Guideline for the Management of Hypertensive Disorders of Pregnancy

2014

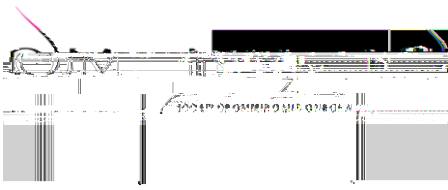
Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, Paech M. Said JM.

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	



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 Ò2 mm per second to avoid underestimating systolic blood pressure (18).

Measurement Devices

of blood pressure measurement with automated devices to mercury sphygmomanometers on

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

Haematological involvement

Thrombocytopenia <100,000 /ÕL [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).

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, Cushingôs 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. In ' ntE. s is

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.

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 Ó1+ 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 weeksô 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 ñendpointsò 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

steroid prophylaxis may be beneficial in this group.

At mature gestational age, delivery should not be delayed in the case of severe preeclampsia. Even

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 ñtightò versus ñless tightò 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	75-300Õg tds			Withdrawal effects: rebound hypertension
Labetalol				
Ox				

Treatment of severe hypertension

Sudden and severe increases in blood pressure may be the presenting feature of hypertensive

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

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

6. Eclampsia

A recent Australian study demonstrated that eclampsia remains rare in Australia (in singleton

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.

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 (0.2ï5%) 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 obsP epe

White coat hypertension

Although treatment of chronic hypertension

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

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

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 Ó 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

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

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

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 Ó50% FI02 for >1 hr or intubation or pulmonary edema
Haematological: transfusion of Ó10 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.

15. REFERENCES

18. Reinders LW, Mos CN, Thornton C, Ogle R, Makris A, Child A, et al. Time poor: rushing decreases the accuracy and reliability of blood pressure measurement technique in pregnancy. Hypertension in Pregnancy. 2006;25(2):81-91.
19. Brown MA, Robinson A, Bowyer L, Buddle ML, Martin A, Hargood JL, et al. Ambulatory blood pressure monitoring in pregnancy: what is normal? Am J OG. 1998;178(4):836-42.
20. Gupta M, Shennan AH, Halligan A, Taylor DJ, de Swiet M. Accuracy of oscillometric blood pressure monitoring in pregnancy and pre-eclampsia. BJOG : an international journal of obstetrics and gynaecology. 1997;104(3):350-5.
21. Lo C, Taylor RS, Gamble G, McCowan L, North RA. Use of automated home blood pressure monitoring in pregnancy: is it safe?[see comment]. Am J OG. 2002;187(5):1321-8.
22. Chung Y, de Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy: microlife WatchBP home. Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy. 2009;28(3):348-59.
23. Reinders A, Cuckson AC, Lee JT, Shennan AH. An accurate automated blood pressure device

57.

91. Bijlenga D, Boers KE, Birnie E, Mol B-WJ, Vijgen SCM, Van der Post JAM, et al. Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36weeks. Quality of Life Research. 2011;20(9):1427-36.
92. Gulmezoglu AM HG. Bed rest in hospital for suspected impaired fetal growth Oxford: Cochrane Library; 1999 [cited 2013].
93. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews. 2007(1):CD002252.
94. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: a systematic review. Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy. 2002;21(1):85-95.
95. Wallenburg H. Hemodynamics in hypertensive pregancy. In: PC R, editor. Handbook of Hypertension. 10: Elsevier Science Publisheres 1988. p. 91-5.
96. Baggio MR, Martins WP, Calderon AC, Berezowski AT, Marcolin AC, Duarte G, et al. Changes in fetal and maternal Doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial. Ultrasound in Medicine & Biology. 2011;37(1):53-8.
97. Duley L MS, Jones L. 2013, Issue 7. Art. No.: CD001449. DOI: 10.1002/14651858.CD001449.pub3. . Drugs for treatment of very high blood pressure during pregnancy. . Cochrane Database of Systematic Reviews. 2013(7).
98. Cotton DB, Gonik B, Dorman KF. Cardiovascular alterations in severe pregnancy-induced

150. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews. 2007;4(CD004454).
151. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and

210. Visalyaputra S, Rodanant O, Somboonviboon W, Tantivitayatan K, Thienthong S, Saengchote W. Spinal versus epidural anesthesia for cesarean delivery in severe preeclampsia: a prospective randomized, multicenter study. Anesthesia and Analgesia. 2005;101(3):862-8, table of contents.
211. Aya AG, Vialles N, Tanoubi I, Mangin R, Ferrer JM, Robert C, et al. Spinal anesthesia-induced hypotension: a risk comparison between patients with severe preeclampsia and healthy women undergoing preterm cesarean delivery. Anesthesia and Analgesia. 2005;101(3):869-75, table of contents.
212. Henke VG, Bateman BT, Leffert LR. Focused review: spinal anesthesia in severe preeclampsia. Anesthesia & Analgesia. 2013;117(3):686-93.
213. Young P, Johanson R. Haemodynamic, invasive and echocardiographic monitoring in the hypertensive parturient. Best Prac Res Clin Obstet Gynaecol. 2001;15(4):605-22.
214. Martin SR, Foley MR. Intensive care in obstetrics: an evidence-based review. Am J OG. 2006;195(3):673-89.
215. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness.Int J Obstet Anesth. 2011;20(2):160-8.
216. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330(7491):565.
217. North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international

m

20;125(3):005-fonanp bet8(tud80.73(e(ar)1287368(e)9.0097(cri)-0.9951od(Fo)-3382o39(n)2.9986ecti)10013t59(i)-

229. Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of Clinical Investigation. 2003;111(5):649-58.

changes in platelet count, urate, and urinary protein: a randomized control trial.. Hypertens Preg. 2008;27(3):299-304.
247. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews. 2010;8(CD001059).
248. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH, Investigators F. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. Journal of Thrombosis & Haemostasis. 2012;10(1):64-72.
249. Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. Journal of Thrombosis & Haemostasis. 2009;7(1):58-64.

264. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. European Journal of Epidemiology. 2013;28(1):1-19.
265. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
266. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. American Heart Journal. 2008;156(5):918-30.