, 55).

Chronic Hypertension

This category includes essential hypertension as well as hypertension secondary to a range of conditions. *Essential hypertension* is defined by a blood pressure greater than or equal to 140 mmHg systolic and/or 90mmHg diastolic confirmed before pregnancy or before 20 completed weeks gestation without a known cause. It may also be diagnosed in women presenting early in pregnancy taking antihypertensive medications where no secondary cause for hypertension has been determined. Some women with apparent essential hypertension may have white coat hypertension (raised blood pressure in the presence of a clinical attendant but normal blood pressure otherwise as assessed by ambulatory or home blood pressure monitoring). These women appear to have a lower risk of superimposed preeclampsia than women with true essential hypertension but are still at an increased risk compared with normotensive women (32).

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

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

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

Preeclampsia superimposed on chronic hypertension

Pre-existing hypertension is a strong risk factor for the development of preeclampsia (57, 58). Superimposed preeclampsia is diagnosed when a woman with chronic hypertension develops one or more of the systemic features of preeclampsia after 20 weeks gestation. Worsening or accelerated hypertension should increase surveillance for preeclampsia but is not diagnostic. Similarly, SGA occurs more frequently in women with chronic hypertension and evidence of fetal effect other than SGA eg. oligohydramnios or abnormal uterine artery Doppler flows is required to diagnose superimposed preeclampsia

In women with pre-existing proteinuria, the diagnosis of superimposed preeclampsia is often difficult as pre-existing proteinuria normally increases during pregnancy. In such women substantial increases in proteinuria and hypertension should raise suspicion of preeclampsia and therefore justifies closer surveillance but the diagnosis is not secure without the development of other maternal systemic features or fetal effects with or without SGA ie the presence of oligohydramnios or abnormal uterine artery Doppler flows.

4. Investigation of new onset hypertension after 20 weeks gestation

Any woman presenting with new hypertension after 20 weeks gestation should be assessed for signs and symptoms of preeclampsia. Initially, assessment and management in a day assessment unit may be appropriate. If features of preeclampsia are detected, admission to hospital is indicated. The presence of severe hypertension, headache, epigastric pain, oliguria or nausea and vomiting are ominous signs which should lead to urgent admission and management, as should any concern about fetal wellbeing (59, 60).

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

- Spot urine PCR
- Full blood count
- Creatinine, electrolytes, urate
- Liver function tests
- Ultrasound assessment of fetal growth, amniotic fluid volume and umbilical artery Doppler assessment.
- The clinical utility of measuring PlGF alone or in combination with sFlt1, remains unclear (61, 62). A recent study has demonstrated that among women with suspected preeclampsia before 35 weeks gestation, a low plasma PlGF accurately identified those who are at high risk of requiring delivery within 14 days [sensitivity 0.96; CI 0.89-0.99 and NPV 0.98; CI 0.93-0.995] (63). Further research is required before implementing this prognostic test into routine clinical practice.

NOTES

- Blood test abnormalities should be interpreted using pregnancy-specific ranges, some of which are gestation dependent.
- If features of preeclampsia are present, additional investigations should include:
    - Urinalysis for protein and urine microscopy on a carefully collected mid-stream urine sample.
    - If there is thrombocytopenia or a falling hemoglobin, investigations for disseminated intravascular coagulation and/or haemolysis (coagulation studies, blood film, LDH, fibrinogen) are indicated.
- Patients with severe, early onset preeclampsia warrant investigation for associated conditions e.g. systemic lupus erythaematosus, underlying renal disease or antiphospholipid syndrome. The timing of these investigations will be guided by the clinical features.
- Although a very rare disorder, undiagnosed phaeochromocytoma in pregnancy is potentially fatal and may present as preeclampsia (64, 65) . In the presence of very labile or severe hypertension, measurement of fasting plasma free metanephrines/normetanephrines or 24 hour urinary catecholamines should be undertaken.
- Amongst women referred for assessment of new onset hypertension, a number will have normal blood pressure and investigations. These women are considered to have transient or labile hypertension. Repeat assessment should be arranged within 3-7 days as some of these women will subsequently develop preeclampsia (66).

Subsequent investigation and management will be based on the results of ongoing blood pressure measurement and these investigations (Tables 2 and 7) (67-69).

Ongoing investigation of women with hypertension in pregnancy

At each assessment following the detection of hypertension in pregnancy, the clinician should systematically review the woman's symptoms, examination, laboratory investigations and fetal wellbeing.

Further laboratory assessment of women with hypertension in pregnancy should be based on the following recommendations: Table 2.

Table 2: Ongoing investigation of women with hypertension in pregnancy

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

*Urinalysis by dipstick followed by spot urine PCR if ≥1+ proteinuria (see Section 3.) Once significant proteinuria has been detected, there is no established role for serial testing as the severity or progress of proteinuria should not alter management decisions.
** FBC, Electrolytes and creatinine, LFT and coagulation studies only if indicated

5. Management of preeclampsia and gestational hypertension

Preeclampsia is a progressive disorder that will inevitably worsen if pregnancy continues. Current therapy does not ameliorate the placental pathology nor alter the pathophysiology or natural history of preeclampsia. Delivery is the definitive management and is followed by resolution, generally over a few days but sometimes much longer. Obstetric consultation is mandatory in all women with severe preeclampsia. In those women with preeclampsia presenting at extreme preterm gestations (< 32 weeks), consultation with a tertiary institute should be arranged since the neonate may require intensive care after delivery. Every effort should be made to transfer a woman with very preterm preeclampsia to a unit with appropriate neonatal and maternal care facilities prior to delivery.

Timing of delivery

Timing of delivery is dependent upon the severity of the maternal disease and the gestation at which the preeclampsia or gestational hypertension presents (Table 3). Immediate management refers to delivery planned within 48 hours, usually after blood pressure stabilisation and corticosteroid administration to accelerate fetal pulmonary maturity. Expectant management refers to prolongation of the pregnancy beyond these 48 hours with maternal and fetal monitoring.

Table 3. Timing of delivery and gestation of presentation of preeclampsia

Gestation at onset	**Previable <23^{6} weeks**	**24-31^{6} weeks**	**32-36^{6}**	**37+0 onwards**
Delivery plan	Consult with Tertiary institution: likely to need termination of pregnancy or extreme preterm delivery. High risk patient	Consult and transfer to Tertiary institution: likely to need preterm delivery. Aim to prolong pregnancy where possible	Aim to prolong pregnancy where possible, deliver in institution with appropriate Paediatric care	Plan delivery on best day in best way

Fetal mortality and morbidity is strongly associated with gestational age at delivery. Prolongation of pregnancy in the presence of preeclampsia carries no benefit for the mother but is desirable at early gestations to improve the fetal prognosis (70-72). When the onset of preeclampsia occurs at a pre-viable gestation(i.e.< 24 weeks' gestation) there is little to be gained from prolonging the pregnancy with serious maternal morbidity rates of 65-71% and high perinatal mortality rates of greater than 80% (73-75). The onus remains on the clinician to advise termination of pregnancy, particularly in resource poor settings (76).

The management of women with preeclampsia below 32-34 weeks gestation should be restricted to those centres with appropriate experience and expertise and appropriate neonatal intensive care facilities. Clear "endpoints" for delivery should be defined for each patient (Table 4), such that the decision to terminate the pregnancy is based on agreed criteria. In many cases, the timing of delivery will be based upon a number of factors, maternal and/or fetal rather than a single absolute indication for delivery.

Table 4. Indications for delivery in women with preeclampsia or gestational hypertension

Maternal	Fetal
Gestational age ≥ 37 weeks	Placental abruption
Inability to control hypertension	Severe FGR
Deteriorating platelet count	Non-reassuring fetal status
Intravascular haemolysis	
Deteriorating liver function	
Deteriorating renal function	
Persistent neurological symptoms	
Persistent epigastric pain, nausea or vomiting with abnormal LFTs	
Pulmonary edema	

In cases of preterm preeclampsia before 34 weeks, delivery should be delayed for at least 24-48 hours, if maternal and fetal status permit, to allow fetal benefit from antenatal corticosteroids administered for lung maturation. Additionally, at early gestations, magnesium sulphate administered antenatally may provide neonatal neuroprotection (77). Unfortunately up to 40% of women presenting with preeclampsia at less than 34 weeks gestation are ineligible for expectant care (78). A number of trials have shown that 25-41% of women managed expectantly with preeclampsia will develop severe morbidity including HELLP syndrome, abruption, pulmonary edema and eclampsia and that the mean duration of prolongation is less than 12 days (70, 79-81). The lower the gestation, the less the mean duration of prolongation (72).

Continuation of pregnancy carries fetal risk and some stillbirths will occur despite careful monitoring (82). These trials have excluded women with the HELLP variant of preeclampsia and with other evidence of severe morbidity.

In the presence of HELLP syndrome, expectant management is harmful with a 6.3% incidence of maternal death and an increased risk of placental abruption (78). In such cases, delivery should be planned as soon as feasible.

Preeclampsia presenting in the late preterm period, $34\text{-}36^{6}$ weeks gestation, is associated with increasing risk of SGA neonates with a higher risk of delivery via Caesarean section, respiratory distress syndrome and longer neonatal intensive care admissions (83, 84). Therefore, antenatal

steroid prophylaxis may be beneficial in this group.

At mature gestational age, delivery should not be delayed in the case of severe preeclampsia. Even so, it is important to control severe hypertension and other maternal derangements before subjecting the woman to the stresses of delivery.

The HYPITAT study was a multicentre, unblinded study comparing outcomes after induction of labour and expectant monitoring in pregnant women with gestational hypertension or mild preeclampsia between 36 and 41 weeks' gestation (85). The study reported that immediate induction of labour was associated with a reduction in the incidence of severe hypertension, without an increase in the Caesarean section rate. No significant difference was seen in important clinical morbidity outcomes such as HELLP, thromboembolism, eclampsia or placental abruption and costs were not increased (86, 87). This management approach was beneficial even in those women whose cervix was unfavourable for induction of labour (88).

Critics of this active approach to milder disease suggest this is unnecessary intervention in a group of women and babies with generally good outcomes. In this group, there was no difference in health-related quality of life up to 6 months postpartum between expectant or immediate management (89-91). We await the publication of two recently completed randomised trials to inform this debate. (HYPITAT-II and Mild Preeclampsia Near Term: Deliver or Deliberate. In women with gestational hypertension who are at low risk of adverse outcomes, an expectant management approach beyond 37 weeks should be considered (13).

A team approach, involving obstetrician, midwife, neonatologist, anaesthetist and physician provides the best chance of achieving a successful outcome for mother and baby. Regular and ongoing reassessment of both the maternal and fetal condition is required. Careful daily assessment for clinical symptoms and signs should be complemented by regular blood and urine tests as indicated (Table 2).

The only controlled studies of bed rest for preeclampsia have shown no significant maternal or fetal benefit (92). However, admission to hospital allows close supervision of both mother and fetus as progress of the disorder is unpredictable. Outpatient monitoring may be appropriate in milder cases after a period of initial observation.

Treatment for mild-moderate hypertension

Antihypertensive treatment should be commenced in all women with a systolic blood pressure of greater than or equal to 160mm Hg or a diastolic blood pressure greater than or equal to 110 mm Hg because of the risk of intracerebral haemorrhage and eclampsia(6, 7, 11, 13).
There is controversy regarding the need to treat mild to moderate hypertension in women with preeclampsia. Antihypertensive therapy does not prevent preeclampsia (RR 0.99; 95% CI 0.84–1.18) or the associated adverse perinatal outcomes, but it decreases by half the incidence of development of severe hypertension among women with mild hypertension (RR 0.52; 95% CI 0.41–0.64) (24 trials, 2815 women) (93). Approximately 10 women need to be treated with an antihypertensive drug to prevent an episode of severe hypertension (93).

Uncontrolled hypertension is a frequent trigger for delivery and control of hypertension may allow prolongation of pregnancy. In addition, as summarised in the Cochrane review above, it is possible that treatment of even mild-moderate hypertension may lead to a clinically relevant reduction in the risk of preeclampsia and fetal or neonatal death, particularly early pregnancy loss (93).

Arguments against treatment include that there is little risk to the mother in having relatively mild hypertension for a short time (usually only a few days or at the most weeks), that fetal perfusion is dependent upon adequate maternal blood pressure and that lowering blood pressure suppresses an

important sign of the severity or progression of preeclampsia. There is no clear effect of antihypertensive treatment on the risk of neonatal death, preterm birth or SGA, placental abruption, Caesarean section or admission to the neonatal nursery (93). A large randomised trial of "tight" versus "less tight" control of blood pressure in women with non-severe high blood pressure in pregnancy has been completed and results are awaited [http://www.utoronto.ca/cmicr/chips].

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

Antihypertensive therapy

In terms of lowering blood pressure in preeclampsia, a number of drugs have demonstrated safety and efficacy (Table 5). First line drugs include methyldopa, labetalol and oxprenolol (55-57). Second line agents are hydralazine, nifedipine and prazosin (58-61). These same agents may be used for treating gestational or chronic hypertension.

Table 5. Guidelines for selecting antihypertensive drug treatment in pregnancy

Drug	**Dose**	**Action**	**Contraindications**	**Practise Points**
Methyl dopa	250-750mg tds	Central	Depression	Slow onset of action over 24 hours, dry mouth, sedation, depression, blurred vision
Clonidine	75-300µg tds			Withdrawal effects: rebound hypertension
Labetalol	100-400mg q8h	β Blocker with mild alpha vasodilator effect	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling (labetalol only) which usually resolves within 24 hours
Oxprenolol	20-160 mg q8h	β Blocker with intrinsic sympathomimetic activity		
Nifedipine	20mg -60 mg slow release bd	Ca channel antagonist	Aortic stenosis	Severe headache in first 24 hours Flushing, tachycardia, peripheral oedema, constipation
Prazosin	0.5-5 mg q8h	α blocker		Orthostatic hypotension especially after first dose
Hydralazine	25-50 mg q8h	Vasodilator		Flushing, headache, nausea, lupus-like syndrome

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. Their use in the third trimester has been associated with fetal death and neonatal renal failure. All of the drugs in Table 4 along with enalapril, captopril and quinapril are considered compatible with breastfeeding (94) .

Treatment of severe hypertension

Sudden and severe increases in blood pressure may be the presenting feature of hypertensive disease in pregnancy, intrapartum or in the postnatal period. Blood pressure greater than or equal to 170mmHg systolic or 110mmHg diastolic constitute severe hypertension requiring urgent treatment. Whilst there is no controlled trial to determine how long severe hypertension may be left untreated, it is recommended that treatment be administered promptly aiming for a gradual and sustained lowering of blood pressure (10-13). A variety of medications have been used for the treatment of severe hypertension in pregnancy (Table 6). There is concern that a precipitous fall in blood pressure after antihypertensive treatment, particularly intravenous hydralazine, may impair placental perfusion resulting in fetal distress. This can be prevented by co-administration of a small bolus of fluid e.g. normal saline 250mL, at the time of administration of antihypertensive therapy (95). Continuous CTG monitoring should be considered in these situations, particularly when there is evidence of existing fetal compromise. However, fetal distress as a result of such treatment is rare (96).

The concurrent administration of longer acting oral agents (see Table 5) will achieve a more sustained blood pressure lowering effect.

A recent systematic review of the literature regarding antihypertensive agents used for the management of severe hypertension acknowledged that each medication had benefits and risks (97). Both intravenous and oral agents may be used to lower blood pressure depending on the clinical setting (13). Intravenous magnesium sulphate is not primarily an antihypertensive agent, and should not be used as such, although there may be a transient decrease in blood pressure after commencement (98).

Table 6: Acute blood pressure lowering for severe hypertension (99-103)

	Dose	**Route**	**Onset of Action**	**Adverse Effects**
Labetalol	20 -80mg Max 80mg	IV bolus over 2 min, Repeat every 10 mins prn	Maximal effect usually occurs within 5 minutes after each dose	Bradycardia: Hypotension Fetal Bradycardia
Nifedipine	10-20MG tablet Max 40mg	ORAL	30-45 minutes Repeat after 45 minutes	Headache Flushing
Hydralazine	10mg (First dose 5mg if fetal compromise]) Max 30mg	IV bolus, repeat every 20mins	20 mins	Flushing Headache Nausea Hypotension Tachycardia
Diazoxide	15-45mg Max 300mg	IV rapid bolus	3-5 mins, repeat after 5 mins	Flushing Warmth along Injection site Hypotension

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

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

It is recommended that protocols for the management of severe hypertension should be readily accessible in all obstetric units.

Thomboprophylaxis

Large population studies have confirmed that preeclampsia is an independent risk factor for venous thromboembolism (VTE) occurring in pregnancy or the puerperium. Some studies report increased risk both during pregnancy and postpartum while others only report an increased risk in the postpartum period [AOR range between 2.8 and 16] (104-107). The presence of additional risk factors for VTE, including nephrotic range proteinuria, increases this risk further (108-114).

All women should undergo risk factor assessment for VTE in early pregnancy (108). This assessment should be repeated if a pregnant woman is admitted to hospital or develops a complication. Hospitalised women are generally less mobile and mechanical thromboprophylaxis such as graduated compression stocking should be considered (115). Preeclampsia is considered a major risk factor for VTE and pharmacological prophylaxis is indicated in a woman who has 2 major or 1 major and 2 minor risk factors as recommended in the Australian guidelines, unless there are surgical contraindications (108). Each maternity unit should have clear protocols regarding timing of thromboprophylaxis in relation to insertion and withdrawal of epidural and spinal canulae (108, 109, 116).

Fluid management

Although maternal plasma volume is often reduced in women with preeclampsia, there is no maternal or fetal benefit to maintenance fluid therapy (117). The choice between colloid and crystalloid remains controversial as previous trials generally excluded pregnant women. (118). Administration of fluid at a rate greater than normal requirements should only be considered for:

1. Women with severe preeclampsia immediately prior to parenteral hydralazine, regional anaesthesia or immediate delivery: 250 mL bolus (95, 119).
2. Initial management in women with oliguria where there is a suspected or confirmed deficit in intravascular volume: 300 mL challenge, repeat with careful assessment (119).

As vascular permeability is increased in women with preeclampsia, administration of large volumes of intravenous fluid before or after delivery may cause pulmonary edema and worsen peripheral edema (120). This tendency is further aggravated by hypoalbuminemia. Appropriate blood product replacement is necessary when there has been haemorrhage, as in cases of placental abruption.

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

able to prevent this rare complication.

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

Haematological and hepatic manifestations

Thrombocytopenia is the commonest haematologic abnormality seen in preeclampsia; the lower limit of the normal platelet count in pregnancy is approximately $140x10^9$/L but as a mild reduction in platelet count may occur in normal pregnancy (gestational thrombocytopenia), the cut-off for an abnormal platelet count in preeclampsia is $100x10^9$/L. Serial monitoring of the platelet count is essential in preeclampsia as the count may fall rapidly (See Table 3). When thrombocytopenia is detected, recheck the platelet count more frequently ie at least daily or twice daily. A progressive decline in platelet count is an indication for delivery (Table 4).

The risk of peripartum bleeding complications is not significantly increased until the platelet count falls below $50x10^9$/L. Even so, there are concerns with central neuraxial anaesthetic and analgesic techniques at higher levels ($50\text{-}75x10^9$/L), and surgical bleeding may be increased even with moderate thrombocytopenia.

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

Intravascular haemolysis may occur and should be checked for with appropriate laboratory tests, FBC, blood film, LDH and haptoglobins, as this is an indication for expedient delivery.

Epigastric, right upper quadrant pain or even chest pain in a woman with preeclampsia often represents hepatic involvement (121). The pain responds poorly to analgesia but both the pain and associated increases in liver enzymes (AST, ALT) may subside (albeit temporarily) after blood pressure lowering, particularly with vasodilators. If the cause of epigastric or right upper quadrant pain is not clear, close ongoing assessment is required, with careful review of all indicators of maternal and fetal wellbeing (as above). Imaging of the liver and gallbladder is only indicated if other pathologies eg cholelithiasis, require exclusion.

The combination of haemolysis, elevated liver enzymes and low platelets has been coined HELLP syndrome (122). Whether HELLP syndrome is a separate entity or just a clinical syndrome of severe preeclampsia complications remains open, but from a clinical perspective should be managed as severe preeclampsia (123). The presence of "ELLP" (elevated liver enzymes with low platelets) occurs more frequently than HELLP (haemolysis, elevated liver enzymes and low platelets).

Steroid therapy (other than for fetal lung maturation) is not indicated for the management of thrombocytopenia or hepatic dysfunction in women with preeclampsia, even with HELLP syndrome (124, 125). These abnormalities recover spontaneously postpartum within a few days of delivery, without specific treatment (126-128). If abnormalities worsen or show no improvement after 72 hours post partum, differential diagnoses such as thrombotic thrombocytopenic purpura or antiphospholipid syndrome should be considered, and appropriate therapy instituted.

6. Eclampsia

A recent Australian study demonstrated that eclampsia remains rare in Australia (in singleton pregnancies 8.6/10,000) equivalent to 0.1% of all births (129). Classically, headache, visual disturbance or an altered level of consciousness are considered the symptoms of imminent eclampsia. However, there are no reliable clinical markers that predict eclampsia and conversely, the presence of neurological symptoms and/or signs is rarely associated with seizures (130). Seizures may occur antenatally, intra-partum or postnatally, usually within 24 hours of delivery but occasionally later. Hypertension and proteinuria may be absent prior to the seizure and not all women will have warning symptoms such as headache, visual disturbances or epigastric pain (131).

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

Management of eclampsia

Comprehensive protocols for the management of eclampsia (and severe hypertension) should be available in all appropriate areas.

There are four main aspects to care of the woman who sustains eclampsia.

1. Resuscitation
   These seizures are usually self-limiting. Resuscitation requires assuring a patent airway, oxygen by mask and institution of intravenous access. Intravenous diazepam (2mg/min to maximum of 10mg) or clonazepam (1-2mg over 2-5 mins) may be given whilst the magnesium sulphate is being prepared if the seizure is prolonged.

2. Prevention of further seizures
   Following appropriate resuscitation, treatment should be commenced with magnesium sulphate given as a 4g loading dose (diluted in normal saline over 15-20 minutes) followed by an infusion of (1-2g/hr, diluted in normal saline). Prediluted magnesium sulphate should be available in all appropriate areas for this purpose (4g/100ml normal saline). In the event of a further seizure, a further 2-4g of magnesium sulphate is given IV over 10 minutes. Magnesium sulphate is usually given as an intravenous loading dose although the intramuscular route is equally effective. Monitoring should include blood pressure, respiratory rate, urine output, oxygen saturation and deep tendon reflexes. Magnesium sulphate by infusion should continue for 24 hours after the last fit (132, 133). Serum magnesium levels do not need to be measured routinely unless renal function is compromised.

   Magnesium sulphate is excreted via the kidneys and extreme caution should be used in women with oliguria or renal impairment. Serum magnesium concentration should be closely monitored in this situation. Magnesium is not universally successful and the recurrence rate of seizures despite appropriate magnesium therapy is 10-15% (60).

3. Control of hypertension [See Section 3]
   Control of severe hypertension to levels below 160/100 mmHg is essential as the threshold for further seizures is lowered after eclampsia, likely in association with vasogenic brain edema. In addition, the danger of cerebral haemorrhage is real.

4. Delivery

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

Prevention of eclampsia in the woman with preeclampsia

The drug of choice for the prevention of eclampsia is magnesium sulphate, given as a 4g loading dose (diluted in normal saline) followed by an infusion of 1g/hour (133). Although there is good evidence for the efficacy of this therapy, the case for its routine administration in women with preeclampsia in countries with low maternal and perinatal mortality rates is less than compelling. In some units, the presence of symptoms or signs such as persistent headache, hypereflexia with clonus, evidence of liver involvement or severe hypertension are considered indications for prophylaxis with magnesium sulphate although these symptoms have poor positive and negative predictability for eclampsia (130). It is appropriate for individual units to determine their own protocols and monitor outcomes.

7. Fetal Surveillance

Adverse perinatal outcome is increased in women with all subcategories of hypertensive disease in pregnancy as compared to normotensive women (134, 135). This increase in adverse outcomes is greatest in those with early gestation at onset of disease, severe hypertension and/or chronic hypertension with superimposed preeclampsia and is predominantly related to an increase in the rate of FGR (134-137). Balancing the fetal risks of FGR with the neonatal risks of prematurity is particularly important in early onset disease (138).

Although fetal surveillance is commonly recommended and performed in women with hypertensive disease in pregnancy, there is no established consensus on how this should be performed (11, 13, 34, 139). A recent randomized controlled trial evaluating expectant management versus labour induction in women with hypertensive disease after 36 weeks included maternal reporting of fetal movements, electronic fetal monitoring and "ultrasound examination" as part of the protocol for expectantly managed pregnancies, but did not specify the nature or frequency of this monitoring. (85). The frequency, intensity, and modality of fetal evaluation will depend on individual pregnancy (maternal and fetal) characteristics. Individual obstetric units should devise their own protocols for monitoring the fetus in pregnancies complicated by hypertension. In compiling such protocols, the following issues should be considered.

1. Accurate dating of pregnancy is important for women with chronic hypertension or those at high risk of preeclampsia
2. Symphysis-fundal height measurement is a poor screening tool for detection of SGA (140). Therefore, ultrasound should be performed by an experienced operator to assess fetal size, amniotic fluid volume and umbilical artery Doppler flows in all women with hypertension in pregnancy. Assessing growth trends by serial ultrasound is recommended if pregnancy continues.
3. Umbilical artery Doppler flow is the only fetal surveillance modality that has been shown by systematic review to reduce the need for fetal interventions, improve neonatal outcome and predict adverse perinatal outcome (141, 142). Severe early onset SGA should be monitored at institutions experienced in advanced fetal Doppler waveform analysis. Absent or reversed end diastolic flow is unlikely to occur within 7-10 days after a normal umbilical artery Doppler waveform analysis. Umbilical artery Doppler flow studies have limited value after 36 weeks gestation.

4. Although numerous observational studies have suggested improved outcome in the high-risk pregnancy monitored using protocols that included Biophysical Profile, cardiotocography, and combinations of both, none of these has shown significant benefit in systematic reviews (143-147).
5. No fetal testing can predict an acute obstetric event such as placental abruption or cord accident
6. Fetal surveillance via a Day Assessment Unit is associated with good perinatal outcome in women with various obstetric complications, including women with well controlled hypertension (148, 149)
7. An appropriately grown fetus in the third trimester in women with well-controlled chronic hypertension without superimposed preeclampsia is associated generally with a good perinatal outcome. Fetal monitoring using methods other than continued surveillance of fetal growth and amniotic fluid volume in the third trimester is unlikely to be more successful in preventing perinatal mortality/morbidity.

Table 7 demonstrates commonly used International and National protocols for fetal surveillance in women with hypertensive disease in pregnancy where immediate delivery is deferred. None of these protocols has been tested in prospective, randomised trials; thus they are based only on the opinion and experience of the authors. As preeclampsia is an ever changing and unpredictable disease, for those women where expectant management is employed, the frequency and modality of fetal surveillance should be adjusted based on the current maternal and/or fetal condition. Each obstetric unit should develop an agreed institutional approach to fetal surveillance and/or fetal medicine referral.

Table 7. Protocol for fetal surveillance in women with hypertension in pregnancy

Hypertension	**Modality**	**Frequency**
Chronic hypertension	Early dating ultrasound U/S for fetal growth/AFV/Doppler	First trimester 3rd trimester: repeat as indicated
Gestational hypertension	U/S for fetal growth/AFV/Doppler	At time of diagnosis and 3-4 weekly
Preeclampsia	U/S for fetal growth/AFV/Doppler Cardiotocography	At time of diagnosis and 2-3 weekly Twice weekly or more frequently if indicated
Preeclampsia with FGR	Cardiotocography U/S for fetal /AFV/Doppler U/S for fetal growth	Twice weekly or more frequently if indicated On admission and weekly or more frequently if abnormalities in Doppler flow or amniotic fluid volume are detected. 2 weekly

AFV= assessment of amniotic fluid volume.

Antenatal Corticosteroid administration

Contrary to popular belief, accelerated fetal lung maturation does not occur in preeclampsia (149). A systematic review has shown that a single course of antenatal corticosteroid given to women expected to deliver preterm reduces the risk of neonatal death, respiratory distress syndrome (RDS), cerebrovascular haemorrhage, necrotizing enterocolitis, respiratory support, and intensive care admission (150). This systematic review showed that infants born to pregnancies complicated by hypertensive disease of pregnancy, treated with corticosteroids, had significantly reduced risk of neonatal death, RDS, and cerebrovascular haemorrhage. The optimal choice of steroid (Betamethasone or Dexamethasone), mode of administration or timing of dosage regime (12 hourly versus 24 hourly dosage) remains uncertain, and the advantages or disadvantages of these choices have not been specifically investigated in the setting of hypertensive diseases (151). There is insufficient evidence to support antenatal corticosteroids for those pregnancies that have reached 34 weeks gestation (150), however, a single randomized trial demonstrated a small benefit of antenatal corticosteroids when given to mothers undergoing a term (37 to 39 weeks gestation) elective Caesarean section and follow up of children enrolled in this study has not demonstrated any longer term adverse sequelae (152, 153). The use of antenatal steroids beyond 34 weeks should be considered based on individual patient circumstances (154). In women with hypertensive disorders of pregnancy undergoing planned Caesarean section after 34 weeks gestation, urgent delivery should not be delayed purely for the benefits of corticosteroid therapy.

The administration of further courses of corticosteroid in women who remain undelivered and still at risk of preterm birth after an initial course of corticosteroids remains controversial. Several studies have reported short term improvements in neonatal outcomes including respiratory distress, but these are not translated into improved short term childhood outcomes. (155, 156) Concerns also remain about potential longer term outcomes. Ongoing follow up studies are underway. If repeat doses of corticosteroids are considered necessary, the protocol described by Crowther et al should be employed (157-159).

Antenatal Magnesium Sulphate administration for fetal neuroprotection

There is now established Level I evidence that Magnesium sulphate should be administered to women requiring preterm delivery for the purposes of fetal neuroprotection (77). Maternally administered Magnesium sulphate has been shown to significantly reduce the risk of cerebral palsy (RR 0.69, 95% CI 0.54-0.87). The National Health and Medical Research Council endorsed Australian national guidelines recommend administration of Magnesium sulphate for all women at risk of preterm delivery prior to 30 weeks (160). In the setting of preeclampsia, Magnesium sulphate may be considered on maternal grounds as seizure prophylaxis (see Section 6), however strong consideration should be given to its use even in the setting of milder degrees of hypertensive disease where delivery is indicated prior to 30 weeks. There is less certain evidence concerning the benefits of administration beyond 30 weeks gestation but ongoing trials may help to clarify this.

8. Resolution of preeclampsia and gestational hypertension

After delivery, all clinical and laboratory derangements of preeclampsia recover, but there is often a delay of several days, and sometimes longer, in return to normality (161). On the first day or two after delivery, liver enzyme elevations and thrombocytopenia will often worsen before they improve (162). Non-steroidal anti-inflammatory drugs are therefore contraindicated as they may adversely affect hypertension, renal function and platelet function. Hypertension may persist for days, weeks or even up to three months and will require monitoring and slow withdrawal of antihypertensive therapy. Resolution is still assured if the diagnosis was preeclampsia and there is no other underlying medical disorder.

The woman and her family are often overwhelmed and distressed from their experience and appropriate management post partum should include psychological and family support. Engaged patient advocacy organizations include the Australian Action on Pre-eclampsia (AAPEC) and New Zealand Action on Pre-eclampsia (NZ APEC) groups.

All women who develop preeclampsia and gestational hypertension are at risk of these disorders in future pregnancies and should be referred for review by a clinician with expertise in the management of hypertensive disorders of pregnancy before embarking upon another pregnancy. [See Sections 11 and 12]

9. Chronic hypertension in pregnancy

A substantial number of pregnancies (0.2–5%) are complicated by pre-existing hypertension and the prevalence in western societies is likely to increase due to the advancing age of the prospective mother at conception and the rising tide of obesity (163-165). The diagnosis can be difficult in women whose blood pressure before pregnancy or early in the first trimester is unknown as the physiological fall in blood pressure in the second trimester can obscure pre-existing hypertension and very rarely, preeclampsia can present before 20 weeks' gestation.

Pregnancy outcome

Adverse outcomes of pregnancy are more common in women with pre-existing hypertension. In one prospective study of women with chronic hypertension, the risk of superimposed preeclampsia was associated with a previous history of preeclampsia (AOR 1.95 [95%CI 1.25-3.04]) or the presence of one or more other risk factors, such as obesity or diabetes (58). Smoking was also associated with an increased AOR for superimposed preeclampsia (1.82 [1.02-3.04]). Table 8 shows the rate of complications in this cohort of 822 women with chronic hypertension, with and without superimposed preeclampsia. Absolute blood pressure levels in pregnancy do not appear to correlate with poor outcome except when hypertension is uncontrolled in the first trimester, at which time both fetal and maternal morbidity and mortality are markedly increased (166).

Table 8 Outcomes of pregnancy in women with chronic hypertension (58)

Outcome	**All**	**No preeclampsia**	**With superimposed preeclampsia**
Preeclampsia	22%*		
Preeclampsia <34/40	9.7%		
Preterm birth <37/40		15%	51%
Preterm birth <34/40		7%	23%
Caesarean section	50%	44%	70%
SGA	27%	21%	48%
BW <2.5kg	20%	13%	44%
Need for additional antihypertensive medication	Oral 24% Parental 4%		

LDA: low-dose aspirin;* On LDA: 28%; no LDA: 21% [NS] SGA: <10th centile using customised growth charts, BW = birth weight,

White coat hypertension in early pregnancy is common and not necessarily a benign condition, as 40% of these women progress to persistent hypertension after 20 weeks' (gestational hypertension) and 8% to preeclampsia (32, 167). The risks of severe hypertension, preterm delivery and NICU admission appear to be intermediate between normotension and either pre-existing or gestational hypertension.

The significance of masked hypertension (measured blood pressure of < 140/90 mmHg and ambulatory blood pressure of ≥ 135/85mm Hg) is uncertain. Its incidence appears to be relatively common, at least 20%, in patients presenting as hypertensive in early pregnancy. Outcomes in patients presenting after 20 weeks' appear to equate with gestational hypertension patients (168). The woman with chronic hypertension, whether essential or secondary, should be observed frequently during the pregnancy by an obstetrician and by a physician familiar with the management of hypertension in pregnancy. The frequency of review will be determined by such factors as how successfully blood pressure is controlled, the number of agents used, associated disorders (e.g. renal disease, proteinuria) and by the gestation. Vigilance is also required for the woman with white-coat hypertension.

Investigation

More than 95% of women with pre-existing hypertension will have essential hypertension; however a detailed history, careful examination, and relevant laboratory tests are essential to ascertain both potential secondary causes or end-organ damage (169). This should preferably be performed prior to pregnancy, but if this is not possible, investigations should concentrate on those conditions likely to affect pregnancy management or outcome.
Common baseline tests include:

Urine

- Urinalysis for protein. If proteinuria is evident on dipstick analysis, a 'spot' urine protein:creatinine ratio should be obtained
- Microscopy of centrifuged urinary sediment for white and red blood cells (including red cell morphology) and for casts
- Mid-stream urine culture

Blood

- Serum electrolytes and creatinine, uric acid and full blood examination, and fasting blood glucose
- ECG
- Renal ultrasound
- Screening for phaeochromocytoma if indicated: fasting free plasma metanephrines and normetanephrines

NOTE

- Plasma and urinary aldosterone, cortisol and renin measurements are unable to be interpreted with confidence in pregnancy. Expert advice should be sought if Conn's or Cushing's syndrome is suspected.
- End-organ effects of hypertension (retinal assessment, albuminuria, renal function and echocardiogram) should be considered and sought, particularly when hypertension is severe, longstanding, or when it has not previously been detected.

Clinical and laboratory monitoring (Table 2)

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

- Appraisal for features of superimposed preeclampsia (including proteinuria) at each visit after 20 weeks' gestation
- Appropriate and timely assessment of fetal growth and wellbeing
- Laboratory assessment for secondary hypertension (as detailed above) if other symptoms or features are suggestive. It should be remembered that hypertension per se is associated with an increased risk of preeclampsia.

It is unusual for pre-existing hypertension alone (unless not previously recognized) to result in severe hypertension, especially in the first half of pregnancy. Before 20 weeks' gestation, consideration of secondary causes of hypertension should be entertained and investigated. After 20 weeks', superimposed preeclampsia must be strongly suspected.

Admission to hospital or to a day assessment unit is recommended for women with worsening hypertension or proteinuria at any stage of pregnancy. This enables appropriate assessment and management of maternal and fetal status and facilitates discussion by all involved in the woman's care.

Treatment

Non-pharmacological treatment:

There is insufficient evidence to advise appropriately on the efficacy or safety of non-pharmacological interventions for managing pre-existing hypertension during pregnancy. This applies to maintenance of salt restriction, calorie restriction in obese women, 'heart-healthy' diets, exercise, a reduction in stress (e.g. meditation) or workload, or bed rest. Some of these measures are untried but are unlikely to inflict harm on either the gestation or the mother and advice regarding their continuance or avoidance should be on a case-by-case basis. Other measures, such as salt restriction and bed rest have not been shown to improve maternal or fetal outcomes. Furthermore, it is possible that lowering blood pressure may increase the risk of SGA; results of current studies are awaited.

Unless severe or poorly controlled (see below), most women with pre-existing hypertension, without other complications or co-morbidities, can be managed at home, incorporating hospital day units or outpatient clinics.

Antihypertensive therapy:

The pharmacological management of ongoing chronic hypertension should follow the principles outlined above for gestational hypertension and preeclampsia. [Section 5]

Many women with chronic hypertension will have a physiological fall in blood pressure in the first half of pregnancy that may allow them to reduce or cease antihypertensive therapy. In some cases, antihypertensive therapy should be ceased prior to conception because they are considered unsuitable for other reasons (170-173):

- ACE-inhibitors and Angiotensin Receptor Blockers are nephrotoxic for the fetus in late pregnancy. Earlier reports also suggested ACE-inhibitors might be associated with, particularly, cardiovascular malformations although more recent data suggests this is unlikely (174, 175).
- When used for prolonged periods in pregnancy, atenolol and other highly selective beta blocker drugs are associated with fetal growth restriction (112, 176, 177).
- There is no compelling evidence that antihypertensive therapies are associated with adverse neurodevelopment
- Diuretics may restrict the natural plasma volume expansion of pregnancy

- Although treatment of chronic hypertension is associated with a significant reduction in severe hypertension, it has not been shown to alter the risk of superimposed preeclampsia, preterm delivery, placental abruption or perinatal death. Treatment reduces the risk of severe hypertension (RR 0.52; 95% CI 0.41-0.64), but it is unknown whether this affects perinatal outcomes (10, 93).

The appropriate blood pressure target for women with chronic hypertension and other conditions such as diabetes mellitus, chronic kidney disease or cardiovascular disease may be lower than for women without such complications, but there is insufficient data currently to state whether this provides benefit either to the mother or the fetus. Extrapolating from non-pregnancy data may or may not be valid and the decision to aim for levels between 130-140 mmHg systolic and 80-90 mmHg diastolic during pregnancy will depend on multiple factors that at this stage must be weighed individually.

In the third trimester of pregnancy, chronic hypertension frequently becomes more difficult to manage and an increase in antihypertensive therapy should be anticipated. Such increases are not always associated with the development of preeclampsia.

Timing of delivery

Pre-existing hypertension during pregnancy is associated with up to a 3-fold risk of perinatal death compared with singleton, normotensive pregnancies (165, 178). The risk may be highest from 39 weeks' gestation, indicating appropriate monitoring of these women to the end of the pregnancy is mandatory. As in all such cases, these data must not be construed to imply that intervention before term will necessarily reduce mortality or otherwise favourably affect outcome.

Post partum management

First six weeks:

In many women with pre-existing hypertension (with or without superimposed preeclampsia), blood pressure is often unstable immediately after delivery and may require a medication adjustment. Non-steroidal inflammatory drugs should not be given postpartum if the hypertension is difficult to control, there is evidence of acute kidney injury or CKD, or in the setting of thrombocytopenia (179).

Women with chronic hypertension, a long duration of antihypertensive treatment in pregnancy, higher maximum systolic and diastolic blood pressures, higher body mass index, or occurrence of preterm preeclampsia are more likely to have sustained hypertension postpartum (exceeding 6 weeks) (161, 180). Blood pressure usually stabilises in the first two months following pregnancy and treatment and appraisal should be based on the assumption that levels will decline.

Severe postpartum hypertension requires the same management approach as during pregnancy. Postpartum, women with co-morbidities should be treated according to standard guidelines for their specific medical condition when not pregnant e.g. <130/80 mmHg for albuminuric diabetic women. This should be a longer-term target and may not be achievable whilst the patient is hospitalised. Conversely, a reduction in medication may be required within one to two weeks of delivery if the woman's antihypertensive therapy was augmented in relation to the pregnancy.

Women with pre-existing hypertension who did not require treatment during the pregnancy often need treatment postpartum (181). Those at highest risk appear to be preterm deliveries and multiparous women with elevated serum urate concentrations.

All agents mentioned earlier (including the ACE inhibitors enalapril, captopril and quinapril) are compatible with breast feeding. Clonidine has been found to accumulate significantly in neonatal serum, although the significance is undetermined (182) .

After six weeks:

Follow-up after 6 weeks is required to ensure resolution of pregnancy-related changes and ascertain the need for ongoing care, particularly further investigation and management of renal disease. In women whose blood pressure control before pregnancy remains uncertain, it is important to ensure normalization of blood pressure (and albuminuria) postpartum. Women with persistent hypertension not previously assessed should undergo routine work-up according to standard regimens.

Advice regarding future lifestyle and optimization of risk factors in subsequent pregnancies may be required. This is particularly relevant for women who are obese, have cardiovascular risk factors, secondary hypertension, or end-organ disease.

10. Anaesthetic considerations in hypertensive disorders of pregnancy

Whenever possible an anaesthetist should be informed about a woman with severe preeclampsia, preferably well prior to labour or operative delivery, because appropriate anaesthetic management is associated with reduction in both fetal and maternal morbidity (183). Relevant issues include anaesthetic risk assessment, blood pressure control, fluid management, eclampsia prophylaxis and planning of analgesia or anaesthesia (184-186).

Fluid management

Fluid management is a challenging area in preeclampsia and there is no clear evidence regarding optimal type or volume of fluid (185, 187). Fluid therapy aims to maintain organ perfusion in the setting of vasoconstriction, endothelial dysfunction and either left ventricular systolic or more often diastolic dysfunction. Intravenous fluid should be administered incrementally in small volumes (e.g. crystalloid 250 mL) while monitoring maternal hemodynamic parameters, urine output and fetal heart rate, because over-hydration contributes to maternal mortality from pulmonary oedema and adult respiratory distress syndrome (188). Particular caution is necessary in women with oliguria, renal impairment or pulmonary oedema, in whom the left ventricle may adapt less well to volume load (189).

Fluid loading is not mandatory prior to regional analgesia during labour when low-dose local anaesthetic and opioid methods are used (190). Prior to regional anaesthesia for operative delivery, intravenous crystalloid loading is ineffective in preventing hypotension (191). Colloid is of modest effect but renal dysfunction, allergic reactions and coagulation disturbance are potential consequences. Prevention or treatment of hypotension with drugs such as ephedrine, phenylephrine or metaraminol is effective and appears safe in preeclamptic women-see below (192, 193).

Anaesthetic technique

Vaginal birth

During labour and childbirth, epidural analgesia is a useful adjunct to antihypertensive therapy for blood pressure control and improves renal and utero-placental blood flow (194, 195). When relatively contraindicated (e.g. severe thrombocytopenia, coagulopathy or sepsis), fentanyl or remifentanil patient-controlled intravenous analgesia is preferred. Although ephedrine usually does not cause rebound hypertension, occasionally vasopressors and epidural adrenaline [epinephrine] cause worrisome blood pressure elevation.

Caesarean birth

Sufficient preoperative preparation time reduces the risk of anaesthesia and other complications in women with preeclampsia (188, 196). Anti-hypertensive therapy and eclampsia prophylaxis should be instituted [See Section 5 and 6]. Regional anaesthesia is preferred to general anaesthesia for Caesarean birth, especially as airway problems, including laryngeal oedema, may be increased (197, 198). However, well-conducted general anaesthesia is also suitable and can be indicated in the presence of severe fetal compromise, pulmonary oedema, maternal hemodynamic instability, increased intraspinal haematoma risk (e.g. placental abruption induced coagulopathy, severe thrombocytopenia) or after eclampsia when altered consciousness or neurological deficit persists (199, 200).

Emergency operative delivery is associated with increased maternal morbidity, so early anaesthetic notification by the obstetrician and in-utero resuscitation provide additional time for assessment, planning and establishment of regional anaesthesia. When a well-functioning epidural catheter is present, conversion to epidural anaesthesia can be achieved only marginally less rapidly than establishing general anaesthesia (201, 202). Prophylaxis against pulmonary aspiration is recommended using clear antacid and ranitidine, with or without metoclopramide. Skilled anaesthetic assistance is mandatory, as is left lateral tilt on a pelvic displacement wedge or table tilt to minimise aortocaval compression. Oxytocin should be given slowly in small doses of less than 5 IU to minimise its' significant hemodynamic effects (203). Drugs that are ideally avoided in severe preeclampsia include ergometrine and ketamine (hypertensive episodes) and the non-steroidal anti-inflammatory drugs including COX-2 specific inhibitors (impaired renal function or hypertension) (188).

Attenuation of pressor responses at general anaesthesia for Caesarean birth

Laryngoscopy and tracheal intubation present a particularly dangerous time for the hypertensive woman, especially if the intracranial pressure is elevated or the blood pressure is inadequately controlled (188, 196). The transient but severe hypertension that typically accompanies intubation can cause myocardial ischaemia, cerebral haemorrhage or pulmonary oedema, all of which are important causes of maternal death. Attenuation of pressor responses, aiming to maintain systolic blood pressure < 180 mmHg, is best achieved with drugs such as remifentanil 1 mcg/kg; or magnesium sulphate 30 mg/kg combined with alfentanil 7.5 mcg/kg (204-206). Fentanyl 2.5 mcg/kg, alfentanil 10 mcg/kg or magnesium 40 mg/kg are partially effective (207). Neuromuscular block must be monitored closely after intravenous magnesium administration (208). Other options, including at the time of extubation, are beta-blockers such as esmolol or vasodilators such as glyceryl trinitrate (209).

Regional anaesthesia for Caesarean birth

All the regional anaesthetic techniques (spinal, epidural or combined spinal-epidural) appear safe provided meticulous attention is paid to cautious fluid management, prevention of aortocaval compression and minimisation of hypotension. Spinal anaesthesia with usual drug doses is now a recommended technique (185, 210-212). Cardiac output is well maintained and spinal anaesthesia is associated with less hypotension and lower vasopressor requirements than when used for healthy parturients (210). Combined spinal-epidural anaesthesia appears to offer further advantages in specific cases (185).

Low dose aspirin therapy is not a contraindication to regional techniques, which in the absence of clinical bleeding are considered of very low risk if the platelet count is >75 $x10^9$/L (52) . Platelet counts of < 50 $x10^9$/L are considered a contraindication unless there are compelling reasons to avoid general anaesthesia. Within the range 50-75 $x10^9$/L an individual assessment, considering patient risks, coagulation status and if available platelet function tests; and risk reduction strategies (an

experienced operator, single-shot spinal anaesthesia or insertion of a flexible tip epidural catheter) are advised.

Post-Caesarean analgesia can be achieved with many options, but the non-steroidal anti-inflammatory drugs and those which reduce the seizure threshold (tramadol, pethidine, meperidine) are best avoided in women at risk of eclampsia.

Admission to an Intensive Therapy Unit

Anaesthetists are an important speciality group within critical care teams. Women who develop organ failure require intensive monitoring and medical management, either in a high dependency or intensive care setting. Indications for admission include severe pulmonary oedema, sepsis, intractable hypertension, anuria or renal failure, seizures, massive blood loss with disseminated intravascular coagulation, neurological impairment requiring ventilation (eg intracerebral haemorrhage or infarction, cerebral oedema) and critical intra-abdominal pathology.

Invasive monitoring

Direct intra-arterial blood pressure monitoring is often extremely useful in hypertensive women, during anaesthesia and operative delivery as well as in critical care, but obtaining arterial access should not delay treatment of acute severe hypertension. Central venous pressure correlates poorly with pulmonary capillary wedge pressure, so although it may provide trend monitoring and a central catheter allows safer administration of potent vasoactive drugs, central venous pressure monitoring is seldom used as an indicator of intravascular volume status (213). Pulmonary artery catheters for assessment of left ventricular preload can cause serious complications, are not of proven outcome benefit in preeclampsia, and are consequently rarely used. There is increasing support for the value of echocardiography and more dynamic measures of cardiac output, such as devices based on pulse contour analysis or pulse power algorithms (184, 185, 214, 215) .

11. Preconception management and prophylaxis

Risk factors for hypertensive disorders of pregnancy

It is likely that development of preeclampsia requires a combination of underlying susceptibility and a triggering event. Many susceptibility factors for preeclampsia have been identified (see Table 9). The absolute risk for an individual will be determined by the presence or absence of these and other predisposing or protective factors but to date no adequately accurate predictive tool, using either clinical or laboratory markers, has been developed (216). Such a tool applied early in pregnancy would allow management that might modify outcomes. When considering prophylactic treatment or stratification of women to high or low risk models of antenatal care, these risk factors should be assessed for each woman.

Table 9. Risk factors associated with preeclampsia (216-218)

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

Other rare risk factors include fetal hydrops, fetoplacental triploidy and gestational trophopblastic disease may cause severe, early onset preeclampsia.

In a prospective study of 3529 nulliparous women, 5.3% developed preeclampsia and the risk of preeclampsia was increased when more than one risk factor was present (217). For example, the rate of preeclampsia when the systolic blood pressure was >120 mmHg at 15 weeks (n=310) was 14% (95%CI 10-18). The rate of preeclampsia in women with a higher systolic blood pressure at 15 weeks was further increased if she was obese [16% (95%CI 10-18), had a family history of preeclampsia [20% (95%CI 11-33)], or whose own birth weight was <2500g [33% (95%CI 17-55)]. Of note, the combinations of risk factors conferring the greatest risks of preeclampsia occurred in fewer women and comprised a small proportion of all nulliparas who develop preeclampsia. A small number of factors have been identified that are protective for preeclampsia. These include miscarriage with the same partner in nulliparous women, high fruit intake, smoking and taking greater than 12 months to conceive (217) . The independent detrimental effects of smoking on fetal growth should be emphasized. Interestingly, this protective effect is not seen in women with chronic hypertension (58).

Inherited thrombophilias e.g., Factor V Leiden were suggested to be strongly associated with preeclampsia on the basis of early case control studies however recent large prospective cohort studies, and a systematic review of these cohort studies do not support an association between the common Factor V Leiden and Prothrombin gene mutations and preeclampsia (219, 220). Testing for inherited thrombophilias is therefore no longer recommended following a preeclamptic pregnancy (108, 221, 222).

The association between periodontal disease and preeclampsia remains controversial with a recent meta-analysis concluding that there is a modest association between periodontal disease and preeclampsia on the basis of several case-control studies, however there is significant heterogeneity in methodological rigor between studies (223).

The value of measuring angiogenic and anti-angiogenic factors in maternal serum during pregnancy (such as endoglin and placental growth factor) or using biophysical parameters such as uterine artery Doppler velocimetry to predict later development of preeclampsia remains controversial (224). The recognition of the association between these markers and the subsequent development of preeclampsia has provided valuable insights into the pathogenesis of this condition, but the clinical utility and cost effectiveness of using these markers as early pregnancy screening tests to predict preeclampsia remains uncertain (225-230).These tests appear to perform best in the prediction of preterm or early onset disease but this only represents a small proportion (25 % and 10% of women with preeclampsia deliver before 37 and 34 weeks, respectively) of the overall burden of disease (231-233).

To be cost effective, there must either be an effective treatment available to prevent development of the disease and its associated morbidity, or it must allow diversion of limited antenatal resources away from those considered at low risk (224, 226). At present, there are insufficient data to support the beneficial effects of routine marker testing and as such they are not currently recommended in clinical practice (234, 235). It is certainly possible, however, that ongoing refinements of testing protocols may improve the efficacy of these tests in predicting preeclampsia in the near future.

Recurrence of preeclampsia

Women who have experienced hypertension in a previous pregnancy are at increased risk in any future pregnancies (13, 236, 237). They should receive appropriate counselling and prophylaxis if the risk is considered significant (see Section 11).

Table 10. Based on data summarized in Reference (see Appendix G) (13)

	Recurrence risk in subsequent pregnancies	
	Gestational hypertension	Preeclampsia
Previous gestational hypertension	16-47%	2-7%
Previous proteinuric preeclampsia	13-53%	16%
Severe preeclampsia <34 weeks <28 weeks		 25% 55%

12. Prevention of preeclampsia

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

Antiplatelet agents

Studies of the pathophysiology of preeclampsia have previously identified an imbalance between the circulating prostaglandins, prostacyclin and thromboxane. The hypothesis leading to the aspirin trials was the ability of low-dose aspirin to correct this imbalance by inhibiting platelet aggregation and dilating blood vessels. However, further studies have suggested the anti-inflammatory action of aspirin could also be important (238).

Prophylactic therapy with anti-platelet agents has been the subject of a large number of studies and various systematic reviews (239-242). Over 37,000 women have participated in randomised trials of anti-platelet agents to prevent preeclampsia, with the majority of trials using aspirin 50-150mg.

Table 11. Effects of antiplatelet agents on risk of preeclampsia: summarised in Reference (243)

Population	RR [95%CI] for preeclampsia	NNT [CI]
Primary prevention	0.90 [0.84-0.97]	
Low risk women	0.93 [0.81–1.08]	
All at risk	0.83 [0.77-0.89]	72 [52-119}
High risk women	0.75 [0.66-0.85]	19 [13-34]
Recurrent preeclampsia	0.86 [0.77-0.97]	
Aspirin dose >75 mg/day	0.64 [0.51-0.80]	

Of clinical importance, there was a 14% reduction in stillbirth, neonatal or infant death (RR 0.86 95%CI 0.76-0.98) and a 10% reduction in SGA infants (RR 0.90 95%CI 0.83-0.98).

Anti-platelet treatment commenced before 20 weeks (RR 0.87 95%CI 0.79-0.96) but not at ≥20 weeks, reduced the risk of preeclampsia. In a meta-analysis of 34 studies including 11,348 women, the reduction in the risk of preeclampsia was demonstrated to be significant only if aspirin was commenced prior to 16 weeks gestation (RR 0.47, 95% CI 0.34-0.65) compared to commencement after 16 weeks (RR 0.81, 95% CI 0.63-1.03). However, this meta-analysis was confounded by the risk status of women included, with the studies where treatment commenced before16 weeks (9 trials of 734 women) comprising of higher risk women (21% of controls developed preeclampsia). In contrast, preeclampsia occurred in 8% of controls in trials where treatment commenced at ≥16 weeks (n=10,584), indicating the lower risk status of participants. Of importance, the individual patient data meta-analysis found no difference in the rate of bleeding complications such as antepartum and postpartum haemorrhage or placental abruption between treatment and placebo groups.

In translating these results into clinical practice, the underlying risk of preeclampsia in the population being treated must be taken into consideration. If the baseline risk is 8%, treating 114 women will prevent one case of preeclampsia. In a population with a 20% risk of preeclampsia, the number needed to treat to prevent one case of preeclampsia is 50. In view of this potential benefit, and the relative absence of maternal or neonatal complications, low dose aspirin is indicated for women with at least moderate to high risk of preeclampsia ie secondary prevention of preeclampsia in women at increased risk and in women with significantly increased risk in their first pregnancy (see Section 11 (13). In most cases, aspirin may be ceased at 37 weeks gestation although continuation beyond this period is not unsafe (239).

Calcium supplements

Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle and leading to vasoconstriction (244). A possible mode of action for calcium supplementation is that it reduces parathyroid hormone release and intra-cellular calcium, and so reduces smooth muscle contractility. Calcium might also have an indirect effect on smooth muscle function by increasing magnesium levels. Recent evidence indicates that calcium supplementation affects uteroplacental blood flow by lowering the resistance index in uterine and umbilical arteries (245). Calcium supplementation in

the second half of pregnancy appears to reduce blood pressure directly rather than preventing the endothelial damage associated with preeclampsia (246).

The use of calcium supplementation has been demonstrated to significantly reduce the risk of preeclampsia, particularly in high risk women and those with low dietary calcium intake (247). It has also been shown to reduce the risk of preterm birth (247). There was no significant effect on fetal and neonatal outcomes including low birth weight, fetal growth restriction, stillbirth or death before discharge from hospital. Calcium supplementation (1.5g/day) should therefore be offered to women with moderate to high risk of preeclampsia, particularly those with a low dietary calcium intake (247).

Heparins

There has been considerable interest in the potential role of prophylactic heparin in preventing preeclampsia in women at risk of preeclampsia. Several recent RCTs have provided encouraging results. Much of this interest has been based on the apparent association between inherited thrombophilias and adverse pregnancy outcomes with one trial reporting a significant reduction in recurrent, early onset (<34 weeks) hypertensive disease in thrombophilic women who received weight adjusted daily dalteparin injections compared to those who received standard care (248).

Rey et al reported a significant reduction in the rate of recurrent preeclampsia and fetal growth restriction in non-thrombophilic women with daily dalteparin injections (5000IU) (OR 0.15, 95% CI 0.03-0.70) (249). Likewise Kupferminc et al reported a significant reduction in the overall rate of pregnancy complications (including severe preeclampsia) in a non-randomised study (250). However, not all studies have demonstrated such improvements. Martinelli et al recently reported the findings of an RCT investigating the role of nadroparin in preventing placenta-mediated adverse pregnancy events and concluded that antenatal prophylaxis with this drug did not prevent adverse pregnancy events (251).

Despite the comparative safety of low molecular weight heparins during pregnancy, the current data do not support widespread use of these agents during pregnancy for the purposes of prevention of adverse pregnancy outcomes (other than perhaps in the specific case of antiphospholipid antibody syndrome (109, 252, 253). Further studies to determine the efficacy of low molecular weight heparins in specific at-risk patient population eg previous early onset preeclampsia, are required.

Other Therapies

Markers of oxidative stress are present in the placenta and maternal circulation of women with preeclampsia suggesting it may play a role in the disorder. Randomised, placebo controlled trials of antioxidants Vitamins C and E failed to demonstrate any significant effect on the incidence of preeclampsia (254-257). Of concern, a number of adverse effects were seen including an increased risk of stillbirth and of birthweight <2.5kg but there were fewer fetal deaths due to immaturity. Prophylactic antioxidant therapy with vitamins C and E is therefore not recommended (254-259).

Preeclampsia shares pathogenic similarities with adult cardiovascular diseases as well as many risk factors. A recent review has summarised a number of excellent studies that have demonstrated that prior to the onset of preeclampsia there is a rise in circulating antiangiogenic factors including sFlt-1 and sEng and a reduced level of important angiogenic factors including PlGF and vascular endothelial growth factor (260). Modification of these factors is a strategy now being pursued to prevent or reduce the severity of preeclampsia in the future. Several studies are examining the effectiveness of pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor which may act on this pathway or by activating the heme oxygenase-1/carbon monoxide (HO-1/CO) pathway, protecting the endothelium and reducing the inflammatory and oxidative insults (261, 262).

Recent observational studies have suggested that supplementation with multivitamins containing folic acid during pregnancy is associated with a reduced risk of preeclampsia (263). Folic acid may reduce the risk of preeclampsia by improving placental and systemic endothelial function or by lowering blood homocysteine levels (263). Randomized, controlled trials are underway to address this potential therapy (Canadian FACT Trial).

13. Long-term consequences

Women who have been diagnosed with either preeclampsia or gestational hypertension are at increased risk of subsequent hypertension and cardiovascular disease. Several systematic reviews and meta-analyses have determined that after a diagnosis of preeclampsia the relative risks for developing hypertension, cardiovascular disease and cerebrovascular disease are significantly increased (Table 12) (264-266). One meta-analysis did not find evidence that preeclampsia associated with pre-term delivery was associated with any additional risk for cardiovascular disease. However, a prospective, population based, cohort study found that women with pre-term (<37weeks gestation) preeclampsia and no subsequent pregnancies had a 9.4 fold increased risk of cardiovascular death (267). Women with term preeclampsia and no subsequent pregnancies had a 3.4 fold increased risk of cardiovascular death. Women with term preeclampsia who went on to have further pregnancies only had a 1.5 fold increase in cardiovascular death, suggesting that women who only have one preeclamptic pregnancy may have health problems that discourage further pregnancies.

These associations are likely to reflect a common cause for preeclampsia and cardiovascular disease, or an effect of preeclampsia on vascular disease development, or both. It has been estimated that life style interventions after preeclampsia will decrease cardiovascular risk by 4-13% (268). We recommend counselling women who have had preeclampsia that they will benefit from avoiding smoking, maintaining a healthy weight, exercising regularly and eating a healthy diet. It is recommended that all women with previous preeclampsia or hypertension in pregnancy have an annual blood pressure check and regular (5 yearly or more frequent if indicated) assessment of other cardiovascular risk factors including serum lipids and blood glucose.

Not only has preeclampsia been shown to be a risk factor for adverse cardiovascular outcomes, it has also been linked with increased risks of developing deep vein thrombosis, end stage renal disease, type II diabetes and hypothyroidism (Table 12) (269). Given that preeclampsia is more common in women with renal disease it is no surprise that end-stage renal disease is more common years after preeclampsia. Preeclampsia does not appear to influence a woman's risk of developing cancer (265).

Table 12: Risk of developing subsequent disease after preeclampsia. (265, 266, 269)

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

Cognitive functioning also appears to be affected after severe preeclampsia and eclampsia. Three to eight months after severe preeclampsia, women have measurably impaired memory which is unrelated to scores of depression, anxiety or attention (270). Women who have had eclampsia self report more cognitive failures and impaired vision several years after pregnancy compared to those women who had preeclampsia or normal pregnancies (271, 272).

Children born to a pregnancy complicated by preeclampsia have increased cardiovascular risk factors from an early age. A systematic review of 18 studies looking at cardiovascular risk factors in the offspring of pregnancies affected by preeclampsia found an increase in systolic blood pressure of 2.39 mmHg, an increase in diastolic blood pressure of 1.35 mmHg and an increase of 0.62 kg/m2 in BMI (273). There is also weak, inconsistent evidence that hypertensive disorders of pregnancy may be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalizing behaviours (274, 275). Further research in this area is required.

14. Auditing outcomes

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

Selected maternal and fetal/neonatal clinical indicators for women with hypertensive disorders of pregnancy (276).

1. Maternal mortality: death during pregnancy or within 42 days of delivery.
2. Composite severe adverse maternal outcome: one or more of the following morbidities
    - Cardiovascular: positive inotrope support or myocardial infarction
    - Hepatic: failure or haematoma/rupture
    - Renal: Dialysis or transplantation

- Neurological: Glascow coma score <13 or stroke or cortical blindness or 2 or more seizures
- Respiratory: requirement of ≥50% FI02 for >1 hr or intubation or pulmonary edema
- Haematological: transfusion of ≥10 units blood products
- Death

3. Perinatal mortality: death during the perinatal period ie 20 completed weeks of gestation to 28 days after birth.
4. Rate of admission of term babies to neonatal intensive care units

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

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