Appendices

The reference numbers cited in the appendices refer to the references given at the end of the relevant chapter in the main section of the textbook

Appendix 1.1

Training module for automated blood pressure measurement by community health care workers – adapted from materials from the CLIP Trial for use with the Microlife 3AS1-2 with guidance from the Piers On the Move (POM) app

The CRADLE BP device (Microlife 3AS1-2) is a hand-held, upper-arm, semi-automated blood pressure device that has been successfully validated for use in a non-pregnant population[108] and for use in pregnancy (including pre-eclampsia)[109]. It is being used for BP measurement in the community setting in the CLIP Trial.

Instructions for use of the Microlife 3AS1-2 by community health care workers are as follows:

1. Have the woman rest for at least 5 minutes. She should be seated, without talking or reading.
2. Position the woman properly. She should be seated with her back against a chair. Both feet should be on the floor.
3. Place the cuff on her arm. Either arm may be used. Ensure that there is no tight clothing around her upper arm. The cuff should be placed so that the bottom is 1–2 cm above the elbow. The arm should then rest on a table or the arm rest of the chair if the arm rest is high enough. The woman must remain still, with no movement and no talking.
4. Take the blood pressure. Turn on machine and inflate the cuff by hand, the cuff will then deflate automatically. Keep the device as still as possible during cuff deflation or alternatively, let it rest on the table during deflation. If the cuff has not been inflated to the correct pressure, the device will indicate this with a 'beeping' sound; if this occurs, inflate the cuff to 30 mmHg higher than the previous inflation pressure that caused the beeping and then try letting the cuff deflate again.
5. Record the first blood pressure measurement.
6. Wait 1 minute during which time the woman should remain still, without moving, talking, or reading.

7. Repeat the blood pressure measurement (i.e., step #4). All women will receive two blood pressure measurements, and an average of the two measurements should be used to indicate the blood pressure for that visit (i.e., the two measurements are added and divided by two).
8. If the second measurement differs significantly (>10 mmHg) from the first, a third measurement is required. In this case the second and third measurements will be averaged to determine the blood pressure.
9. If at any time an 'error' message is received, repeat the measurement.

Appendix 1.2

GRADE evaluation of best practice points regarding hypertension

Recommendation	*Quality of evidence**	*Strength of recommendation†*
Diagnosis of hypertension		
1. The diagnosis of hypertension should be confirmed by health facility BP measurements.	Low	Strong
2. Hypertension in pregnancy should be defined as a sBP ≥140 mmHg and/or dBP ≥90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.	Low	Weak (sBP) Strong (dBP)
3. For the purposes of defining superimposed pre-eclampsia in women with pre-existing hypertension, resistant hypertension should be defined as the need for three antihypertensive medications for BP control at ≥20 weeks' gestation.	Low	Weak
4. A 'transient' hypertensive effect should be defined as a sBP ≥140 mmHg or a dBP ≥90 mmHg which is not confirmed on the same visit after the woman rests, or on subsequent visits.	Very low	Weak
5. A 'white coat' hypertensive effect refers to BP that is elevated in a health facility (i.e., sBP ≥140 mmHg or dBP ≥90 mmHg) but by ABPM or HBPM, sBP is <135 mmHg and dBP is <85 mmHg.	Very low	Strong
6. 'Masked' hypertension refers to BP that is normal in the health facility (i.e., sBP <140 mmHg and dBP <90 mmHg) but elevated by ABPM or HBPM (i.e., sBP of ≥135 mmHg or dBP ≥85 mmHg).	Very low	Weak
7. Severe hypertension should be defined as a sBP of ≥160 mmHg or a dBP of ≥110 mmHg based on the average of *at least* two measurements, taken at least 15 minutes apart, using the same arm.	Low	Strong
BP measurement		
1. BP should be measured using standardised technique, particularly with the woman seated and her arm at the level of the heart.	Low	Strong
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used.	Low	Strong
3. Korotkoff phase V (marked as disappearance of Korotkoff sounds) should be used to designate dBP.	Moderate	Strong
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements.	Very low	Weak
5. BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in pre-eclampsia.	Low	Strong
6. Automated BP machines that have not been validated for use in pre-eclampsia may under- or over-estimate BP, so those readings should be compared with those using mercury sphygmomanometry or a calibrated aneroid device.	Low	Strong

continued

Appendix 1.2 *continued*

Recommendation	*Quality of evidence**	*Strength of recommendation†*
7. In a health facility setting, when BP elevation is non-severe and pre-eclampsia is not suspected, ABPM or HBPM is useful to confirm persistently elevated BP.	Very low	Weak
8. When HBPM is used, maternity care providers should ensure that women have adequate training in measuring their BP and interpreting the readings taken.	Very low	Strong
9. The accuracy of all BP measurement devices used in health facilities should be checked regularly (e.g. annually) against a calibrated device.	Very low	Strong
10. The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device (e.g., at multiple ANC for an individual woman).	Very low	Strong

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that the majority of people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 1.3

Sample policy brief for blood pressure measurement

ELEVATED BLOOD PRESSURE IS AN ESSENTIAL DIAGNOSTIC CRITERIA FOR THE HYPERTENSIVE DISORDERS OF PREGNANCY

Approximately 99% of all global maternal deaths occur in resource-constrained regions. Between one-third and one-half of those deaths result from the hypertensive disorders of pregnancy which cannot be diagnosed if blood pressure is not measured.

WE ARE FALLING SHORT OF OUR BLOOD PRESSURE MEASUREMENT TARGETS

Routine blood pressure measurement is part of prescribed antenatal and postnatal care in all countries for the purpose of detecting the hypertensive disorders of pregnancy and preventing complications for mothers and babies. WHO recommends blood pressure measurement at each antenatal visit, shortly after birth, and again within 6 hours after birth. Furthermore, hypertension may worsen transiently postpartum, especially between days 3 and 6 when blood pressure peaks. Monitoring of blood pressure should continue in the 6 weeks postpartum to prevent long-term complications.

Although blood pressure measurement is one of the more commonly received components of antenatal care in LMICs, many women still do not have their blood pressure measured and rates are as low as 40%.

WHICH BLOOD PRESSURE MEASUREMENT DEVICE SHOULD BE USED?

There are three types of blood pressure measurement devices available: mercury sphygmomanometers, aneroid (dial) devices and automated devices. Availability and accuracy in pregnancy are the key concepts that need to be considered when choosing a device.

Mercury manometers and aneroid (dial) devices require a trained health care provider to use a stethoscope. For health and safety reasons, mercury devices are largely unavailable outside of biomedical departments that check the accuracy of institutional blood pressure measurement devices. Those devices are usually aneroid. These need to be checked ('calibrated') at least once every 2 years, something that is often not done.

Automated blood pressure measurement devices can be used without stethoscopes by all health care workers, or in the home by the woman herself. While training/instruction in their use is necessary, they do not demand the skill required to use a stethoscope, therefore enabling task-sharing across health worker cadres. They maintain their accuracy over time and many are inexpensive. A critically important point is that devices used must be accurate for use in pregnancy; most devices have been neither tested nor found to be accurate. Furthermore, devices must be validated for use specifically in pre-eclampsia, the most dangerous of the hypertensive disorders of pregnancy; many of the devices used in pregnancy that have been tested have not been found to be accurate for this purpose. Microlife and OMRON have marketed devices suitable for use in pre-eclampsia. The Microlife 3AS1-2 is a low-cost device suitable for use in pre-eclampsia as well as in under-resourced settings.

ACTIONS

Ensure provision of accurate blood pressure devices at the primary and all health care levels.

Integrate blood pressure measurement into routine antenatal and postnatal care, especially at the primary health centre level.

Task shift to enable midwives, nurses and lower-level workers to correctly measure and

interpret blood pressure, and subsequently refer women to the appropriate level of care.

Update national protocols and clinical guidelines to facilitate education and training about blood pressure measurement by health care workers, including all of those in the community.

Integrate blood pressure measurement into quality assurance checklists and initiatives.

Appendix 1.4

Recommendations for blood pressure measurement and diagnosis from international clinical guidelines*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Measurement of BP			
Position	BP should be measured with the woman seated comfortably with her legs resting on a flat surface		
Cuff size	An appropriately sized cuff (i.e., use large cuff with inflatable bladder covering 80% of arm circumference when upper arm circumference is greater than 33 cm) should be used	Measure BP with equipment that is accurate in individual hypertensive pregnant women Use appropriate *cuff size*–thigh cuffs (18×36 cm) for women with an arm circumference of 41 cm or more. Follow PRECOG recommendation 6 for reducing errors in BP measurement	
Korotkoff phase for BP	Disappearance of Korotkoff (K) phase V should be used to designate diastolic BP First sound heard of K phase I defines the systolic BP		
Which arm to use	Measurements should be undertaken in both arms at the initial visit to exclude vascular abnormalities		
Type of device	Mercury sphygomomanometers remain the gold standard. Other devices that may be used are automated BP recorder and aneroid devices		
Choice of automated BP device	Automated BP recorders and aneroid devices are prone to errors and each unit should maintain a mercury sphygmomanometer for validation of those devices		

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
				BP should be measured with the woman in the sitting position with the arm at the level of the heart
				An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used Weak
				Korotkoff phase V should be used to designate diastolic BP Weak
				If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements
				BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in PE
				Automated BP machines that have not been validated for use in PE may under- or over-estimate BP in those women and comparison of readings using mercury sphygmomanometry or a calibrated aneroid device is recommended

continued

Appendix 1.4 *continued*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Measurement of BP			
Home and ambulatory BP monitoring	24-h ambulatory BP monitoring or repeated home BP monitoring can be used to diagnose white coat hypertension in early pregnancy		
Precautions to take when choosing HBPM			
Maintenance of hospital BP measurement devices	All devices should be calibrated on a regular basis (ideally monthly)		
Maintenance of home BP measurement devices			
Diagnosis of hypertension			
Location/type for measurements			
Defining hypertension	Defined as sBP ≥140 mmHg and/or dBP ≥90 mmHg confirmed by repeated readings over several hours		dBP ≥90 mmHg
Defining resistant hypertension			

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
			For women with GH we suggest BP be monitored at least once weekly with proteinuria assessment in the office and with an additional weekly *measurement of BP at home* or in the office. For pregnant women with chronic hypertension and poorly controlled BP we suggest the use of HBPM For women with suspected white coat hypertension, we suggest the use of ABPM to confirm the diagnosis before the initiation of antihypertensive therapy	In the office setting, when BP elevation is non-severe and PE is not suspected, ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) are useful to confirm persistently elevated BP
				When HBPM is used, maternity care providers should ensure that patients have adequate training in measuring their BP and interpreting the readings taken
				The accuracy of all BP measurement devices used in hospitals or offices should be checked regularly against a calibrated device
				The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device
				The diagnosis of hypertension should be based on office or in-hospital BP measurements
			sBP ≥140 mmHg and/or a dBP ≥90 mmHg Two occasions at least 4 h apart	Hypertension in pregnancy should be defined as an office (or hospital) sBP ≥140 mmHg and/or dBP ≥ 90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm
				For the purposes of defining superimposed PE in women with pre-existing hypertension, resistant hypertension should be defined as the need for three antihypertensive medications for BP control at ≥20 weeks' gestation

continued

Appendix 1.4 *continued*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Diagnosis of hypertension			
Defining transient hypertension	Defined as women referred for assessment of new onset hypertension with normal BP and investigations *Repeat assessment should be arranged within 3–7 days* *Synonymous for labile hypertension*		
Defining white coat hypertension	Defined as hypertension in a clinical setting with normal BP away from this setting assessed by 24-h ABPM		
Defining masked hypertension			
Defining severe hypertension	Defined as a sBP ≥170 mmHg or a dBP of ≥110 mmHg		

PE, pre-eclampsia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[118]
† Techniques for measurement of BP in pregnancy are described in 'Antenatal care' (NICE clinical guidance 62)
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
				A 'transient' hypertensive effect should be defined as office sBP ≥140 mmHg or a dBP ≥90 mmHg which is not confirmed after rest, on repeat measurement on the same or on subsequent visits
				A 'white coat' hypertensive effect refers to BP that is elevated in the office (i.e., sBP ≥140 mmHg or dBP ≥90 mmHg) but ABPM or HBPM sBP is <135 mmHg and dBP is <85 mmHg
				A 'masked' hypertensive effect refers to BP that is normal in the office (i.e., sBP <140 mmHg and dBP <90 mmHg) but elevated by ABPM or HBPM (i.e., sBP of ≥135 mmHg or dBP ≥85 mmHg)
			sBP ≥160 mmHg and/or a dBP ≥110 mmHg Diagnosis can be confirmed within a shorter interval (even minutes) to facilitate timely antihypertensive therapy	Severe hypertension should be defined, in any setting, as a sBP of ≥160 mmHg or a dBP of ≥110 mmHg based on the average of *at least* two measurements, taken at least 15 minutes apart, using the same arm

PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
SOMANZ 2014: Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ guideline for the management of hypertensive disorders of pregnancy. Sydney: SOMANZ; 2014
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 2.1

Proteinuria – policy brief

PROTEINURIA – Policy brief

Urinary dipsticks should be made consistently available wherever antenatal and postnatal care is provided.

WHY SCREEN FOR PROTEINURIA IN PREGNANCY?

The presence of proteinuria identifies women who are at increased risk of adverse outcomes for themselves and their babies.

Although a level of proteinuria above which risk is substantially increased has not been determined, in resource-constrained settings where maternal symptoms and signs alone are used to guide treatment, dipstick proteinuria of 4+ is associated with an increased risk of stillbirth.

Above: A diagram showing the procedure of proteinuria measurement. © PRE-EMPT Project

HOW TO SCREEN FOR PROTEINURIA AND BY WHOM?

Use of urinary dipsticks for proteinuria screening is easy and inexpensive. Testing can be performed following minimal training and is a method well-suited to task-shifting.

Dipsticks should be used for screening in preference to other methods until such time that another method proves to be superior.

ACTIONS

- Screening for proteinuria should be integrated into existing antenatal and postnatal programmes.
- Urinary dipsticks should be made consistently available wherever antenatal and postnatal care is provided. This will require strengthening of the supply chain and procurement services at national and sub-national levels.
- National and international guidelines should include guidance around proteinuria measurement.
    - At minimum, proteinuria should be performed at first of the four WHO recommended antenatal visits AND whenever hypertension is detected.
    - Proteinuria testing should be performed at the six-week postpartum visit in women who developed proteinuria in pregnancy.

At minimum, proteinuria testing should be performed at the first of the four WHO-mandated antenatal visits, when hypertension is detected, and at the 6-week postpartum visit in women who developed proteinuria in pregnancy.

Appendix 2.2

Methods of proteinuria assessment

	Advantages	*Disadvantages*	*Comments**
Random urine samples	*Easy to perform*	*Excretion may vary over a 24-hour period*	
Dipstick testing			
For protein	Widely used in pregnancy	Poor sensitivity and specificity for quantification of proteinuria Results vary according to urine concentration	Results vary according to test strips and analyser used; testing using automated analyser may decrease reading bias
For albumin	More specific for glomerular proteinuria	Results vary according to urine concentration	No studies for diagnosis of significant proteinuria
For PrCr	Urinary creatinine 'correction' for concentration	No information in pregnancy	No studies for diagnosis of significant proteinuria
For ACR	More specific for glomerular proteinuria	Less information and validation for use in pregnancy compared with urinary dipstick	Available on strips for visual read, point of care or on laboratory automated analyser More costly than urinary dipstick for protein
*Spot testing**			
Urinary PrCr	Widely studied	Less reliable at high range proteinuria	Current cut-off is 30 mg/mmol to detect 0.3 g/d of proteinuria but optimal threshold may be slightly higher and published cut-offs range from 17 to 71 mg/mmol
Urinary ACR	More specific for glomerular proteinuria	Less information and validation for use in pregnancy compared with PrCr	Ideal cut-off to identify 0.3 g/d of proteinuria unclear, possibly within the range of 2–8 mg/mmol.
Other methods			
Heat coagulation test	Low cost	Requires test tubes, burner, and test reference card	This is an alternative to urinary dipstick testing when test strips are not available and pre-eclampsia (or renal disease) is suspected
Sulfosalicylic acid test	Low cost	False positive in alkaline or dilute urine	Same as for heat coagulation test

continued

Appendix 2.2 *continued*

	Advantages	*Disadvantages*	*Comments**
*Timed urine collections**	*Reflect total 24 h excretion in complete collection*	*Inconvenient* *Inaccurate when incomplete*	*Urinary creatinine excretion is helpful to estimate under or over-collection*
24 hour			
For proteinuria	Traditional gold standard for quantification of proteinuria		
For albuminuria		Less studied in pregnancy compared with total proteinuria	
2–12 hour			
For proteinuria or albuminuria		Less studied and used in clinical practice	

ACR, albumin : creatinine ratio; PrCr, protein : creatinine ratio
* The values of proteinuria and albuminuria vary according to local laboratory methods; urinary creatinine reporting is now standardized in many laboratories

Appendix 2.3

GRADE evaluation of best practice points regarding proteinuria

	*Quality of evidence**	*Strength of recommendation†*
1. All pregnant women should be assessed for proteinuria, at minimum, at their first antenatal visit.	Low	Weak
2. Urinary dipstick testing (or SSA or heat coagulation testing if dipsticks are not available) may be used for screening for proteinuria when the suspicion of pre-eclampsia is low.	Low	Weak
3. Significant proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥2+.	Moderate	Strong
4. Definitive testing for proteinuria (by urinary protein : creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of pre-eclampsia.	Moderate	Strong
5. Significant proteinuria is ≥0.3 g/d in a complete 24-hour urine collection or ≥30 mg/mmol (≥0.3 mg/mg) urinary creatinine in a random urine sample.	Moderate	Strong
6. There is insufficient information to make a recommendation about the accuracy of the urinary albumin:creatinine ratio, although values <2 mg/mmol (<18 mg/g) are normal and all values ≥8 mg/mmol (≥71 mg/g) are elevated..	Low	Strong
7. In well-resourced settings with sophisticated fetal monitoring, proteinuria testing does not need to be repeated once the significant proteinuria of pre-eclampsia has been confirmed.	Moderate	Strong
8. In under-resourced settings, proteinuria testing should be repeated to detect 4+ dipstick proteinuria that is associated with an increased risk of stillbirth.	Low	Weak

GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SSA, sulfosalicylic acid

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 2.4

Recommendations for proteinuria diagnosis in international pregnancy hypertension guidelines*

See next page – this appendix requires a double-page layout

	PRECOG II (DAU) 2009	*PRECOG 2005*	*AOM 2012*
General considerations			Urinary protein should also be reassessed by dipstick at the time of the second BP measurement
Screening means/ method	Estimate proteinuria by dipsticks and follow PRECOG recommendation 7 to improve reliability; 6 Accuracy is not increased by retesting a new sample. Use the higher of the dipstick results from the community and the day assessment unit		
Definition of significant proteinuria	Exclude significant proteinuria by calculating the urinary protein to creatinine ratio from a random sample or confirm and quantify by 24 hour urine collection. Use a threshold ratio of 30 to exclude significant proteinuria	≥1+ (300 mg/L) on dipstick testing, a protein : creatinine ratio of ≥30 mg/mmol on a random sample, or a urine protein excretion of ≥300 mg/24 h	For urine dipstick values equivalent to ≥0.3 g/L (≥+1 on urine dipstick) in addition to other signs or symptoms of pre-eclampsia, further investigation and/or a prompt medical consult should be arranged
Reading urinary dipstick tests			

BP, blood pressure; PE, pre-eclampsia; PET, pre-eclamptic toxaemia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[63]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_ Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

NICE 2010	*QLD 2013*	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
					All pregnant women should be assessed for proteinuria ideally at each routine antenatal visit
Use an automated reagent-strip reading device or a spot urinary protein : creatinine ratio for estimating proteinuria in a secondary care setting					Urinary dipstick testing (by visual or automated testing) may be used for screening for proteinuria when the suspicion of PE is low
Diagnose significant proteinuria if the urinary protein : creatinine ratio is >30 mg/mmol or a validated 24-hour urine collection shows >300 mg protein Where 24-hour urine collection is used to quantify proteinuria, there should be a recognized method of evaluating completeness of the sample	–	Definition of PET lists ≥0.3 g/d	Definition of PET lists ≥0.3 g/d	–	Significant proteinuria should be defined as ≥0.3 g/d in a complete 24-hour urine collection or ≥30 mg/mmol urinary creatinine in a spot (random) urine sample
If an automated reagent-strip reading device is used to detect proteinuria and a result of ≥1+ is obtained, use a spot urinary protein : creatinine ratio or 24-hour urine collection to quantify proteinuria	Proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥"2+"				Significant proteinuria should be suspected when urinary dipstick proteinuria is ≥1+

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 3.1

GRADE evaluation of best practice points regarding classification of hypertensive disorders of pregnancy

	*Quality of evidence**	*Strength of recommendation†*
1. HDPs should be classified as pre-existing hypertension or gestational hypertension with or without pre-eclampsia, or 'other' hypertension on the basis of different diagnostic and therapeutic considerations.	Low	Strong
2. The presence or absence of pre-eclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes.	Low	Strong
3. In women with pre-existing hypertension, pre-eclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, one or more adverse conditions, or one or more severe complications.	Low	Strong
4. In women with gestational hypertension, pre-eclampsia should be defined as new-onset proteinuria, one or more adverse conditions, or one or more severe complications.	Low	Strong
5. The assessment of maternal angiogenic factor balance appears to inform the diagnosis of pre-eclampsia, and other placental complications of pregnancy, where uncertainty exists, especially when 'superimposed pre-eclampsia' is suspected.	Moderate	Strong
6. Severe pre-eclampsia should be defined as pre-eclampsia complicated by one or more severe complications.	Low	Strong
7. For women with pre-existing hypertension, serum creatinine, fasting blood glucose, serum potassium, and urinalysis should be performed in early pregnancy if not previously documented.	Low	Weak
8. Among women with pre-existing hypertension or those with a strong clinical risk marker for pre-eclampsia, additional baseline laboratory testing may be based on other considerations deemed important by health care providers.	Very low	Weak
9. Women with suspected pre-eclampsia should undergo the maternal laboratory and a schedule of pertinent fetal testing described in Table 3.3.	Moderate	Strong
10. Doppler velocimetry-based assessment of the fetal circulation may be useful to support a placental origin for hypertension, proteinuria, and/or adverse conditions (including IUGR), and for timing of delivery.	Moderate except for timing of delivery which is high	Weak except for timing of delivery which is strong
11. The BPP is not recommended as part of a schedule of fetal testing in women with a HDP.	Moderate	Weak
12. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about pre-eclampsia (e.g., change in maternal and/or fetal condition).	Low	Weak

continued

Appendix 3.1 *continued*

	*Quality of evidence**	*Strength of recommendation†*
13. In resource-constrained settings, the miniPIERS model can provide personalised risk estimation for women with any HDP. In many of these women, the ultimate diagnosis cannot be confirmed until at least three months after delivery.	High	Strong
14. Health care providers should be alert to symptoms of post-traumatic stress following a HDP; and refer women for appropriate evaluation and treatment.	Low	Weak
15. Health care providers should inform their patients, antepartum and postpartum, about pre-eclampsia, its signs and symptoms, and the importance of timely reporting of symptoms to health care providers.	Very low	Weak
16. Information should be re-emphasised at subsequent visits.	Very low	Weak

GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HDP, hypertensive disorder of pregnancy; BPP, biophysical profile

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 3.2

Classification of the hypertensive disorders of pregnancy according to international clinical practice guidelines*

See next page – this appendix requires a double-page layout

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Pre-existing (chronic) hypertension					
Definition	dBP ≥90 mmHg before pregnancy or at booking before 20 weeks	dBP ≥90 mmHg before pregnancy or at booking before 20 weeks	(specify essential without known cause) BP >140/90 mmHg before pregnancy or 20 weeks or if woman taking antihypertensive(s) when she conceives	"Hypertension" at booking or before 20 weeks or if woman taking antihypertensives when referred to maternity services.	
With comorbid conditions			"Secondary" causes are listed		
Superimposed PET	New features of ET (includes women with pre-existing proteinuria)	New features of PET	New systemic features of PET after 20 weeks		
Includes women with pre-existing proteinuria	√				
Superimposed PET without severe features					
Superimposed PET with severe features					
Resistant hypertension					

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
BP ≥140/90 mmHg before pregnancy or 20 weeks	Hypertension before pregnancy or 20 weeks	Hypertension (≥140/90) before pregnancy or 20 weeks	Hypertension (≥140/90) before pregnancy or 20 weeks
	Comorbid conditions are listed and some include some secondary causes (e.g., CKD)		Comorbid conditions are listed and some include some secondary causes (e.g., CKD)
Symptoms of PET after 20 weeks	One/more at ≥20 weeks: resistant hypertension or new or worsening proteinuria or one or more other adverse conditions	"More likely" when: New proteinuria after 20 weeks Sudden, substantial, and sustained increase in proteinuria AND (1) sudden increase in BP or need to increase antihypertensive dose; sudden signs and symptoms of PET, such as (2) abnormal liver enzymes; (3) platelet count <100,000 cells/mm^3; (4) PET symptoms such as right upper quadrant pain and severe headaches; (5) pulmonary congestion or edema; (6) renal insufficiency (creatinine level doubling or rising to ≥1.1 mg/dL (97.2 μM) in women without other renal disease	One/more at ≥20 weeks: Resistant hypertension, *or* New or worsening proteinuria, *or* One/more adverse condition(s), *or* One/more severe complication(s)
	√	√	√
		Without organ system dysfunction #2–6 above (i.e., only hypertension and proteinuria)	
		With one/more organ dysfunctions (#2–6 above)	
			Need for three antihypertensives for BP control at ≥20 weeks

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Gestational or 'new' hypertension					
Definition	New hypertension at ≥20 weeks	New hypertension at ≥20 weeks	New hypertension at >20 weeks, without features of PET, with normal BP by 12 weeks postpartum	New hypertension at >20 weeks without proteinuria	
With comorbid conditions					
With evidence of pre-eclampsia					
Pre-eclampsia					
Definition	Gestational hypertension and quantified proteinuria that resolves after delivery	Gestational hypertension and proteinuria that resolves after delivery	Gestational hypertension (confirmed twice) and proteinuria or one/more of: renal involvement (creat ≥90 μmol/L or oliguria), haematological involvement (thrombocytopaenia, haemolysis, DIC), liver involvement (raised transaminases, severe epigastric or RUQ pain), neurological involvement (severe headache, persistent visual disturbances of photopsia, scotomata, or cortical blindness, retinal vasospasm, hyperreflexia with sustained clonus, convulsions (eclampsia), stroke, pulmonary oedema, IUGR, placental abruption	Gestational hypertension and proteinuria	Gestational hypertension and proteinuria (>0.3 g/24 h)

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
New sBP ≥140 mmHg and/or dBP ≥90 mmHg (KV) at >20 weeks, measured twice, with normal BP at 12 weeks postpartum	New hypertension at ≥20 weeks	New hypertension at >20 weeks without proteinuria, with normal BP "postpartum"	New hypertension at ≥20 weeks
	Co-morbid conditions are listed and some include some secondary causes (e.g., CKD)		Co-morbid conditions are listed and some include some secondary causes (e.g., CKD)
	New proteinuria *or* one or more of the other adverse conditions (see Table 3.3)		New proteinuria or one/more of: adverse condition(s)[¥] *or* severe complication(s)[¥]
Gestational hypertension and proteinuria (>0.3 g/24 h) Also defines mild pre-eclampsia	Hypertension and proteinuria or one/more of signs and symptoms associated with end-organ dysfunction	Gestational hypertension and new proteinuria or one/more of: thrombocytopenia (<100,000 platelets/mL), impaired liver function (elevated blood levels of live transaminases to 2× normal), new development of renal insufficiency (creat >1.1 mg/dL or a doubling of serum creat in the absence of other renal disease), pulmonary edema, or cerebral or visual disturbances	Gestational hypertension and new proteinuria or one/more of: adverse condition(s)[¥] *or* *severe* complication(s)[¥]

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Pre-eclampsia					
Eclampsia			With PET, one/more seizures	With PET, a convulsive condition	With PET, generalized seizures not attributable to other causes
Severe pre-eclampsia			One/more of: platelet count $<100{,}00 \times 10^9$/L, elevated transaminases, microangiopathic haemolytic anaemia with fragments/schistocytes on blood film (essentially HELLP syndrome)	Severe hypertension and/or symptoms, and/or biochemical and/or haematological impairment	One/more of: severe hypertension, heavy proteinuria, and substantial maternal organ dysfunction Onset at <32–34 weeks and fetal morbidity are used in some parts of the world
HELLP syndrome			HELLP spelled out Highlighted as variant of severe pre-eclampsia	HELLP spelled out	
Other 'hypertensive effects'					
Transient hypertensive effect					
White-coat effect			BP that is elevated in a clinical setting but normal in a non-clinical setting by (24 h) ABPM or HBPM using an appropriately validated device		
Masked hypertensive effect					
Hypertension (sBP and/or dBP)	dBP ≥90 mmHg	dBP ≥90 mmHg	sBP ≥140 mmHg and/or dBP ≥90 mmHg	dBP ≥90 mmHg (on two occasions, >4 hours apart) or dBP >110 mmHg (measured once)	-

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
	With PET, new onset of convulsions	With PET, new onset grand mal seizures	
Severe hypertension or PET symptoms (headache, epigastric pain, nausea, malaise), or proteinuria >5 g/24 h	PET with onset at <34 weeks, with heavy proteinuria (>0.3–0.5 g/24 h) or with one/more adverse conditions	(p32) ** ". . . consideration of pre-eclampsia as mild should be avoided."	PET with one/more severe complications‡
		HELLP spelled out Highlighted as a pre-eclamptic subtype	
			Elevated BP may be due to environmental stimuli or the, pain of labour, for example
			BP that is elevated in a clinical setting but normal in a non-clinical setting (<135/85 mmHg) by ABPM or HBPM
			BP that is normal in the clinical setting but elevated in a non-clinical setting (≥135/85 mmHg) by ABPM or HBPM
sBP ≥140 mmHg and/or dBP ≥90 mmHg	dBP ≥90 mmHg	sBP ≥140 mmHg or dBP ≥90 mmHg	sBP ≥140 mmHg and/or dBP ≥90 mmHg (based on average ≥2 measurements, taken ≥15 min apart, using the same arm)

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Other 'hypertensive effects'					
Mild				sBP 140–149 mmHg dBP 90–99 mmHg	
Moderate				sBP 150–159 mmHg dBP 100–109 mmHg	
Severe			≥160/ and/or 110 mmHg	≥160/110 mmHg	
Late postpartum hypertension					
Definition					

ABPM, ambulatory blood pressure monitoring); ACOG, American College of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; BP, blood pressure; CKD, chronic kidney disease; Creat, creatinine; dBP, diastolic blood pressure; DIC, disseminated intravascular coagulation; HBPM, home blood pressure monitoring; HELLP syndrome, Haemolysis, Elevated Liver enzymes and Low Platelet count syndrome; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; RUQ, right upper quadrant; sBP, systolic blood pressure; SOGC, Society of Obstetricians and Gynaecologists of Canada; WHO, World Health Organisation

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[58]

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
		sBP 140–159 mmHg or dBP 90–109 mmHg	
sBP 140–159 mmHg or dBP 90–109 mmHg			
≥160/or 110 mmHg	≥160/or 110 mmHg	≥160/or 110 mmHg (as greater than mild)	≥160/or 110 mmHg (based on average ≥2 measurements, taken ≥15 min apart, using the same arm)
		Hypertension (usually mild) that develops 2 weeks to-6 mos postpartum, usually normalizing by the end of the first year	

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 3.3

Definitions of pre-eclampsia and severe pre-eclampsia

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Proteinuria	✓	✓	✓	✓	✓	✓	✓	✓	✓
Heavy proteinuria									
Proteinuria is not mandatory – one/more other manifestations sufficient			✓				✓	✓	✓
Gestational age at onset <34 weeks									
Maternal symptoms									
Headache/visual symptoms			✓				✓	✓	✓
Chest pain/dyspnoea							✓		✓
Nausea/vomiting							✓		✓
Right upper quadrant/ epigastric pain			✓				✓		✓
Maternal signs									
Cardiac/cardiovascular									
Severe hypertension							✓		✓
Uncontrolled severe hypertension									

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
									1. Not mandatory. In absence of proteinuria, one or more of ✓
				✓	✓	✓			
				✓		✓			1. <32–34 weeks 2. Mentioned in text as risk factor for poor outcome
			✓		✓	✓	✓		1. Cerebral or visual disturbances 2. Cerebral or visual disturbances (with proteinuria)
			✓			✓			
			✓		✓	✓			
			✓		✓	✓	✓		1. Severe, persistent, unresponsive to medication, not otherwise explained (with proteinuria)
			✓	✓	✓	✓	✓		
			(✓)	(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Maternal signs									
Positive inotropic support									
Myocardial ischaemia/ infarction									
Neurologic									
Eclampsia			✓				✓		
PRES									
Cortical blindness or retinal detachment			✓						
Glasgow coma scale <13									
Stroke, TIA or RIND			✓						
Hyperreflexia (with clonus)			✓						
Pulmonary									
Oxygen saturation <97%									✓
Oxygen saturation <90%									
Pulmonary oedema			✓				✓	✓	
Need for ≥50% oxygen for >1 h									
Intubation (other than for Caesarean delivery),									
Renal									
Oliguria			✓						

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
				(✓)				✓	
				(✓)				✓	
				(✓)		✓		✓	
				(✓)				✓	
				(✓)		✓		✓	
				(✓)				✓	
				(✓)				✓	
				(✓)				✓	
				(✓)		✓	✓	✓	1. With proteinuria
				(✓)				✓	
				(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Abnormal maternal laboratory tests									
Haematology/coagulation									
Elevated WBC count									✓
Platelet count decreased but ≥50 × 10^9/L									✓
Platelet count decreased but <50 × 10^9/L			✓				✓	✓	
Elevated INR or aPTT			✓ 1						✓
Renal									
Elevated serum uric acid									✓
Elevated serum creatinine			✓				✓		✓
Acute kidney injury (creatinine >150 μM with no prior renal disease)								✓	
New indication for dialysis									
Hepatic									
Elevated serum AST, ALT, LDH or bilirubin			✓				✓	✓	✓
Hepatic dysfunction (INR >2 in absence of DIC or warfarin)									
Low plasma albumin							✓		✓
Hepatic haematoma or rupture									

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
		✓							1. "Microangiopathic haemolytic anaemia"
		✓	(✓)	(✓)		✓	✓	✓	1. Thrombocytopaenia 2. <100,000/mL 3. <100,000/mL with proteinuria
									1. Haemolysis and DIC
						✓			
			(✓)	(✓)			✓	✓	1. Progressive renal insufficiency (serum creatinine >1.1 mg/dL or a doubling of serum creatinine concentration in absence of other renal disease) 2. With proteinuria
			(✓)	(✓)				✓	
		✓				✓	✓		1. Twice normal 2. With proteinuria
			(✓)	(✓)				✓	
						✓			
			(✓)	(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Fetoplacental manifestations									
Non-reassuring FHR									✓
IUGR			✓				✓		✓
Oligohydramnios							✓		✓
Absent/reversed end-diastolic flow by Doppler velocimetry							✓		✓
Abruption *without* evidence of maternal or fetal compromise			(✓)				(✓)		✓
Abruption with evidence of maternal or fetal compromise			(✓)				(✓)		
Reverse ductus venosus A wave									
Stillbirth							✓		
Interventions									
Transfusion of any blood product									

ACOG, American College of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; aPTT, activated partial thromboplastic time; ASH, American Society of Hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FHR, fetal heart rate; INR, international normalised ratio; IUGR, intrauterine fetal growth restriction; LDH, lactate dehydrogenase; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PRECOG, pre-eclampsia community guideline; PRES, posterior reversible encephalopathy syndrome; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; RIND, reversible ischaemic neurological deficit; SOGC, Society of Obstetricians and Gynaecologists of Canada; TIA, transient ischaemic attack; WBC, white blood cell count; WHO, World Health Organization

* A checkmark indicates that the diagnostic criterion was listed by the guideline. A checkmark in brackets indicates that although not listed specifically, the criterion could reasonably be interpreted as being part of the definition in the relevant guideline

† The NICE 2010 guidelines include "symptoms, and/or biochemical and/or haematological impairment" as part of the definition of severe pre-eclampsia. It is assumed that those complications indicated by ( ) would meet this definition

** The WHO 2011 guidelines include "substantial maternal end-organ dysfunction" as part of the definition of severe pre-eclampsia. It is assumed that those complications indicated by ( ) would meet this definition. "Fetal morbidity" also required interpretation

*** Pre-eclampsia with severe feature

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
				✓					
				✓		✓			1. Not included (as IUGR with PET managed the same way as IUGR w/o PET)
				✓		✓			
				✓		✓			
						(✓)			
				(✓)		(✓)		✓	
				✓				✓	
				✓		✓		✓	
								✓	

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80

PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 4.1

Literature searches

PREGNANCY-INDUCED HYPERTENSION SEARCHES: COMPLICATIONS, EPIDEMIOLOGY

Removed duplicates, non-Eng, non-Fre, animal research using EndNote searches and de-duping function.

COMPLICATIONS

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present Search Strategy:

#	*Searches*	*Results*
1	complications.fs. or exp Infant, Newborn, Diseases/et, cn or exp Pregnancy Outcome/ or (sequel* or later life or late life).mp. or Pregnancy Complications/et, cn or exp Abortion, Spontaneous/et, cn or exp Chorea Gravidarum/et or exp Diabetes, Gestational/et or exp Fetal Death/et or exp Fetal Diseases/et, cn or exp Maternal Death/et or exp Morning Sickness/et or exp Nuchal Cord/et or exp Obstetric Labor Complications/et or exp Oligohydramnios/et or exp Pelvic Floor Disorders/et or exp Pemphigoid Gestationis/et, cn or exp Perinatal Death/et or exp Phenylketonuria, Maternal/et or exp Placenta Diseases/et, cn or exp Polyhydramnios/et, cn or exp Pregnancy Complications, Cardiovascular/et or exp Pregnancy Complications, Hematologic/et, cn or exp Pregnancy Complications, Infectious/et or exp Pregnancy Complications, Neoplastic/et, cn or exp Pregnancy in Diabetics/et or exp Pregnancy, Ectopic/et or exp Pregnancy, Prolonged/et or exp Prenatal Injuries/et or exp Puerperal Disorders/et, cn	1759552
2	exp Hypertension, Pregnancy-Induced/ or ((exp Pregnancy/ or exp Pregnancy Complications/) and exp Hypertension/)	34751
3	1 and 2	10375
4	limit 3 to yr="2011 -Current"	1499
5	limit 4 to (humans and (english or french))	1358
6	(complicat* and (((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex))).ti,ab.	9813
7	limit 6 to yr="2013 -Current"	1505
8	5 or 7 EXPORTED THESE	2668

Database(s): **EBM Reviews – Cochrane Central Register of Controlled Trials** March 2015, **EBM Reviews – Database of Abstracts of Reviews of Effects** 1st Quarter 2015 Search Strategy:

#	*Searches*	*Results*
1	(complicat* and (((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex))).mp.	735
2	limit 1 to yr="2011 -Current" [Limit not valid in DARE; records were retained] EXPORTED THESE	221

EPIDEMIOLOGY

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present Search Strategy:

#	*Searches*	*Results*
1	exp Hypertension, Pregnancy-Induced/ or ((exp Pregnancy/ or exp Pregnancy Complications/) and exp Hypertension/)	34751
2	(epidemiology or ethnology).fs.	1328387
3	exp Epidemiology/	22151
4	exp incidence/ or exp prevalence/	368169
5	(incidence or prevalen* or epidemiol*).ti,ab.	1178435
6	2 or 3 or 4 or 5	2053499
7	1 and 6	6092
8	limit 7 to (yr="2010 -Current" and (english or french))	1736
9	(((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex)).ti,ab.	41767
10	(incidence or prevalen* or epidemiol*).ti,ab.	1178435
11	9 and 10	5706
12	limit 11 to yr="2013 -Current"	945
13	8 or 12 EXPORTED THESE	2383

Database(s): **EBM Reviews – Cochrane Central Register of Controlled Trials** March 2015, **EBM Reviews – Database of Abstracts of Reviews of Effects** 1st Quarter 2015 Search Strategy:

#	*Searches*	*Results*
1	(((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex)).mp.	2235
2	(incidence or prevalen* or epidemiol*).mp.	76380
3	1 and 2	447
4	limit 3 to yr="2010 -Current" [Limit not valid in DARE; records were retained] EXPORTED THESE	208

Appendix 5.1

Studies of predictive tests for pre-eclampsia

See next page – this appendix requires a double-page layout

Risk factor¥ or predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*RR or OR**	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Predictors										
Clinical examination										
BP	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51%)		0.76	35	90	3.5	0.72
UAD	Cnossen† (2008)[96]	Systematic review and bivariable meta-analysis	Any PET	79,547 (3.14 %)		–	90	70	3.0	0.14
	Papageorghiou† (2002)[108]	Review	Any PET	18,683 (2.5%)			24–89	86–96	5.90	0.55
	Afrakhteh† (2014)[162]	Prospective	PET, stillbirth, placental abruption and preterm labour	205 (17.5%)			57.5	98.2	31.9	0.43
	Napolitano† (2012)[112]	Retrospective observational	Any PET Early-onset pre-eclampsia Preterm PET	3549 (3.6%) (0.6%) (1.2%)		0.682 0.851 0.786	–	–	–	–
Laboratory markers										
Podocyturia	Jim† (2014)[104]	Prospective	Any PET	91 (15.4%)			36	96	9	0.67
	Craici† (2013)[105]	Prospective	Any PET Any HDP (PET and GH)	267 (5.6%) (11.2%)		 1 0	 100 54	 100 100	 ∞ ∞	 0 0.46
	Kelder† (2012)[103]	Case–control	Any PET	69 (50.7%)		0.82	68.6	88.2	5.81	0.36
IPG/creatinine ratio	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)		0.862	84.2	83.6	5.13	0.19
Calcium/creatinine ratio	Vahdat† (2012)[106]	Prospective cohort	Any PET	150 (9.3%)		–	77	78	3.5	0.29

Hs-CRP	Kashanian† (2013)[121]	Prospective cohort	Any PET	394 (10.7%)		0.855	78.1	72.1	2.80	0.30
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)		–	50–100	43–88	1.24–11.5	0–0.74
Platelets	Yang† (2011)[169]	Case–control	Any HDP (PET and GH)	1288 (35.8%)		0.662	47.12	81.67	2.57	0.65
Angiogenic factors										
PlGF sFLT1 sENG	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –		–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET (1st vs 2nd trimester)	1244 (1.5%)	18.83* 2.76*	0.98 0.97	84 58	78 66	3.82 1.71	0.21 0.67
	Ghosh† (2013)[129]	Prospective cohort	EO-PET in Obese/overweight	1678 (1.7%)	7.64*	0.98	79	68	2.46	0.31
	Chappell (2013)[125]	Prospective	PET delivered within 14 days	625 (55%)		0.87	96	55	2.13	0.07
	Ghosh† (2013)[123]	Prospective cohort	EO-PET EO-IUGR	722 (1.5%)	8.35* 10.73*	0.982 0.982	82 84	65 67	2.36 2.54	0.28 0.24
Sflt/PlGF	Hanita (2014)[132]	Prospective	Any PET	84 (14.3%)		0.873	92	68	2.89	0.12
	Engels (2013)[130]	Prospective	PET/HELLP	338 (64%)		0.964	70.3	95.1	14.3	0.31
	Teixeira† (2013)[131]	Prospective longitudinal	Any PET	71 (16.9%)		0.95	–	–	–	–
	Delic† (2014)[163]	Prospective	Any PET	69 (49.2%)		0.895	–	–	–	–
	Villa (2013)[134]	Nested case–control	EO-PET	106 (5.7%)		1	100	99.8	500	0
	Forest† (2014)[133]	Nested case–control	EO-PET	7929 (0.2%)		0.977	88.9	90	8.89	0.12
PlGF/sFlt-1	McElrath† (2012)[124]	Prospective longitudinal	Any PET	2243 (6.2%)		0.74	61	75.1	2.45	0.52

continued

Risk factor¥ or predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*RR or OR**	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Predictors										
Multivariables										
BP and UAD	Kleinrouweler (2013)[111]	Individual patient data meta-analysis	Any PET	6708 (4.5%)		0.85				
MC, PP-13, β-hCG	Schneuer† (2012)[142]	In-house study and systematic review	Any PET EO-PET	2678 (2.7%) (0.2%)		0.72 0.82	24 45	95 95	4.8 9	0.8 0.58
MC, UAD, Biomarkers	Kuc (2011)[143]	Systematic review	Any PET	138,571 (2.6%)		–	43–100	90	–	–
MC, UAD and PAPP-A	Goetzinger† (2014)[148]	Prospective cohort	Any PET	1200 (8.5%)		0.76	36.7	93.2	5.4	0.68
MC and UAD	Lai† (2013)[110]	Prospective screening	Intermediate PET LO-PET	4,294 (0.9%) (3.4%)		0.838 0.792	70.3 54.6	90 90	7.03 5.46	0.33 0.51
MC and BP	Gallo† (2014)[98]	Prospective	Any PET EO-PET Preterm PET	17,383 (3.1%) (0.4%) (0.8%)		0.893 0.88 0.813	52.5 84.3 65.7	90 90 90	5.25 8.43 8.13	0.12 0.17 0.21
MC, BP and UAD	Caradeux† (2013)[99]	Prospective cohort	EO-PET	627 (1.5%)		0.895	62.5	95.5	13.9	0.39
MC, PlGF, BP and UAD	Myers† (2013)[149]	Prospective cohort	Preterm PET	3529 (1.3%)	0.65*	0.81	45	95	9	0.58
MC, PIGF and free β-hCG	Di Lorenzo† (2012)[144]	Prospective cohort	EO-PET	2118 (0.57%)		0.893	75	90	7.5	0.28
MC, BP PAPPA, ADAM12 and PlGF	Myatt† (2012)[137]	Observational study	Any PET	2218 (7.9%)		0.73	46.1	80	2.31	0.67
MC, hCG-h , PAPP-A and BP	Keikkala† (2013)[145]	Nested case–control	EO-PET	707 (4.1%)		0.863	69	90	6.9	0.34

MC, UAD, PlGF, sFlt-1 and lipid-related markers	Diguisto† (2013)[153]	Prospective observational study	Any PET	235 (23.8%)		0.795	39.6	90	3.96	0.67
MC, PlGF, and UAD	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)		–	46	99	19	0.56
PAPP-A and sFlt-1/PlGF	Park† (2014)[90]	Prospective cohort	LO-t PET	262 (3%)		0.969	87.5	95	17.5	0.13
PWV and sFlt-1	Katsipi† (2014)[151]	Prospective	Any PET EO-PET	118 (17.8%) (9.3%)		0.965 0.963	90 92	90 90	9 9.2	0.11 0.09
IPG/creatinine	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)		0.862	84.2	83.6	5.13	0.19
MC, BP, PAPPA, ADAM12 and PlGF	Kuc† (2013)[97]	Nested case–control	EO-PET LO-PET EO-PET + SGA LO-PET+SGA	667 (10.2%) (14.8%) (1.9%) (7.3%)		0.88 0.88 0.95 0.95	72 49 92 57	90 90 90 90	7.2 4.9 9.2 5.7	0.31 0.57 0.09 0.48
MC, BP and taurine	Kuc† (2014)[143]	Case–control	EO-PET	167 (10.2%)		0.93	55	90	5.5	0.5
BP and sENG	Abdelaziz† (2012)[162]	Nested case–control	Any HDP EO-PET LO-PET	1898 (4.69%) (0.84%) (3.16%)		0.83 0.86 0.83	71.8 83.8 80.3	90 90 90	7.18 8.38 8.03	0.31 0.18 0.22
HRG and UAD	Bolin† (2012)[109]	Case–control	Preterm PET	175 (15.4%)		0.85	91	62	2.39	0.15
PlGF, PP13, PAPP A and IL-1β	Siljee† (2013)[168]	Retrospective case–control	EO-PET	70 (50%)		0.830	55.9	90	5.59	0.49
Uric acid and BP	Martell-Claros (2013)[167]	Prospective cohort	GH	283 (6.0%)	4.02* 3.6*	0.75	50	84.2	3.16	0.59

† Studies including proteinuria for the definition of pre-eclampsia; ¥Risk factors, *Odd ratios
PET, pre-eclampsia; GH, gestational hypertension; EO, early onset; LO, late onset; UAD, uterine artery Doppler; BP, blood pressure; SGA, small for gestational age; MC, maternal characteristics

Appendix 5.2

Predictors of pre-eclampsia

Demographics and family history	*Past medical or obstetric history*	*Current pregnancy*	
Independent predictors			
Maternal			
		Clinical examination	
		First trimester	*Second or third trimester*
		• MAP	• MAP
			• Uterine artery Doppler
		Laboratory markers	
		First trimester	*Second or third trimester*
		• Fibronectin	• sFlt-1:PlGF
		• hs-CRP	• Podocyturia
		• Platelets	• PlGF
		• PlGF	• Calcium:creatinine ratio
		• sFLT-1	• Fibronectin
		• sENG	
Multivariable predictors			
Maternal			
Maternal age	Previous pre-eclampsia	Multiple pregnancy	Excessive weight gain in pregnancy
Afro-Caribbean or South Asian race	Pre-existing medical condition(s)	Overweight/obesity (BMI)	
Family history of pre-eclampsia (mother)	Pre-existing hypertension	First ongoing pregnancy	
Education level	Pre-existing diabetes mellitus		
	Preterm labour/delivery		
	Non-smoking		
		Clinical examination	
		First trimester	*Second or third trimester*
		• MAP	• MAP
		• sBP	• Uterine artery Doppler
		• dBP	
		• Uterine artery Doppler	

continued

Appendix 5.2 *continued*

Demographics and family history	*Past medical or obstetric history*	*Current pregnancy*	
Multivariable predictors			
		Laboratory markers	
		First trimester	*Second or third trimester*
		• PIGF	• PIGF
		• Uric acid	• sFlt-1
		• PP-13	• PAPP-A
		• sENG	• HRG
		• β-hCG	• PWV
		• PAPP-A	• Leptin,
		• ADAM12	• Triglycerides
		• Taurine	
		• IL-1β	

Appendix 5.3

Performance of predictors (summary of evidence by trimester)

See next page – this appendix requires a double-page layout

Appendix 5.3

Predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
First trimester predictors									
Individual predictors									
Clinical examination									
BP (MAP)	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51 %)	0.79	–	–	–	–
Laboratory markers									
hs-CRP	Kashanian† (2013)[121]	Prospective cohort	Any PET	394 (10.7%)	0.855	78.1	72.1	2.80	0.30
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)	–	50–100	63–88	1.47–4.0	0–0.74
Platelets	Yang† (2011)[169]	Case–control	Any HDP (PET and GH)	1288 (35.8%)	0.662	47.12	81.67	2.57	0.65
Angiogenic factors									
PlGF sFLT-1 sENG	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –	–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET	1244 (1.5%)	0.972	58	66	1.71	0.64
Multivariables									
MC, PP-13, β-hCG	Schneuer† (2012)[142]	In-house study and systematic review	Any PET EO-PET	2678 (2.7%) (0.2%)	0.72 0.82	24 45	95 95	4.8 9	0.8 0.58
MC, UAD, Biomarkers	Kuc (2011)[166]	Systematic review	Any PET	138,571 (2.6%)	–	43–100	90	–	–
MC, UAD and PAPP-A	Goetzinger† (2014)[148]	Prospective cohort	Any PET	1200 (8.5%)	0.76	36.7	93.2	5.4	0.68
MC, BP and UAD	Caradeux† (2013)[99]	Prospective cohort	EO-PET	627 (1.5%)	0.895	62.5	95.5	13.9	0.39
MC, PIGF and free b-hCG	Di Lorenzo† (2012)[144]	Prospective cohort	EO-PET	2118 (0.57%)	0.893	75	90	7.5	0.28
MC, BP PAPPA, ADAM12 and PlGF	Myatt† (2012)[137]	Observational study	Any PET	2218 (7.9%)	0.73	46.1	80	2.31	0.67

MC, hCG-h, PAPP-A and BP	Keikkala† (2013)[145]	Nested case–control	EO-PET	707 (4.1%)	0.863	69	90	6.9	0.34
MC, PlGF, and UAD	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)	–	46	99	19	0.56
MC, BP, PAPP-A, ADAM12 and PlGF	Kuc† (2013)[97]	Nested case–control	EO-PET LO-PET EO-PET + SGA LO-PET + SGA	667 (10.2%) (14.8%) (1.9%) (7.3%)	0.88 0.88 0.95 0.95	72 49 92 57	90 90 90 90	7.2 4.9 9.2 5.7	0.31 0.57 0.09 0.48
MC, BP and taurine	Kuc† 2014[143]	Case–control	EO-PET	167 (10.2%)	0.93	55	90	5.5	0.5
BP and sENG	Abdelaziz† (2012)[164]	Nested case–control	Any HDP EO-PET LO-PET	1898 (4.69%) (0.84%) (3.16%)	0.83 0.86 0.83	71.8 83.8 80.3	90 90 90	7.18 8.38 8.03	0.31 0.18 0.22
PlGF, PP13, PAPP A and IL-1β	Siljee† (2013)[168]	Retrospective case–control	EO-PET	70 (50%)	0.830	55.9	90	5.59	0.49
Uric acid and BP	Martell-Claros (2013)[167]	Prospective cohort	GH	283 (6.0%)	0.75	50	84.2	3.16	0.59
Second and third trimester predictors (summary of the evidence)									
Individual predictors									
Clinical examination									
BP (MAP)	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51 %)	0.76	35	90	3.5	0.72
UAD	Cnossen† (2008)[96]	Systematic review and bivariable meta-analysis	Any PET	79,547 (3.14 %)	–	90	70	3.0	0.14
	Papageorghiou† (2002)[108]	Review	Any PET	18683 (2.5%)		24–89	86–96	5.90	0.55
	Afrakhteh† (2014)[162]	Prospective	PET, stillbirth, placental abruption and preterm labor	205 (17.5%)		57.5	98.2	31.9	0.43
	Napolitano† (2012)[112]	Retrospective observational	Any PET Early-onset pre-eclampsia Preterm PET	3549 (3.6%) (0.6%) (1.2%)	0.682 0.851 0.786	–	–	–	–

continued

Appendix 5.3 *continued*

Predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Second and third trimester predictors (summary of the evidence)									
Individual predictors									
Laboratory markers									
Podocyturia	Jim† (2014)[104]	Prospective	Any PET	91 (15.4%)		36	96	9	0.67
	Craici† (2013)[105]	Prospective	Any PET Any HDP (PET and GH)	267 (5.6%) (11.2%)	1 0	100 54	100 100	∞ ∞	0 0.46
	Kelder† (2012)[103]	Case–control	Any PET	69 (50.7%)	0.82	68.6	88.2	5.81	0.36
Calcium: creatinine ratio	Vahdat† (2012)[106]	Prospective cohort	Any PET	150 (9.3%)	–	77	78	3.5	0.29
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)	–	50–85	43–96	1.24–11.5	0.20–0.69
Angiogenic factors									
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET	1244 (1.5%)	0.98	84	78	3.82	0.21
	Ghosh† (2013)[129]	Prospective cohort	EO-PET in obese/ overweight	1678 (1.7%)	0.98	79	68	2.46	0.31
	Chappell (2013)[125]	Prospective	PET delivered within 14 days	625 (55%)	0.87	96	55	2.13	0.07
	Ghosh† (2013)[123]	Prospective cohort	EO-PET	722 (1.5%)	0.982	82	65	2.36	0.28
sFlt-1:PlGF	Hanita (2014)[130]	Prospective	Any PET	84 (14.3%)	0.873	92	68	2.89	0.12
	Engels (2013)[130]	Prospective	PET/HELLP	338 (64%)	0.964	70.3	95.1	14.3	0.31
	Teixeira† (2013)[131]	Prospective longitudinal	Any PET	71 (16.9%)	0.95	–	–	–	–
	Delic† (2014)[163]	Prospective	Any PET	69 (49.2%)	0.895	–	–	–	–
	Villa (2013)[134]	Nested case–control	EO-PET	106 (5.7%)	1	100	99.8	500	0
	Forest† (2014)[133]	Nested case–control	EO-PET	7929 (0.2%)	0.977	88.9	90	8.89	0.12
PlGF/sFlt-1	McElrath† (2012)[124]	Prospective longitudinal	Any PET	2243 (6.2%)	0.74	61	75.1	2.45	0.52

Multivariables									
BP and UAD	Kleinrouweler (2013)[111]	Individual patient data meta-analysis	Any PET	6708 (4.5%)	0.85				
MC, PlGF, BP and UAD	Myers† (2013)[149]	Prospective cohort	Preterm PET	3529 (1.3%)	0.81	45	95	9	0.58
MC, UAD, PlGF, sFlt-1 and lipid-related markers	Diguisto† (2013)[153]	Prospective observational study	Any PET	235 (23.8%)	0.795	39.6	90	3.96	0.67
PAPP-A and sFlt-1/PlGF	Park† (2014)[90]	Prospective cohort	LO-PET	262 (3%)	0.969	87.5	95	17.5	0.13
PWV and sFlt-1	Katsipi† (2014)[151]	Prospective	Any PET EO-PET	118 (17.8%) (9.3%)	0.965 0.963	90 92	90 90	9 9.2	0.11 0.09
HRG and UAD	Bolin† (2012)[109]	Case–control	Preterm PET	175 (15.4%)	0.85	91	62	2.39	0.15
Not specified (any) trimester predictors (summary of the evidence)									
IPG/creatinine ratio (2 weeks prior to diagnosis)	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)	0.862	84.2	83.6	5.13	0.19
PlGF sFlt-1 sENG (Combination of trimesters)	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –	–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF (confirmed PET and delivered within 14 days)	Chappell (2013)[125]	Prospective	PET	625 (55%)	0.87	96	55	2.13	0.07
MC and BP (Combination of 1st and 2nd trimester)	Gallo† (2014)[98]	Prospective	Any PET EO-PET Preterm PET	17,383 (3.1%) (0.4%) (0.8%)	0.893 0.88 0.813	52.5 84.3 65.7	90 90 90	5.25 8.43 8.13	0.12 0.17 0.21
MC, PlGF, and UAD (Combination of trimesters)	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)	–	46	99	19	0.56

† Studies including proteinuria for the definition of pre-eclampsia

PET, pre-eclampsia; GH, gestational hypertension; EO, early onset; LO, late onset; UAD, uterine artery Doppler; BP, blood pressure; SGA, small for gestational age; MC, maternal characteristics

Appendix 5.4

Recommendations for prediction of pre-eclampsia from international clinical guidelines

	PRECOG 2005	*NICE 2010*
Prediction		
Risk assessment		

Prediction

Clinical risk markers for pre-eclampsia	History of previous PET Multiple pregnancy Antiphospholipid antibodies Significant proteinuria at booking or pre-existing renal disease Pre-existing diabetes mellitus Pre-existing hypertension First pregnancy ≥10 years since last baby Age ≥40 years BMI ≥35 Family history of preeclampsia (mother/sister) Booking diastolic BP ≥80 mmHg	"High" risk markers: HDP in prior pregnancy Autoimmune disease (e.g., SLE) Antiphospholipid syndrome Renal disease Pre-existing diabetes mellitus Pre-existing hypertension "Moderate" risk factors: Multiple pregnancy First pregnancy Age ≥40 years >10 years since 1st baby BMI ≥35 kg/m^2 at first visit Family history of PET ≥10 year since last baby

ACOG, American Congress of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; BMI, body mass index; DM, diabetes mellitus; GP, general practitioner; GPP, good practice point; NICE, National Institute for Health and Clinical Excellence; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; WHO, World Health Organization; SOGC, Society of Obstetricians and Gynaecologists of Canada

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

WHO 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
	Screening for PET should be assessed by known clinical risk factors assessment in early pregnancy, and decide whether or not to undertake preventive measures (IIIB) (IIIA/B)	Screening for PET except the use of medical history is not recommended (Moderate, Strong)	Screening for PET risk should be offered by clinical risk assessment in early pregnancy (II-2C/Low, Strong) Screening using biomarkers or Doppler ultrasound velocimetry of uteroplacental circulation, is not recommended (II-2C/Very low,Weak)
Obesity, chronic hypertension, DM, nulliparity, adolescent pregnancy, conditions leading to hyperplacentation and large placentas (e.g., twin pregnancy)	Presence of antiphospholipid antibodies, previous PET, pre-existing DM, multiple pregnancy, nulliparity, family history of PET, raised pre-pregnancy BMI, maternal age ≥40 years	First degree relative with history of PET, PET in previous PET, multiple gestation, maternal age ≥40 years, DM, obesity, pre-existing hypertension	History of previous pre-eclampsia Multiple pregnancy Antiphospholipid antibody syndrome Significant proteinuria at booking or pre-existing renal disease Pre-existing diabetes mellitus Pre-existing hypertension (II-2 B/Very low, Strong)

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 5.5

GRADE evaluation of best practice points

	*Quality of evidence**	*Strength of recommendation*†
1. Women should be screened for clinical risk markers of pre-eclampsia from early pregnancy.	Low	Strong
2. Consultation with an obstetrician or an obstetric internist/physician should be offered to women with a history of previous pre-eclampsia or another clinical marker of increased risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking, or a pre-existing condition of hypertension, diabetes mellitus, or renal disease.	Very Low	Strong
3. Screening for non-clinical risk markers cannot be recommended routinely at present for women at low or increased risk of pre-eclampsia until such screening has been shown to improve pregnancy outcome.	Very Low	Weak

* The judgments about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 6.1

Randomised trials and systematic reviews of trials of interventions in pregnancy to prevent pre-eclampsia in women at low (to moderate) risk (unless indicated by an '*' when all women were presented together)

See next page – this appendix requires a double-page layout

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Aspirin				
Duley 2007[6] (systematic review of 59 trials, 37,500 women with only moderate-risk women included here when possible; see Appendix 6.2 for data on high-risk women)	25 trials (N = 28,469)	". . . *wide variation in study quality. The poorer quality studies were mostly the small early trials, with the more recent large studies tending to be of higher quality.*"	Low-dose aspirin or dipyridamole (N = 14,326)	Placebo or no anti-platelet agent (N = 14,143)
Henderson 2014[81] (systematic review of 23 trials, 22,988 women with both low and high-risk women included here; see Appendix 6.2 for data on high-risk women)	23 trials (N = 22,988) 8 trials (average-risk women) (N not specified)	(Of 23 trials) "*18 described adequate randomisation, with 2 trials not clearly reporting appropriate allocation concealment*" OAB: "*all RCTs reported valid outcome measures*" LFU <20%: 14/23 trials	Aspirin (50–150 mg/d) (N = not specified)	Placebo or no treatment (N = not specified)
Calcium				
Hofmeyr 2014[7] (systematic review of 24 trials, 17,954 women with only low-risk women included here when possible; see Appendix 6.2 for data on high-risk women. Data on women at unclear risk not presented)	HIGH-DOSE 8 trials (N = 15,143)	Alloc con low risk: 11/19 trials. OAB low risk: 12/19 trials IOD low risk: 10/19 trials	HIGH-DOSE (≥1 g/d) (N = 7821)	Placebo or no calcium (N = 8935)
	LOW DOSE 10 trials (N = 2234 with low and high risk women combined)		LOW DOSE (<1 g/d) (N = 1178)	

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.86 [0.79–0.95] NNT 119 [73,333] (25 trials, N = 28,469) Eclampsia RR 0.94 [0.59–1.48]* (9 trials, N = 22,584)	GH RR 1.00 [0.92–1.08] (22 trials, N = 19,863) Abruption RR 1.17 [0.93–1.48] (12 trials, N = 2 2,272) Maternal death RR 2.57 [0.39–17.06]* (3 trials, N = 12,709) CS RR 1.02 [0.98–1.06]* (24 trials, N = 31,834) IOL RR 1.03 [0.98–1.08]* (5 trials, N = 19,295) Hospital admission during pregnancy RR 1.03 [0.97–1.10]* (3 trials, N = 12,964)	RR 0.91 [0.83–0.99] (23 trials, N = 19,399)	Perinatal death RR 0.92 [0.80–1.07] NNT 243 [131–1666] (23 trials, N = 28655) PTB <37 weeks RR 0.93 [0.88–0.99] (19 trials, N = 27,899)
	Abruption RR 1.17 [0.93–1.48]* (8 trials, N = 22,988)		Perinatal death RR 0.92 [0.76–1.11]* (14 trials, N = 22,848)
HIGH-DOSE RR 0.59 [0.41–0.83] (8 trials, N = 15,143)	HIGH-DOSE Hypertension (+/–PET) RR 0.71 [0.57–0.89] (8 trials, N = 15,143) Death or serious morbidity RR 0.80 [0.65–0.97] (4 trials, N = 9732) HELLP RR 2.67 [1.05–6.82] (2 trials, N = 12,901)	HIGH-DOSE RR 1.05 [0.86–1.29]* (4 trials, N = 13,615)	
LOW DOSE Calcium alone RR 0.36 [0.23–0.57]* (4 trials, N = 980) Calcium ± supplements RR 0.38 [0.28–0.52] (9 trials, N = 2234)	LOW DOSE Calcium with or without co-supplements Hypertension (±PET) RR 0.53 [0.38–0.74]* (5 trials, N = 665)	LOW DOSE Calcium alone Not estimable Calcium plus supplements RR 0.81 [0.54–1.21]* (4 trials, N = 854)	

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Calcium				
Imdad 2012[10] (systematic review)	15 trials (N = 16,754)	"*The studies included in this review were in general of good methodological quality… allocation concealment [was] adequate in most of the studies*."	500 mg–2 g/d starting at <32 weeks (N = 8,367)	Placebo or no calcium (N = 8387)
Villar 2006[9] (single trial)	N = 8325	Alloc con: yes. OAB: yes LFU <20%: yes	Calcium (1.5 g/d) (N = 4157)	Placebo (N = 4168)
Dietary changes				
Duley 2005[13] (systematic review)	2 trials (N = 603)	Alloc con low risk: 1/2 trials. OAB: NR. IOD low risk: 2/2 trials.	Advice to reduce dietary salt intake to 20 or 50 mmol/d (N = 294)	Advice to continue normal diet (N = 309)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
Any PET RR 0.48, [0.34–0.67] (15 trials, N = 16,490) Severe PET RR 0.75, [0.57–0.98] (5 trials, N = 13,724)	Mortality/severe morbidity RR 0.80 [0.65–0.97] (2 trials, N = 9732) ("*No increased risk of kidney stones*")	RR 1.01 [0.84–1.21] (7 trials, N = 14,438] LBW RR 0.85 [0.72–1.01] (6 trials, N = 14,479) BWt (g) Mean difference 85.75 [37.91–133.58] (13 trials, N = 8574)	PTB <37 weeks RR 0.76 [0.60–0.96] (10 trials, N = 15,275) Perinatal mortality RR 0.90 [0.74–1.09] (11 trials, N = 15,665]
PET/eclampsia RR 0.91 [0.69–1.19] Severe PET/eclampsia RR 0.73 [0.49–1.07] Early onset PET or eclampsia RR 0.77 [0.54–1.11] Eclampsia RR 0.68 [0.48–0.97]	Abruption RR 0.77 [0.43–1.39] GH RR 0.96 [0.86–1.06] Severe GH RR 0.71 [0.61–0.82] Gestational proteinuria RR 1.04 [0.93–1.17] Severe PET complications^ RR 0.76 [0.66–0.89] Any ICU/SCBU admission RR 0.85 [0.75–0.95] ICU admission ≥2 d RR 0.84 [0.57–1.21] Maternal death RR 0.17 [0.03–0.76] Severe maternal M&M index+ RR 0.80 [0.70–0.91]		PTB <37 weeks RR 0.91 [0.79-1.05] PTB <32 weeks RR 0.82 [0.71–0.93] Stillbirth RR 0.93 [0.74–1.17] NND RR 0.70 [0.56–0.88]
RR 1.11 [0.46–2.66] (2 trials, N = 603)	GH RR 0.98 [0.49–1.94] (2 trials, N = 242) Visit to day care unit RR 1.05 [0.48–2.32] (1 trial, N = 361) Antenatal hospital admission RR 0.82 [0.56–1.22] (1 trial, N = 361) Abruption RR 0.19 [0.01–3.98] (1 trial, N = 361) CS RR 0.75 [0.44–1.27] (1 trial, N = 361)	RR 1.5 [0.73–3.07] (1 trial, N = 242)	Perinatal death RR 1.92 [0.18–21.03] (2 trials, N = 409) PTB RR 1.08 [0.46–2.56] (1 trial, N = 242) 5 min Apgar <7 RR 1.37 [0.53–3.53] (1 trial, N = 361) NICU admission RR 0.98 [0.69–1.40] (1 trial, N = 361)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary changes				
Ota 2015[15] (systematic review)	17 trials (N = 9030)	Alloc con low risk: 6/17 trials. OAB low risk: 3/17 trials. IOD low risk 11/17 trials.	Nutritional education to increase energy and protein intake or actual energy and protein supplementation	No education, no supplement or placebo
			NUTRITIONAL EDUCATION (5 trials, N = 553)	No nutritional education (5 trials, N = 544)
			BALANCED ENERGY AND PROTEIN (12 trials, N = 2856)	No intervention (12 trials, N = 2684)
			HIGH-PROTEIN (1 trial, N = 259)	Low or no protein supplement (1 trial, N = 270)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
–	Protein intake (g/d) Mean difference 6.99 [3.02–10.97] (e trials, N = 632] Energy intake (kcal/d) Mean difference 105.61 [–18.94–230.15]	RR 0.97 [0.45–2.11] (1 trial, N = 404) LBW RR 0.04 [0.01–0.14] (1 trial, N = 300) BWt (g) Undernourished Mean difference +489.76 [427.93–551.59] (2 trials, N = 320) BWt (g) Adequately nourished Mean difference +15.0 [–76.30–+106.30] (1 trial, N = 406	PTB RR 0.46 [0.21–0.98] (2 trials, N = 449) Stillbirth RR 0.37 [0.07–1.90] (1 trial, N = 431) Neonatal death RR 1.28 [0.35–4.72] (1 trial, N = 448)
RR 1.48 [0.82–2.66] (2 trials, N = 263)	Weekly gestational weight gain Mean difference 18.63 [–1.81–39.07] (9 trials, N = 2391)	RR 0.79 [0.69–0.90] (7 trials, N = 4408) BWt (g) Mean difference +40.96 [4.66–77.26] (11 trials, N = 5385)	PTB RR 0.96 [0.80–1.16] (5 trials, N = 3384) Stillbirth RR 0.60 [0.39–0.94] (5 trials, N = 3408) NND RR 0.68 [0.43–1.07] (5 trials, N = 3381) Bayley Mental Score at 1 year Mean difference of –0.74 [–1.95–0.47] (1 trial, N = 411)
–	Weekly gestational weight gain (g/week) Mean difference 4.5 [–33.55–42.55] (1 trial, N = 486)	RR 1.58 [1.03–2.41] (1 trial, N = 505) BWt (g) Mean difference –73.0 [–171.26–+25.26] (1 trial, N = 504) Weight at 1 year (g) Mean difference 61.0 [–184.60–+306.60] (1 trial, N = 409)	PTB RR 1.14 [0.83–1.56] (1 trial, N = 505) Stillbirth RR 0.81 [0.31–2.15] (1 trial, N = 529) NND RR 2.78 [0.75–10.36] (1 trial, N = 529)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary changes				
			ISOCALORIC PROTEIN	Protein replaced by an equal quantity of non-protein energy (2 trials, N = 93)
Allen 2014[12] (systematic review of 18 trials, 8712 women with low and high-risk women presented together here; 7 of the trials were with women with no risk factors for preeclampsia; see Appendix 6.2 for data on high-risk women. Data for women at unclear risk not presented)	18 trials (N = 8712)	Alloc con: low risk 9/18 trials OAB: low risk 7/18 trials IOD low risk: 17/18 trials	Dietary change alone or with other change	Placebo or no dietary change
			DIET (6 trials, N = 1334)	Control (6 trials, N = 1361)
			MIXED (Diet, physical activity & lifestyle) (6 trials, N = 733)	Control (not specified) (6 trials, N = 705)
			ESSENTIAL ACIDS (6 trials, N = 2275)	Control (not specified) (6 trials, N = 2304)
Micronutrients other than calcium				
Kubik 2004[23] (single trial)	N = 138	"*double blinded trial*"	Vitamin and mineral supplement containing 15 mg zinc, 2 mg copper, and 20 μg selenium	Placebo

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
–	Weekly gestational weight gain (g/week) Mean difference 110.45 [–82.77–303.76] (2 trials, N = 184)	BWt (g) Mean difference 108.25 [–220.89–437.40] (2 trials, N = 184)	
ANY DIETARY CHANGE RR 0.81 [0.69–0.94] (18 trials, N = 8712) (I^2 = 0%)			
RR 0.67 [0.53–0.85] (6 trials, N = 2695)	–	–	–
RR 0.93 [0.66–1.32 (6 trials, N = 1438)	–	–	–
RR 0.92 [0.71–1.18] (6 trials, N = 4579)	–	–	–
"*6.25% vs. 7.7%*"	SVD ("*natural deliveries*") "*75.0% vs. 53.8%*"		

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Makrides 2014[40] (systematic review of 10 trials, 9090 low and high risk women for whom outcomes were not reported by risk)	(Low and high risk women reported together) 10 trials (N = 9090)	Alloc con low risk: 2/10 trials. OAB low risk: 7/10 trials. IOD low risk: 3/10 trials.	Oral Mg (N = 4516) "*compositions of the Mg supplements, gestational ages at commencement, and doses administered varied*"	Placebo (8 trials, 3241) or no therapy (2 trials, N = 939) (Total N = 4180)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.87 [0.58–1.32] (3 trials, N = 1042)* Eclampsia RR 0.14 [0.01–2.70] (1 trial, N = 100)	Hospitalisation during pregnancy RR 0.65 [0.48–0.86]* (3 trials, N = 1158) Abruption RR 0.96 [0.48–1.94] (1 trial, N = 4082) Pregnancy-induced HTN RR 0.39 [0.11–1.41] (3 trials, N = 4284)	RR 0.76 [0.54–1.07]* (3 trials, N = 1291 infants)	Stillbirth RR 0.73 [0.43–1.25]* (4 trials, N = 5526] Perinatal mortality RR 1.10 [0.72–1.67]* (5 trials, N = 5903 infants NND before hospital discharge RR 2.21 [1.02–4.75]‡* (4 trials, N = 5373 infants) Miscarriage <20 weeks RR 0.85 [0.49–1.49]* (6 trials, N = 3704] (6 trials, N = 3704) Gestational age at birth (weeks) Mean difference 0.06 [–0.07–0.20]* (5 trials, N = 5564] PTB <37 weeks RR 0.89 [0.69–1.14]* (7 trials, N = 5981] LBW <2500 g RR 0.95 [0.83–1.09]* (5 trials, N = 5577) NICU admission RR 0.74 [0.50–1.11]* (3 trials, N = 1435) Apgar <5 at 5 min RR 0.83 [0.41–1.67]* (1 trial, N = 377) Apgar <7 at 5 min RR 0.34 [0.15–0.80]* (4 trials, 1083 infants) Meconium-stained liquor RR 0.79 [0.63–0.99]* (1 trial, 4082 infants) Late FH decelerations RR 0.68 [0.53–0.88]* (1 trial, 4082 infants) Mild HIE RR 0.38 [0.15–0.98]* (3 trials, 4082 infants) Breech presentation RR 1.25 [0.81–1.92]* (1 trial, N = 4082)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Bullarbo 2013[42] (single trial)	N = 59	"*double-blind randomisa-tion*"	Magnesium (300 mg/d from 25 weeks) (N = 29)	Placebo (N = 30)
Mori 2012[43] (systematic review)	20 trials "*over 15,000 women and their babies*"	Alloc con low risk: 10/20 trials. OAB low risk: 13/20 trials. IOD low risk: 5/20 trials.	ZINC (5–90 mg/d) starting before conception to 26 weeks (N not specified)	Placebo or no zinc (N not specified)
Parrish 2013[44] (single trial of 684 low and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	N = 113	Alloc con: yes OAB: yes Loss to follow up <20%: No (f/u was available for N = 267 low and high risk combined)	Fruit and vegetable juice powder concentrate (N = 56)	Placebo (N = 57)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
Average dBP at 37 weeks significantly lower (mmHg) (72/1.4 mean/SEM vs 77/1.2, $p = 0.03$)	Fewer women developed an increase in dBP ≥15 mmHg ($p = 0.01$)		
PET or GH RR 0.83 [0.64–1.08] (7 trials, N = 2975)	APH 2nd trimester RR 1.59 [0.57–4.45] (1 trial, N = 1206) APH 3rd trimester RR 0.96 [0.39–2.33] (1 trial, N = 1206) PROM RR 0.93 [0.78–1.11] (2 trials, N = 1691) Post-term birth RR 1.09 [0.74–1.60] (3 trials, N = 1554) IOL RR 0.27 [0.10–0.73] (1 trial, N = 52) CS RR 0.95 [0.58–1.53] (6 trials, N = 2164) Instrumental vaginal birth RR 1.12 [0.79–1.59] (1 trial, N = 1206) PPH RR 1.13 [0.78–2.26] (3 trials, N = 718)	RR 1.02 [0.94–1.11] (8 trials, N = 4252 babies)	PTB RR 0.86 [0.76–0.97] (16 trials, N = 7637) BWt Mean difference −9.48 [−4.28–15.33] (16 trials, N = 5780) LBW RR 0.93 [0.78–1.12] (14 trials, N = 5643) Meconium in liquor RR 1.16 [0.86–1.56] (2 trials, N = 1385) FHR (beats/min) Mean difference −1.20 [−3.31–0.91] (1 trial, N = 176)
RR 1.22 [0.40–3.77] Mild PET RR 1.02 [0.31–3.32]	GH RR 1.02 [0.21–4.83]	RR 2.04 [0.39–10.7] RR 1.40 [0.45–4.26]	Live birth RR 1.02 [0.96–1.08] RDS RR 1.53 [0.27–8.79] NICU admission RR 1.03 [0.27–3.96] NND RR 0.20 [0.01–4.09]* NICU admission RR 0.57 [0.25–1.30]* IVH gr 3 or 4 RR 0.99 [0.06–15.7]*

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Prostaglandin precursors				
Makrides 2006[45] (systematic review of 2783 low- and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	4 trials (N = 2056)	Alloc con low risk: 3/6 trials OAB: NR IOD "*Most trials reported outcome for at least 83% of all women recruited*"	Marine oil (N = 1024)	Placebo or no marine oil (N = 1032)
Zhou 2012[46] (single trial)	N = 2399	Alloc con: yes OAB: NR Loss to f/u <20%: NR	Fish oil (800 mg DHA/d in second half of pregnancy) (N = 1197)	Placebo (N = 1202)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 1.01 [0.52–1.98] (3 trials, N = 1130)	GH RR 1.09 [0.90–1.33] (5 trials, N = 1831)	RR 1.12 [0.93–1.35] (1 trial, N = 1111)	PTB <37 weeks RR 0.95 [0.80–1.13] (3 trials, N = 1393) Length of gestation (days) Mean difference 2.23 [0.67–3.80] (3 trials, N = 1393) Prolonged gestation (>42 weeks) RR 1.19 [0.73–1.93] (1 trial, N = 533) BWt (g) Mean difference 55.79 [4.83—106.74] (3 trials, N = 1946) LBW <2500 g RR 0.99 [0.87–1.13] (2 trials, N = 1413) Stillbirth ≥24 weeks) RR 1.00 [0.06–15.96] (1 trial, N = 533) NND RR 2.01 [0.18–22.01] (1 trial, N = 579)
PET aRR 1.03 (0.72–1.48] (N = 2399) Clinical PET aRR 0.87 [0.60–1.25]	GH aRR 0.93 [0.71–1.21] GDM aRR 1.04 [0.75–1.44] Clinical GDM aRR 0.97 [0.74–1.27]	For weight aRR 0.90 [0.66–1.22] For length aRR 0.93 [0.75–1.16] (N = 2399) For head circum aRR 0.96 [0.78–1.19] (N = 2399)	LBW aRR 0.65 [0.44–0.96] Macrosomia aRR 1.27 [1.05–1.55]

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Smoking cessation				
Chamberlain 2013[54] (systematic review)	86 trials (N = >29,000 women)	Alloc con low risk: 10/86 trials. OAB: "*not calculable due to insufficient numbers of studies with low risk of bias*" IOD low risk: 22/86 trials.	Smoking cessation interventions (N = 4298)	Routine care (N = 4264)
Coleman 2012[55] (single trial)	N = 1050	Alloc con: yes OAB: yes Loss to f/u <20%: yes (18.5%)	Nicotine patches (15 mg every 16 h for 8 weeks) (N = 521)	Placebo (N = 529)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
		LBW <2500 g RR 0.87 [0.70–1.08] (6 trials, N = 3836) Very LBW RR 1.27 [0.60–2.71] (2 trials, N = 1666) Mean BWt Mean difference 36.72 [0.70–72.74] (9 trials, N = 4846)	PTB <37 weeks RR 0.82 [0.70v0.96] (14 trials, N = 7852) Stillbirths RR 1.08 [0.51–2.30] (4 trials, N = 2212] NND RR 2.06 [0.61–6.92] (3 trials, N = 2095) NICU admission RR 0.82 [0.52–1.29] (2 trials, N = 1140)
PET or eclampsia 3 (0.6%) vs. 5 (0.9%), p = NR	BP >140/90 mmHg on at least 2 occasions 24 (4.6%) vs. 25 (4.7%), p = NR Caesarean OR 1.45 [1.05–2.01] (N = 1024)	LBW OR 1.38 [0.90–2.09] BWt, unadjusted (kg) –0.02 [–0.10–0.05]	Miscarriage OR 1.52 [0.25–9.13] Stillbirth OR 2.59 [0.50–13.4] (N = 1041) PTB OR 0.90 [0.58–1.41] (N = 1024) NICU admission OR 0.95 [0.58–1.57] (N = –1024) 5 min Apgar <7 OR 0.91 [0.45–1.80] (N = 1024) Cord blood arterial pH <7 OR 0.57 [0.17–1.97] (N = 1024) IVH OR 0.67 [0.11–4.05] (N = 1024) Neonatal convulsions OR 1.02 [0.29–3.54] (N = 1024) NEC OR 0.50 [0.12–2.03] (N = 1024)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Thiazide diuretics				
Churchill 2007[56] (systematic review of 5 trials, N = 1836 low and high-risk women of which low and high-risk women are reported together here; see Appendix 6.2 for data on high-risk women)	5 trials (N = 1836)	"*The quality of all five studies was unclear*" Alloc con: unclear OAB: 4/5 trials LFU <20%: 5/5 trials	Thiazide diuretic (N = 1016)	Placebo or no thiazide (N = 820)
Vitamins C & E				
Rumbold 2008[57] (systematic review of 10 trials, N = 6533 low/ moderate- and high-risk women, of which the low/ moderate-risk women are presented here when possible; see Appendix 6.2 for data on the high-risk women)	5 trials (N = 3307)	Alloc con low risk: 3/5 trials. OAB low-risk: 5/5 trials (explicitly stated in 4). OAB low risk: 3/5 trials.	One/more antioxidants (N = 1858 as calculated from tables)	Placebo or no antioxidant (N = 1449)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.68 [0.45–1.03]* (4 trials, N = 1391) Severe PET RR 1.56 [0.26–9.17]* (2 trials, N = 1297)	HTN (new or worsening) RR 0.85 [0.68–1.08]* (2 trials, N = 1475) Nausea and vomiting RR 5.81 [1.04–32.46]* (2 trials, N = 1217) CS RR 1.0 [0.26–3.81]* (1 trial, N = 20)	None in the 1 trial that reported this outcome	Perinatal death RR 0.72 [0.40–1.27]* (5 trials, N = 1836) Stillbirth RR 0.60 [0.27–1.34]* (5 trials, N = 1836) NND RR 0.88 [0.40–1.97]* (4 trials, N = 1816) PTB RR 0.67 [0.32–1.41]* (2 trials, N = 465) BWt Mean difference 139.0 [–484.40–762.40]* (1 trial, N = 20) Gestation at birth Mean difference 0.70 [–0.71–2.11]* (1 trial, N = 20) Postmaturity >42 weeks RR 7.0 [0.41–120.16]* (1 trial, N = 20) 5 min Apgar <7 RR 3.0 [0.14–65.90]* (1 trial, N = 20)
RR 0.85 [0.48–1.51] (4 trials, N = 2441)	Antihypertensive therapy RR 1.77 [1.22–2.57]* (2 trials, N = 4272) Require antenatal hospital admission for HTN RR 1.54 [1.00–2.39]* (1 trial, N = 1877)	RR 0.71 [0.42–1.19]* (2 trials, N = 2104)	PTB RR 1.17 [0.92–1.48]* (2 trials, N = 2067) Any baby death RR 0.90 [0.53–1.51]* (2 trials, N = 2077)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Mahdy 2013[60] (single trial)	N = 299	Alloc con: yes. OAB: NR. LFU <20%: yes (6.3%).	Tocotrienol-rich fraction (TRF) of palm oil (100 mg/d) from early 2nd trimester until delivery (N = 151)	Placebo (N = 148)
Kiondo 2014[61] (single trial)	N = 932	Alloc con: yes OAB: yes LFU <20%: yes (10.6%)	Vitamin C 1000 mg/d from 12–22 weeks until delivery (N = 466)	Placebo (N = 466)
NO donors				
Schleussner 2014[141] (single trial of 111 low and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	N = 74	Allocation method not clear	Nitric oxide donor pentaerithrityl-tetranitrate (PTN) tablet twice daily (N = 33)	Placebo (N = 41)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.20 [0.02–1.66]	PET or GH RR 0.36 [0.12–1.09]		
Any PET RR 0.77 [0.37–1.56] Severe PET RR 1.25 [0.34–4.65]	GH RR 0.67 [0.43–1.03] APH RR 0.78 [0.29–2.1] PROM RR 0.79 [0.41–1.54] Abruption RR 0.5 [0.04–5.53] Vaginal delivery RR 1.0 [0.82–1.22]	LBW RR 1.07 [0.72–1.59]	BWt <2500 g RR 1.07 [0.72–1.59] Apgar <7 RR 1.17 [0.76–1.81] Admission to SCU RR 1.53 [0.95–2.43] Stillbirth RR 1.01 [0.54–1.87] Early NND RR 0.71 [0.27–1.83] Abortion RR 1.01 [0.40–2.51] PTB RR 0.92 [0.63–1.34] Stillbirth RR 1.01 [0.54–1.87]
PET/HELLP 6(21.2%) vs. 8 (19.5%) PET <32 weeks 3 (50%) vs. 5(62.5%)	Abruption 0 vs. 4(9.8%) CS 14 (41.2%) vs. 21 (53.8%)		IUGR or perinatal death 9 (27.3%) vs. 17 (41.5%) PTD <37 weeks 10 (30.3%) vs. 12 (29.3%) PTD <32 weeks 1 (3%) vs. 8 (19.5%) 1 min Apgar score 7.7 (+/–1.9) vs. 7.4 (+/–2.2) 5 min Apgar score 8.5 (+/–1.4) vs. 8.7 (+/–1.1) UA pH 7.3 (+/–0.1) vs. 7.3 (+/–0.1) BWt (g) 2734 (+/–889) vs. 2460 (+/–01004) Ventilation (NICU) 9 (30) vs. 7 (20.0)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Lifestyle changes				
Meher 2006[73] (systematic review)	2 trials (N = 106)	Alloc con low risk: "inadequately reported". OAB: "not possible" LFU <20%: "completeness of follow-up was not reported in either trial"	4–6 h rest/d (N = 16)	Normal activity (N = 16)
			4–6 h rest/d + Nutrient supplementation (N = 37)	Normal activity + placebo (N = 37)
Kramer 2006[26] (systematic review)	14 trials (N = 1014)	Alloc con: "in most of the trials, the method of treatment allocation was either by alternation or was not described". OAB: not specified LFU<20%: not specified	Increase in exercise in sedentary women (N = 280)	Maintain activity level (N = 276)
			Reduction in exercise in physically fit women (N = 28)	Maintain activity level (N = 33)
			Increase then reduction in exercise in physically fit women (N = 25)	Maintain activity level (N = 24)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.05 [0.00–0.83] (1 trial, N = 32)	GH RR 0.25 [0.03–2.00] (1 trial, N = 32)		
RR 0.13 [0.03–0.51] (1 trial, N = 74)	GH RR 0.15 [0.04–0.63] (1 trial, N = 74) CS RR 0.82 [0.48–1.41] (1 trial, N = 74)		
RR 1.17 [0.44–3.08] (2 trials, N = 82)	CS RR 0.96 [0.60–1.53] (3 trials, N = 386] Total gestational weight gain (kg) Mean difference 0.79 [–0.73–2.31] (4 trials, N = 122) Change in maternal fat mass (kg) Mean difference –1.51 [–3.06–0.04] (1 trial, N = 41) Change in maternal lean mass (kg) Mean difference 1.59 [0.38–2.80] (1 trial, N = 41)	BWt (g) Mean difference 49.49 [–27.74–126.73] (6 trials, N = 556)	PTB RR 1.82 [0.35–9.57] (3 trials, N = 111) 1 min Apgar Mean difference 1.0 [–1.37–3.37] (1 trial, N = 20) 5 min Apgar Mean difference 0.15 [–0.10–0.39] (4 trials, N = 462)
			PTB RR 1.18 [0.08–17.99] (1 trial, N = 61) BWt (g) Mean difference –135.0 [–368.66, 98.66] (1 trial, N = 61)
			Gestational weight gain (kg) Mean difference 0.90 [–1.59–3.39] (1 trial, N = 49) Bwt (g) Mean difference 460.0 [251.63–668.37] (1 trial, N = 49)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Lifestyle changes				
			Reduction, then increase in exercise in physically fit women (N = 26)	Maintain activity level (N = 24)
			Increase in exercise in overweight women (N = 37)	Maintain activity level (N = 35)
Periodontal therapy				
Niederman 2010[143]	N = 1082	Alloc con: yes OAB: yes LFU <20%: yes	Periodontal treatment in midpregnancy (N = 542)	Periodontal treatment after pregnancy (N = 540)

Alloc con, allocation concealment; APH, antepartum haemorrhage; aRR, adjusted relative risk; BWt, birth weight; CI, confidence interval; circum, circumference; CS, Caesarean section; ctx, contraction; dBP, diastolic blood pressure; DHA, docosahexanenoic acid; FHR, fetal heart rate; FM, fetal movement; GDM, gestational diabetes mellitus; GH, gestational hypertension; HELLP, haemolysis, elevated liver enzymes, low platelets; HIE, hypoxic ischaemic encephalopathy; IOD, incomplete outcome data; IOL, induction of labour; LBW, low birth weight; LFU, loss to follow up; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; LBW, low birth weight; Mg, magnesium; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; NNT, number needed to treat; NR, not reported; OAB, outcome assessment blinding; OR, odds ratio; PET, pre-eclampsia; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk; SEM, standard error of mean; SGA, small-for-gestational age; SVP, spontaneous vaginal delivery

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
			Gestational weight gain (kg) Mean difference −2.60 [−4.96-9-0.24)] (1 trial, N = 50) BWt (g) Mean difference −100.0 [−308.39–108.39] (1 trial, N = 50)
			PTB RR 1.89 [0.18–19.95] (1 trial, N = 72) BWt (g) Mean difference −5.0 [−241.27–231.27]
OR 0.82 [0.44–1.56]		BWt 3450 vs. 3410 g ($p = 0.12$)	PTB OR 1.05 [0.7–1.58]

† "Sensitivity analysis after excluding women with GDM showed that the reduction in pre-eclampsia did not persist by combining all interventions (RR 0.91 [0.75–1.11]) or in diet only group (RR 0.86 [0.45–1.64])." "2 studies on women with GDM had . . . insulin. We cannot rule out the possibility that insulin use could have been an important contributor to the beneficial effect observed"

‡ These results should be interpreted with caution as a large number of severe congenital anomalies and deaths of two sets of twins (with birth weights <750 g) in the supplemented group likely accounted for the increased risk of death observed. When deaths due to severe congenital abnormalities were excluded from the meta-analysis, no increased risk of NND was seen.

^ Severe PET complications: 1+ of the following outcomes: severe pre-eclampsia or early onset pre-eclampsia (32 weeks gestation), eclampsia, HELLP syndrome, placental abruption, severe gestational HTN (≥160 mmHg and/or ≥110 mmHg systolic and diastolic pressures, respectively)

Appendix 6.2

Randomised trials and systematic reviews of trials of interventions to prevent pre-eclampsia in women at increased risk (unless indicated by an '*' when all women were presented together)

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Antihypertensive drugs				
Abalos 2014[78] (systematic review)	49 trials (N = 4723)	Alloc con low risk: 17/49 trials. OAB low risk: 10/49 trials. IOD low risk: 45/49 trials.	ANY HYPERTENSIVE DRUG (N = 1476)	NO DRUG OR PLACEBO (N = 1375)
			ANY ANTIHYPERTENSIVE DRUG (N = 689)	METHYLDOPA (N = 650)
			ANY ANTIHYPERTENSIVE DRUG (N = 74)	CALCIUM CHANNEL BLOCKER (N = 62)

PET	*Other*	*SGA infants*	*Other*
Proteinuria/PET RR 0.93 [0.80–1.08] (23 trials, N = 2851) Severe PET RR 0.54 [0.24–1.23] (3 trials, N = 416) Eclampsia RR 0.34 [0.01–8.15] (5 trials, N = 578)	Maternal death RR 1.08 [0.24–4.83] (5 trials, N = 525) Severe HTN RR 0.49 [0.40–0.60] (20 trials, N = 2558) HELLP RR 2.02 [0.38–10.78] (1 trial, N = 197)	RR 0.97 [0.80–1.17] (20 trials, N = 2586)	RR 0.71 [0.49–1.02] (27 trials, N = 3230)
Proteinuria/PET RR 0.73 [0.54–0.99] (11 trials, N = 997)	Severe HTN RR 0.54 [0.30–0.95] (11 trials, N = 638) Antenatal hospital admission RR 0.77 [0.58–1.03] (2 trials, N = 275) CS RR 0.93 [0.78–1.12] (10 trials, N = 878) Abruption RR 2.02 [0.19–21.90] (1 trial, N = 173)	RR 0.80 [0.53–1.21] (7 trials, N = 597)	Perinatal death RR 0.73 [0.42–1.27] (19 trials, N = 1339) PTB< 37 weeks RR 0.76 [0.55–1.05] (9 trials, N = 623) Admission to SCBU RR 0.92 [0.67–1.26] (4 trials, N = 478)
Proteinuria/PET RR 2.15 [0.73–6.38] (2 trials, N = 128)	Severe HTN RR 2.09 [0.96–4.57] (2 trials, N = 136) HELLP RR 1.5 [0.26–8.60] (1 trial, N = 100) CS RR 1.57 [0.91–2.71] (1 trial, N = 100)	RR 1.0 [0.10–9.96] (1 trial, N = 36)	Total fetal or NND RR 1.0 [0.06–15.55] (2 trials, N = 136) PTB <37 weeks RR 0.63 [0.20–1.91] (1 trial, N = 36) Admission to SCBU RR 1.47 [0.44–4.89] (1 trial, N = 99)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Antihypertensive drugs				
Magee 2007[79] (single trial)	N = 132		Less tight BP control (N = 66)	Tight BP control (N = 65)
Aspirin				
Duley 2007[6] (systematic review of 59 trials, 37,500 women with only high-risk women included here; see Appendix 6.1 for data on moderate-risk women)	18 trials (N = 4121)	". . . *wide variation in study quality. The poorer quality studies were mostly the small early trials, with the more recent large studies tending to be of higher quality*."	Low-dose aspirin or dipyridamole (N = 14,326)	Placebo or no anti-platelet agent (N = 14,143)
Bujold 2010[86] (systematic review and meta-analysis)	27 trials (N = 11,348)	Alloc con: 12/12 trials. OAB: 4/12 trials. LFU <20%: 12/12 trials.	Low-dose (50–150 mg/d) aspirin started ≤16 weeks or earlier (N = 389)	Placebo or no treatment (N = 375)
		Alloc con: 22/22 trials. OAB: double blinding 16/22 trials LFU <20%: 22/22 trials	Low-dose aspirin (50–150 mg/d) started ≥16 weeks (N = 5691)	Placebo or no treatment (N = 5657)
Groeneveld 2013[84] (meta-analysis)	4 trials (N = 268)	Alloc con: 4/4 trials. OAB: 4/4 trials. LFU <20%: ? (No information provided)	Aspirin 100 mg/d in IVF patients (N = 131) Singletons (N = 96) Twins (N = 24)	Placebo (N = 137) Singletons (N = 91) Twins (N = 41)

PET	*Other*	*SGA infants*	*Other*
16 (24.2) vs. 20 (30.8)	Serious maternal complications 3 (4.6%) vs. 2 (3.1%) CS 35 (53.0%) vs. 37 (56.9%) Antenatal corticosteroids for fetal lung maturation 16 (24.2%) vs. 15 (23.1%) $MgSO_4$ for PET 10 (15.2%) vs. 12 (18.5%)		GA at delivery 36.9 ± 3.0 vs. 36.3 ± 3.3 BWt (g) 2675 ± 858 vs. 2501 ± 855 5 min Apgar <7 0 (0.0) vs. 2 (3.1) 5 min serious perinatal complications 9 (13.6%) vs. 14 (21.5%) NICU stay 15 (22.7%) vs. 22 (34.4%)
RR 0.75 [0.66–0.85] (18 trials, N = 4121)	GH RR 0.54 [0.41–0.70] (12 trials, N = 838) Abruption RR 0.75 [0.42–1.34] (4 trials, N = 2710)	RR 0.89 [0.74–1.08] (13 trials, N = 4239)	Fetal and neonatal death RR 0.69 [0.53–0.90] (17 trials, N = 4443) PTB <37 weeks RR 0.89 [0.81–0.97] (10 trials, N = 3252)
RR 0.47 [0.34–0.65] (9 trials, N = 765) Severe PET RR 0.09 [0.02–0.37] (3 trials, N = 278)	GH RR 0.62 [0.45–0.84] (3 trials, N = 278) Abruption RR 0.62 [0.08–5.03] (4 trials, N = 360)	IUGR (any definition) 16 weeks or less: RR 0.44 (0.30–0.65) (9 trials, N = 853) >16 weeks: RR 0.98 (0.87–1.10) (15 trials, N = 7027)	PTB RR 0.22 [0.10–0.49] (4 trials, N = 387)
RR 0.81 [0.63–1.03) (18 trials, N = 10,584) Severe PET RR 0.26 [0.05–1.26] (2 trials, N = 669)	GH RR 0.63 [0.47–0.85) (14 trials, N = 4303) Abruption RR 1.56 [0.96–2.55] (6 trials, N = 3583)	IUGR RR 0.98 [0.87–1.10] (15 trials, N = 7027)	PTB RR 0.90 [0.83–0.97] (16 trials, N = 10,398)
	"Hypertensive pregnancy complications" Singletons: OR 0.62 [0.22–1.7] Twins: OR 1.2 [0.35–4.4]		PTB Singletons: OR 0.52 [0.16–1.7] (N = 180) Twins: OR 1.6 [0.51–5.0)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Aspirin				
Villa 2013[85] (single trial + meta-analysis)	Single trial (N = 152) Meta-analysis 2 trials: Vainio 2002, Ebrashy 2005 (N = 346)	Alloc con: yes OAB: "double-blinded" LFU <20%: no (20.4%)	Aspirin (100 mg/d) (N = 61)	Placebo (N = 60)
Roberge *et al* 2012[88] (systematic review and meta-analysis)	4 trials (N = 392)	"*Studies with high risk of bias were considered for exclusion*"	Aspirin (50–150 mg/d) (≤16 weeks) (N = 201)	Placebo or no treatment (N = 191)
Henderson 2014[81] (systematic review of 23 trials, 22,988 women with only high-risk women included here; see Appendix 6.1 for data on moderate-risk women	15 trials (N = 12,656)	(Reported only for all 23 trials of low and high risk women together – See 'Henderson 2014', Appendix 6.1)	Aspirin (50–150 mg/d) (N = 6123)	Placebo or no treatment (N = 6522)
Cantu 2015[92] (secondary analysis of single trial)	Stratification by initiation (< or >16 weeks) N = 2539 Stratification by BMI N = 2479	Alloc con: not specified. OAB: no. LFU <20%: yes.	Aspirin (60 mg/d) <16 weeks (N = 225) Aspirin (60 mg/d) >16 weeks (N = 1029) BMI <30 (N = 756) BMI ≥30 (N = 487)	Initiation Placebo <16 weeks (N = 236) Placebo >16 weeks (N = 1013) BMI <30 (N = 756) BMI ≥30 (N = 480)
Bergeron 2016[82] (systematic review of 6 trials, 898 women with multiple gestations)	6 trials (N = 898)	Alloc con low risk: 5/6 trials. OAB low risk: 5/6 trials. IOD low risk: 4/6 trials	Aspirin (61–100 mg/d)	Placebo

PET	*Other*	*SGA infants*	*Other*
SINGLE TRIAL RR 0.70 [0.30–1.7] Severe PET RR 0.4 [0.1–1.2] Early onset PET RR 0.2 [0.03–2.1] META-ANALYSIS 2 trials (N = 346) RR 0.6 [0.37–0.83] Severe PET RR 0.3 [0.11–0.69) Preterm PET RR 0.2 [0.02–1.26] Term PET RR 1.0 [0.25–4.26]	GH RR 1.6 [0.6–4.2]	RR 0.3 [0.1–1.6]	
Severe PET RR 0.22 [0.08–0.57] Mild PET RR 0.81 [0.33–1.96]			
RR 0.76 [0.62–0.95] (13 trials, N = 12,184)	Abruption RR 1.12 [0.86–1.46] (3 trials, N = 12,366)	IUGR RR 0.80 [0.65–0.99] (13 trials, N = 12,504)	Perinatal death RR 0.81 [0.65–1.01] (10 trials, N = 12,240) PTB RR 0.86 [0.76–0.98] (10 trials, N = 11,779)
LDA <16 weeks RR 0.93 [0.67–1.31] LDA >16 weeks RR 0.90 [0.75–1.08] BMI <30 RR 0.91 [0.7–1.13] BMI ≥30 RR 0.89 [0.7–1.13]			
RR 0.67 [0.48–0.94] (5 trials, N = 898) Mild PET RR 0.44 [0.24–0.82] (# trials not specified, N = 724) Severe PET RR 1.02 [0.61–1.72] (# trials not specified, N = 724)		RR 1.09 [0.80–1.47] (4 trials, N = 1573 neonates)	PTB <37 weeks RR 1.11 [0.83–1.49] (# trials not specified, N = 1554 neonates)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Calcium				
Hofmeyr 2014[7] (systematic review of 24 trials, 17,954 women with only high-risk women included here when possible; see Appendix 6.1 for data on low-risk women. Data on women at unclear risk not presented.)	5 trials (N = 587)	Alloc con low risk: 4/5 trials. OAB low risk: 4/5 trials. IOD low risk: 3/5 trials	Calcium (≥1 g/d) (N = 281)	Placebo or no calcium (N = 306)
Calcium + Aspirin				
Asemi 2012[101] (single trial)	N = 42	Alloc con: yes. OAB: no. LFU <20%: yes	Calcium carbonate (500 mg/d) + aspirin (80 mg/d) for 9 weeks (N = 20)	Placebo (N = 22)
Souza 2014[102] (single trial)	N = 49	Alloc con: yes. OAB: yes LFU <20%: yes	Calcium (2 g/d) + aspirin (100 mg/d) (N = 23)	Placebo (N = 26)
Dietary Changes				
Allen 2014[12] (systematic review of 18 trials, 8712 women with low and high-risk women presented together here; see Appendix 6.1 for data on low-risk women. Data for women at unclear risk not presented.)	18 trials (N = 8712)	Alloc con: low risk 9/18 trials OAB: low risk 7/18 trials IOD low risk: 17/18 trials	Dietary change alone or with other change (N = 4342)	Placebo or no dietary change (N = 4370)
			DIET (6 trials, N = 1334)	Control (not specified) (6 trials, N = 1361)
			MIXED (Diet, physical activity & lifestyle) (6 trials, N = 733)	Control (not specified) (6 trials, N = 705)

PET	*Other*	*SGA infants*	*Other*
RR 0.22 [0.12–0.42] (5 trials, N = 587)	Hypertension (±PET) RR 0.47 [0.22–0.97] (4 trials, N = 327)		PTB RR 0.45 [0.24–0.83] (4 trials, N = 568) Admission to NICU RR 0.29 [0.03–2.48] (1 trial, N = 63) Stillbirth or death before hospital discharge RR 0.39 [0.02–9.20] (3 trials, N = 512)
	Serum hs-CRP 102.87 ± 1828.52 vs. 3227.75 ± 4760.70 ($p = 0.001$) Plasma TAC 68.96 ± 236.39 vs. 74.46 ± 199.07 ($p = 0.04$) GSH 304.33 ± 709.32 vs. –39.33 ± 174/33 ($p = 0.03$)		
Superimposed PET 42.2 vs. 73.1% ($p = 0.112$)		IUGR 25.0% vs. 2.8% ($p = 0.07$) BWt (g) 2563 ± 0 1033 vs. 2604 ± 811 ($p = 0.88$)	PTB 33.3% in both treatment and placebo groups LBW (<2500 g) 11 (42.3%) vs. 7 (30.4%) ($p = 0.40$) Very LBW (<1500 g) 5 (19.2%) vs. 3 (13.0%) ($p = 0.71$)
ANY DIETARY CHANGE RR 0.81 [0.69–0.94]† (18 trials, N = 8712) ($I^2 = 0\%$)			
RR 0.67 [0.53–0.85]* (6 trials, N = 2695)			
RR 0.93 [0.66–1.32]* (6 trials, N = 1438)			

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary Changes				
			ESSENTIAL FATTY ACIDS (6 trials, N = 2275)	Control (not specified) (6 trials, N = 2304)
Ziaei 2001[103] (single trial)	N = 100	Alloc con: not specified. OAB: no. LFU <20%: not specified	Allicin (100 mcg/d) in 3rd trimester (N = 50)	Placebo (N = 50)
Teran 2009[104] (single trial)	N = 235	Alloc con: yes. OAB: yes. LFU <20%: yes	CoQ10 (200 mg/d) (20 weeks GA to delivery (N = 118)	Placebo (N = 117)
Heparin				
Rodger 2014[111] (single trial)	N = 292	Alloc con: yes. LFU <20%: yes	Antepartum dalteparin N = 146	No antepartum dalteparin N = 143
			On-treatment analysis (N = 143)	On-treatment analysis (N = 141)

PET	*Other*	*SGA infants*	*Other*
RR 0.92 [0.71–1.18]* (6 trials, N = 6579)			
7 (14%) vs. 9 (18%) ($p = 0.799$)	–9 (18%) vs. 18 (36%) (***p*** = 0.043)		
RR 0.56 [0.33–0.96]	–		
8 (5.5%) vs. 5 (3.5%) difference –0.7 [–3.1–1.6] Severe or early onset PET 7 (4.8%) vs. 4 (2.8%) difference 2.0 (–2.8–6.8)	Symptomatic major VTE 1 (0.7%) vs. 2 (1.4%) difference –0.7 (–3.1–1.6) Abruption 4 (2.7%) vs. 3 (2.1%) difference 0.6 (–2.9–4.2)	SGA <10% 9 (6.2%) vs. 12(8.4%) difference –2.2 (–8.2–3.8) SGA <5% 2 (1.4%) vs. 3 (2.1%)	Pregnancy loss (any) 12 (8.2%) vs. 10 (7.0%) difference 1.2 (–4.9–7.3) Early pregnancy loss (≥3 at <10 weeks) 4 (2.7%) vs. 5 (3.5%) difference 0.8 (–4.8–3.2) Late pregnancy loss (≥2 at >10 weeks or ≥1 at >16 weeks) 6 (4.1%) vs. 2 (1.4%) difference 2.7(–1.0–6.5) PTB <37 weeks (23 (15.8%) vs. 17 (11.9%) difference 3.9 (–4.1–11.8) BWt of live births (g) 3186.2 vs. 3241.4 difference –55.2 [–238.6–128.1]
	Major bleeding 3 (2.1%) vs. 2 (1.4%) difference 0.7(–2.4–3.7) Minor bleeding (non-major) 28 (19.6% vs. 13 (9.2%) difference 10.4 (2.3–18.4) BMD 6 weeks postpartum 2.16 (0.35) vs. 2.23 (0.42) difference –0.07(–0.19–0.04)		

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Heparin				
Rodger 2014[110] (systematic review)	6 trials (N = 848)	Alloc con low risk: 5/6 trials. AB low risk: 3/6 trials. IOD low risk: 5/6 trials	Prophylactic LMWH (N = 425)	No LMWH (N = 423)
Lifestyle				
Meher 2006[126] (systematic review)	2 trials (N = 45)	Alloc con low risk: 2/2 trials. OAB: 1/2 trials. IOD low risk:2/2 trials	Moderate intensity aerobic exercise program (N = 23)	Normal physical activity (N = 22)
Yeo 2008[128] (single trial)	N = 79 (only have access to abstract)		Walking (N = 41)	Stretching (N = 38)
Periodontal therapy				
Kunnen 2010[142] (systematic review of 12 observational studies and 3 RCTs, of which results for 3 RCTs are reported here)	N = 3650	Alloc con: methods not reported. OAB: methods not reported. LFU <20% not reported	Periodontal treatment in midpregnancy (N = 1827)	Periodontal treatment after delivery (N = 1823)

PET	*Other*	*SGA infants*	*Other*
RR 0.46 [0.28–0.75] (N = 739) Severe or early PET RR 0.16 [0.07–0.36] (N = 665)	Abruption RR 0.42 [0.13–1.4] (N = 756)	SGA <10th centile RR 0.42 [0.29–0.59] (N = 713) SGA <5th centile RR 0.52 [0.28–0.94] (N = 604)	Pregnancy loss <20 weeks RR 0.89 [0.50–1.6] (N = 591) Pregnancy loss >20 weeks RR 0.41 [0.17–1.02] (N = 611) NND RR 0.31 [0.07–1.3] (N = 623) PTB <37 weeks RR 0.77 [0.62–0.96] (N = 556) PTB <34 weeks RR 0.45 [0.30–0.69] (N = 678)
RR 0.31 [0.01–7.09] (2 trials, N = 45)	GH RR 1.00 [0.07–13.37] (1 trial, N = 16) CS RR 0.93 [0.22–3.88] (1 trial, N = 29)	RR 3.00 [0.14–64.26] (1 trial, N = 16)	PTB RR 1.00 [0.07–13.37] (1 trial, N = 45)
14.6% [5.6–29.2] vs. 2.6% [0.07–13.8]			
RR 1.0 [0.78–1.28] (3 trials, N = 3650)			

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Kubik 2004[23] (single trial)	N = 138	"*double blinded trial*"	Vitamin and mineral supplement containing 15 mg zinc, 2 mg copper, and 20 μg selenium	Placebo
Makrides 2014[40] (systematic review of 10 trials, 9090 low and high risk women for whom outcomes were not reported by risk)	(Low and high risk women reported together) 10 trials (N = 9090)	Alloc con adequate: 2/10 trials. OAB adequate: 7/10 trials. IOD: low risk of attribution bias 3/10 trials	ORAL Mg (N = 4516) "*compositions of the Mg supplements, gestational ages at commencement, and doses administered varied*"	Placebo (8 trials, 3241) or no therapy (2 trials, 939 women) (Total N = 4180)
Bullarbo 2013[42] (single trial)	N = 59	"*double-blind randomisation*"	Mg (300 mg/d from 25 weeks) (N = 29)	Placebo (N = 30)
Mori 2012[43] (systematic review)	20 trials "*over 15,000 women and their babies*"	Alloc con adequate: 10/20 trials. OAB adequate: 13/20 trials. LFU "*ranged from 1% to 40%. Attrition bias was judged to be at high risk in only 3 trials*	ZINC (5–90 mg/d) starting before conception to 26 weeks (N not specified)	Placebo or no zinc (N not specified)
Parrish 2013[44] (single trial of 684 low and high-risk women with data on high-risk women reported here; see Appendix 6.1 for data on moderate risk women)	N = 154	Alloc con: yes OAB: yes LFU <20%: No (f/u was available for N = 267 low and high risk combined)	Fruit and vegetable juice powder concentrate (N = 76)	Placebo (N = 78)

PET	*Other*	*SGA infants*	*Other*
"*6.25% vs. 7.7%*"	SVD ("*natural deliveries*") "*75.0% vs. 53.8%*"		
RR 0.87 [0.58–1.32]* (3 trials, N = 1042)	Hospitalisation during pregnancy RR 0.65 [0.48–0.86]* (3 trials, N = 1158)	RR 0.76 [0.54–1.07]* (3 trials, N = 1291 infants)	Perinatal mortality RR 1.10 [0.72–1.67]* (5 trials, N = 5903 infants NND before hospital discharge RR 2.21 [1.02–4.75]‡* (4 trials, N = 5373 infants) Apgar <7 at 5 min RR 0.34 [0.15–0.80]* (4 trials, 1083 infants) Meconium-stained liquor RR 0.79 [0.63–0.99]* (1 trial, 4082 infants) Late FH decelerations RR 0.68 [0.53–0.88]* (1 trial, 4082 infants) Mild HIE RR 0.38 [0.15–0.98]* (3 trials, 4082 infants)
Average dBP at 37 weeks significantly lower (mmHg) (72/1.4 mean/SEM vs. 77/1.4, $p = 0.03$)	Fewer women developed an increase in dBP ≥15 mmHg ($p = 0.01$)		
PET or GH RR 0.83 [0.64–1.08] (7 trials, N = 2975)	IOL RR 0.27 [0.10–0.73] (1 trial, N = 52)	RR 1.02 [0.94–1.11] (8 trials, N = 4252 babies)	PTB RR 0.86 [0.76–0.97] (16 trials, N = 7637)
PET RR 0.91 [0.49–1.68] Mild PET RR 1.03 [0.07–16.1] Severe PET RR 1.37 [0.32–5.91] Superimposed PET RR 0.71 [0.32–1.56] (N = 154)	GH RR 1.37 [0.32–5.91]	RR 0.77 [0.17–3.32]	Live birth RR 104 [0.95–1.14] NND RR 0.21 [0.01–4.31] RDS RR 0.34 [0.12–1.01] NICU admission RR 0.34 [0.12–1.01]

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Prostaglandin precursors				
Makrides 2006[45] (systematic review of 2783 low and high risk women with high risk women reported here. See Appendix 6.1 for data on low risk women)	3 trials (N = 1725)	Alloc con low risk: 3/6 trials OAB: NR LFU <20%: "*Most trials reported outcome for at least 83% of all women recruited*"	Marine oil (N = 858)	Placebo or no marine oil (N = 877)
Zhou 2012[46] (single trial)	N = 2399	Alloc con: yes OAB: NR LFU <20%: NR	Fish oil (800 mg DHA/d in second half of pregnancy) (N = 1197)	Placebo (N = 1202)
Smoking cessation				
Chamberlain 2013[54] (systematic review)	86 trials (N = >29,000 women)	Alloc con: low risk of bias 10/86 trials OAB: "*not calculable due to insufficient numbers of studies with low risk of bias*" Incomplete outcome data attrition bias: low risk 22/86 trials	Smoking cessation interventions (N = 4298)	Routine care (N = 4264)
Coleman 2012[55] (single trial)	N = 1050	Alloc con: yes OAB: yes LFU <20%: yes (18.5%)	Nicotine patches (15 mg every 16 h for 8 weeks) (N = 521)	Placebo (N = 529)

PET	*Other*	*SGA infants*	*Other*
RR 0.80 [0.50–1.29] (2 trials, N = 553)		RR 1.17 [0.81–1.69] (1 trial, N = 263)	PTB <37 weeks RR 0.82 [0.60–1.12] (3 trials, N = 523) BWt 47 g [1–93 g] (3 trials, N = 2440) LBW RR 1.03 [0.80–1.33] 3 trials, N = 789) Stillbirth (≥24 weeks) RR 0.68 [0.11–4.08] (2 trials, N = 295) NND RR 1.01 [0.32–3.24] (3 trials, N = 1724)
PET aRR 1.03 (0.72–1.48] (N = 2399)	GH aRR 0.93 [0.71–1.21]	For wt aRR 0.90 [0.66–1.22] For length aRR 0.93 [0.75–1.16] (N = 2399) For head circum aRR 0.96 [0.78–1.19] (N = 2399)	
		LBW <2500 g RR 0.82 [0.71–0.94] (14 trials, N = 8562)	PTB <37 weeks RR 0.82 [0.70–0.96] (14 trials, N = 7852)
PET or eclampsia 3 (0.6%) vs. 5 (0.9%), *p* = NR	BP >140/90 mmHg on at least 2 occasions 24 (4.6%) vs. 25 (4.7%), *p* = NR CS OR 1.45 [1.05–2.01]	LBW OR 1.38 [0.90–2.09]	PTB OR 0.90 [0.58–1.41]

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Thiazide diuretics				
Churchill 2007[56] (systematic review of 5 trials, N = 1836 low and high-risk women of which low and high-risk women are reported here; see Appendix 6.1 for data on low-risk women)	5 trials (N = 1836)	"*The quality of all five studies was unclear*" Alloc con: unclear OAB: 4/5 trials LFU <20%: 5/5 trials	Thiazide diuretic (N = 1016)	Placebo or no thiazide (N = 820)
Vitamins C & E				
Rumbold 2008[57] (systematic review of 10 trials, 6533 low/ moderate-and high-risk women, of which the high-risk women are presented here when possible; see Appendix 6.1 for data on the low/ moderate-risk	5 trials (N = 3226)	Alloc con low risk: 2/5 trials (3/5 trials "unclear, as no information was provided about the methods of randomsation and alloc con") OAB low risk: 4/5 trials ("degree of blinding, if any, was unclear for 1 trial") LFU <20%: 3/5 trials. (2/5 did not mention any losses to follow-up)	One/more antioxidants (N = 1858 as calculated from tables)	Placebo or no antioxidant (N = 1449)

PET	*Other*	*SGA infants*	*Other*
RR 0.68 [0.45–1.03]* (4 trials, N = 1391) Severe PET RR 1.56 [0.26–9.17] (2 trials, N = 1297)	HTN (new or worsening) RR 0.85 [0.68–1.08]* (2 trials, N = 1475) Nausea and vomiting RR 5.81 [1.04–32.46]* (2 trials, N = 1217) CS RR 1.0 [0.26–3.81]* (1 trial, N = 20)	None in the 1 trial that reported this outcome	Perinatal death RR 0.72 [0.40–1.27]* (5 trials, N = 1836) Stillbirth RR 0.60 [0.27–1.34]* (5 trials, N = 1836) NND RR 0.88 [0.40–1.97]* (4 trials, N = 1816) PTB RR 0.67 [0.32–1.41]* (2 trials, N = 465) BWt Mean difference 139.0 [–484.40–762.40]* (1 trial, N = 20) Gestation at birth Mean difference 0.70 [–0.71–2.11]* (1 trial, N = 20) Postmaturity >42 weeks RR 7.0 [0.41–120.16]* (1 trial, N = 20) 5 min Apgar <7 RR 3.0 [0.14–65.90]* (1 trial, N = 20)
RR 0.56 [0.29–1.11] (5 trials, N = 3005) Severe PET RR 1.25 [0.89–1.76] (2 trials, N = 2495)	Antihypertensive therapy RR 1.77 [1.22–2.57]* (2 trials, N = 4272) Require antenatal hospital admission for HTN RR 1.54 [1.00–2.39]* (1 trial, 1877 women)	RR 0.92 [0.63–1.34] (3 trials, N = 3167)	PTB RR 1.09 [0.97–1.22] (3 trials, N = 3131) Any baby death RR 1.27 [0.85–1.90] (2 trials, N = 3067)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Villar 2009[137] (single trial)	N = 1365	Alloc con: method yes. OAB: not specified. LFU <20%: yes	Vitamin C (1000 mg/d) and Vitamin E (400 IU/d) (N = 687)	Placebo (N = 678)

PET	*Other*	*SGA infants*	*Other*
RR 1.0 [0.9–1.3] (N = 1355) Severe PET RR 0.8 [0.4–1.3] (N = 1355)	Eclampsia RR 1.5 [0.2–8.9) (N = 1355) HELLP RR 1.2 [0.5–3.1] (N = 1355) Abruption RR0.7 [0.2–1.8] (N = 1355) GH RR 1.2 [0.9–1.7] (N = 1355) Severe GH RR 0.9 [0.5–1.8] (N = 1355) Maternal ICU admission RR 0.2 [0.02–1.7] (N = 1355)		PTB <37 weeks RR 0.9 [0.7–1.0] (N = 1343) Delivery for PET <37 weeks RR 0.9 [0.6–1.2] (N = 1343) PTB <34 weeks RR 0.8 [0.6–1.0] (N = 1343) Delivery for PET <34 weeks RR 0.9 [0.6–1.5] (N = 1343) LBW <2500 g RR 0.9 [0.8–1.0] (N = 1515) LBW <1500 g RR 0.8 [0.6–1.1] (N = 1515) Any admission to NICU RR 0.8 [0.6–1.1] (N = 1515) >7 days in NICU (RR 0.9 [0.5–1.4] (N = 1515) Perinatal death RR 0.8 [0.6–1.2] (N = 1515) Any congenital malformation RR 1.6 [0.8–3.3] (N = 1515)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Spinnato 2007[138] (single trial)	N = 739	Alloc con: yes. OAB: not specified. LFU <20%: yes	Vitamin C (1000 mg/d) + Vitamin E (400 IU/d) (N = 371)	Placebo (N = 368)
L-arginine				
Dorniak-Wall 2014[117] (systematic review of 7 trials)	N = 884	Alloc con low risk: 3/7 trials. OAB low risk: 7/7. IOD low risk: 4/7 trials.	L-arginine (N = 228)	Placebo (N = 222)
Zhu 2013[114] (meta-analysis of 5 trials)	N = 277	Alloc con: not clear. OAB: 4/5 trials. LFU: "*2 of the 5 studies reported the details of withdrawals, whereas other 3 studies did not address this issue*"	L-arginine (N = 140)	Placebo (N = 137)

PET	*Other*	*SGA infants*	*Other*
aRR 0.78 [0.61–1.25]			Fetal and NND aRR 1.00 [0.53–1.87] PTD <37 weeks aRR 1.15 [0.89–1.50] PTD <34 weeks aRR 1.10 [0.65–1.84] LBW <2500 g aRR 0.98 [0.71-–1.36] Very LBW <1500 g aRR 1.08 [0.58–2.00] Apgar <4 at 1 min aRR 0.72 [0.37–1.39] Apgar <7 at 5 min aRR 0.72 [0.29–1.77] Baby died before discharge, or received NICU care aRR 0.93 [0.61–1.43] RDS aRR 1.11 [0.72–1.71] Ventilator support aRR 1.29 (0.60–2.74] Seizures aRR 2.08 [0.10–134.08)
PET or eclampsia OR 0.34 [0.21–0.55] (1 trial, N = 450)			PTB OR 0.48 [0.28–0.81] (1 trial, N = 450)
	Change in dBP Mean difference fixed −3.07 [−5.17–(−0.98)] (5 trials, 177)		GA at delivery Mean difference fixed 1.23 [0.46–1.99] (5 trials, N = 289)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
NO donors				
Schleussner 2014[141] (single trial of 111 low and high-risk women with high-risk women reported here; see Appendix 6.1 for data on low-risk women)	N = 36	Allocation method not clear	Nitric oxide donor pentaerithrityl-tetranitrate (PTN) tablet twice daily (N = 20)	Placebo (N = 16)

Alloc con, allocation concealment; APH, antepartum haemorrhage; aRR, adjusted relative risk; BMI, body mass index; BWt, birth weight; CI, confidence interval; circum, circumference; CS, Caesarean section; ctx, contraction; dBP, diastolic blood pressure; DHA, docosahexanenoic acid; FH, fetal heart; FHR, fetal heart rate; FM, fetal movement; GA, gestational age; GH, gestational hypertension; GSH, total glutathione; HELLP, haemolysis, elevated liver enzymes, low platelets; HIE, hypoxic ischaemic encephalopathy; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; IOD, incomplete outcome data; IOL, induction of labour; LBW; low birth weight; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; LBW, low birth weight; LFU, loss to follow-up; M&M, morbidity and mortality; Mg, magnesium; $MgSO_4$, magnesium sulphate; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; NNT, number needed to treat; NR, not reported; OAB, outcome assessment blinding; OR, odds ratio; PET, pre-eclampsia; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk; SCBU, special care baby unit; SEM, standard error of mean; SGA, small-for-gestational-age infants; SVP, spontaneous vaginal delivery; TAC, total antioxidant capacity; UA, umbilical artery; VTE, venous thromboembolism); WMD, weighted mean difference

PET	*Other*	*SGA infants*	*Other*
PET/HELLP 6 (30%) vs. 6 (37.5%) PET <32 weeks 5 (62.5%) vs. 1 (16.7%)	0 vs. 1 (6.2%) CS 12 (63.2%) vs. 7 (38.9%)		IUGR or perinatal death 7 (35%) vs. 11 (68.8%) PTD <37 weeks 4 (20%) vs. 7 (43.85) PTD <32 weeks 2 (10%) vs. 4 (25%)

‡ These results should be interpreted with caution as a large number of severe congenital anomalies and deaths of two sets of twins (with birth weights <750 g) in the supplemented group likely accounted for the increased risk of death observed. When deaths due to severe congenital abnormalities were excluded from the meta-analysis, no increased risk of NND was seen

Appendix 6.3

GRADE evaluation of best practice points for preventing pre-eclampsia

Recommendation
Prevention of pre-eclampsia in women at low risk
1. Calcium supplementation (of at least 1 g/d, orally) is recommended for women with low dietary intake of calcium (<600 mg/d, corresponding to less than two dairy servings per day
2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, exercise for maintenance of fitness, periconceptional use of a folate-containing multivitamin for prevention of neural tube defects, and smoking cessation for prevention of low birth weight and preterm birth
3. The following may be useful: periconceptional and ongoing use of a folate-containing multivitamin or exercise
4. The following are not recommended for pre-eclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursors or supplementation with magnesium or zinc
5. The following are not recommended: dietary salt restriction during pregnancy, calorie restriction during pregnancy for overweight women, low-dose aspirin, vitamins C and E, or thiazide diuretics
6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, workload or stress reduction, supplementation with iron with/without folate, vitamin D, pyridoxine, or food rich in flavanoids.
Prevention of pre-eclampsia in women at increased risk
1. The following are recommended for prevention of pre-eclampsia: low-dose aspirin and calcium supplementation (of at least 1 g/d) for women with low calcium intake
2. Low-dose aspirin (75–100 mg/d) should be administered at bedtime (I-B) and initiated after diagnosis of pregnancy but before 16 weeks' gestation (I-B) and may be continued until delivery (I-C)
3. Prophylactic doses of LMWH may be considered in women with previous placental complications (including pre-eclampsia) to prevent the recurrence of 'severe' or early-onset pre-eclampsia, preterm delivery, and/or SGA infants (I-B)

*Quality of the evidence**	*Strength of the recommendation†*
High	Strong
Low (alcohol), moderate (exercise for fitness), moderate (folate-containing vitamin), high (smoking cessation)	Strong (for all)
Low (folate-containing vitamin), Very low (exercise)	Weak (for both)
Low (prostaglandin precursors), low (magnesium), low (zinc)	Weak (for all)
Moderate (salt restriction), moderate (calorie restriction in obesity), moderate (low-dose aspirin), high (vitamins C & E), moderate (thiazides)	Strong (for all but aspirin) Weak (for aspirin)
Very low (heart healthy diet), very low (workload/stress reduction), low (iron supplementation), very low (pyridoxine), low (vitamin D), very low (food rich in flavonoids)	Weak (for all)
High (low-dose aspirin), high (calcium)	Strong (for both)
Moderate (for aspirin at bedtime), high (aspirin initiated after diagnosis of pregnancy but before 16 weeks' gestation), moderate (aspirin continued until delivery)	Weak (for aspirin initiated after diagnosis of pregnancy but before 16 weeks' gestation and for aspirin continued until delivery) Strong (for aspirin at bedtime)
High	Weak

continued

Appendix 6.3 *continued*

Recommendation
Prevention of pre-eclampsia in women at increased risk
4. The following may be useful: L-arginine (I-B), metformin in PCOS and/or overweight women (1-C), increased rest at home in the third trimester (I-C), and reduction of workload or stress (III-C)
5. The following may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-B), magnesium supplementation (I-C), and heparin thromboprophylaxis (I-B)
6. The following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of pre-eclampsia): abstention from alcohol (II-2E) , periconceptional use of a folate-containing multivitamin (I-A), and smoking cessation (I-E)
7. The following are **not** recommended: calorie restriction in overweight women during pregnancy (I-D), weight maintenance in obese women during pregnancy (III-D), antihypertensive therapy specifically to prevent pre-eclampsia (I-D), vitamins C and E (I-E)
8. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet (III-L), exercise (I-L), selenium (I-L), garlic (I-L); zinc, pyridoxine, iron (with or without folate), or multivitamins with/ without micronutrients all (III-L)

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

*Quality of the evidence**	*Strength of the recommendation*†
High (L-arginine), high (metformin), high (rest), low (workload or stress reduction)	Weak (for all)
Moderate (prostaglandin), moderate (magnesium), moderate (heparin)	Weak (for all)
Moderate (alcohol), moderate (folate), high (smoking)	Strong (for all)
Moderate (calorie restriction), moderate (weight maintenance), high (antihypertensive therapy), moderate (vitamins C and E)	Weak (for calorie restriction and weight maintenance) Strong (for antihypertensive therapy and vitamins C and E)
Low (heart healthy diet), moderate (exercise), moderate (selenium), moderate (garlic), low (zinc, pyridoxine, iron, multivitamins)	Weak (for all)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 7.1

GRADE evaluation of best practice points for diet, lifestyle and place of care

	*Quality of evidence**	*Strength of recommendation†*
1. There is insufficient evidence to make a recommendation about the usefulness of the following: ongoing salt restriction among women with pre-existing hypertension, new severe dietary salt restriction for women with any HDP, and a heart-healthy diet or calorie restriction for obese women specifically.	Very low	Weak
2. There is insufficient evidence to make a recommendation about the usefulness of: exercise, workload reduction, or stress reduction.	Very low	Weak
3. For women with gestational hypertension (without pre-eclampsia), some bed rest in hospital (compared with unrestricted activity at home) may be useful to decrease severe hypertension and preterm birth.	Low	Weak
4. For women with pre-eclampsia who are hospitalised, strict bed rest is not recommended.	Moderate	Weak
5. For all other women with HDP, the evidence is insufficient to make a recommendation about the usefulness of some bed rest, which may nevertheless, be advised based on practical considerations.	Very low	Weak
6. Inpatient care should be provided for women with severe hypertension or severe pre-eclampsia, however defined.	Low	Strong
7. A component of care through hospital day units or home care can be considered for women with non-severe pre-eclampsia or non-severe (pre-existing or gestational) hypertension.	Moderate (day units) Low (home care)	Strong
8. Transport from community to facility must be considered a responsibility of women, their communities, and their care providers.	Moderate	Strong

* The judgments about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 7.2

Diet, lifestyle and place of care recommendations from international guidelines*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Dietary & lifestyle change				
General comments				
Dietary changes			For women with chronic hypertension, ongoing salt restriction recommended	
Exercise				
Workload reduction				
Stress reduction				
Bed rest			For women with GH, (any) NOT recommended	For women with any HDP, (strict) NOT recommended (Low, Weak)
Place of care				
Transfer of care from midwifery				
Assessment in 2° care setting by health care provider trained in HDP			Women with GH	
Hospital day unit or antepartum home care				
Admit to hospital	Women with any HDP and BP ≥170/110 mmHg PET & protein-ur3a of ≥2+, or protein : creatinine ratio of ≥30	Women with any HDP and severe hypertension or severe PET	Women with GH	
Refer to critical care setting			Women with any HDP and severe hypertension or severe PET with specific end-organ dysfunction	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For women with chronic hypertension, ongoing salt restriction recommended		For women with chronic hypertension, extreme salt restriction NOT recommended For women with chronic hypertension, weight loss NOT recommended)	For women with chronic hypertension, insufficient evidence to recommend ongoing salt restriction or extreme (new) salt restriction For women with chronic hypertension and obesity, insufficient evidence to recommend calorie restriction or heart healthy diet
		For women with chronic hypertension and BP that is controlled, ongoing exercise recommended	For women with any HDP, insufficient evidence to recommend
			For women with any HDP, insufficient evidence to recommend
			Stress reduction for any HDP – insufficient evidence to recommend
		For women with GH or PET without severe features, (strict) NOT recommended (Low, Qualified)	For women with GH, (In hospital vs. unrestricted activity at home) may be useful For women with PET, (in hospital) NOT recommended For women with chronic hypertension or any HDP out of hospital, Insufficient evidence to recommend
	Women with PET		
			Consider for women with non-severe pre-existing hypertension, GH, or PET
			Women with any HDP and severe hypertension or "severe" PET

continued

Appendix 7.2 *continued*

BP, blood pressure; GH, gestational hypertension; HDP, hypertensive disorder of pregnancy; PET, pre-eclampsia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[41]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 8.1

Treatment wall charts

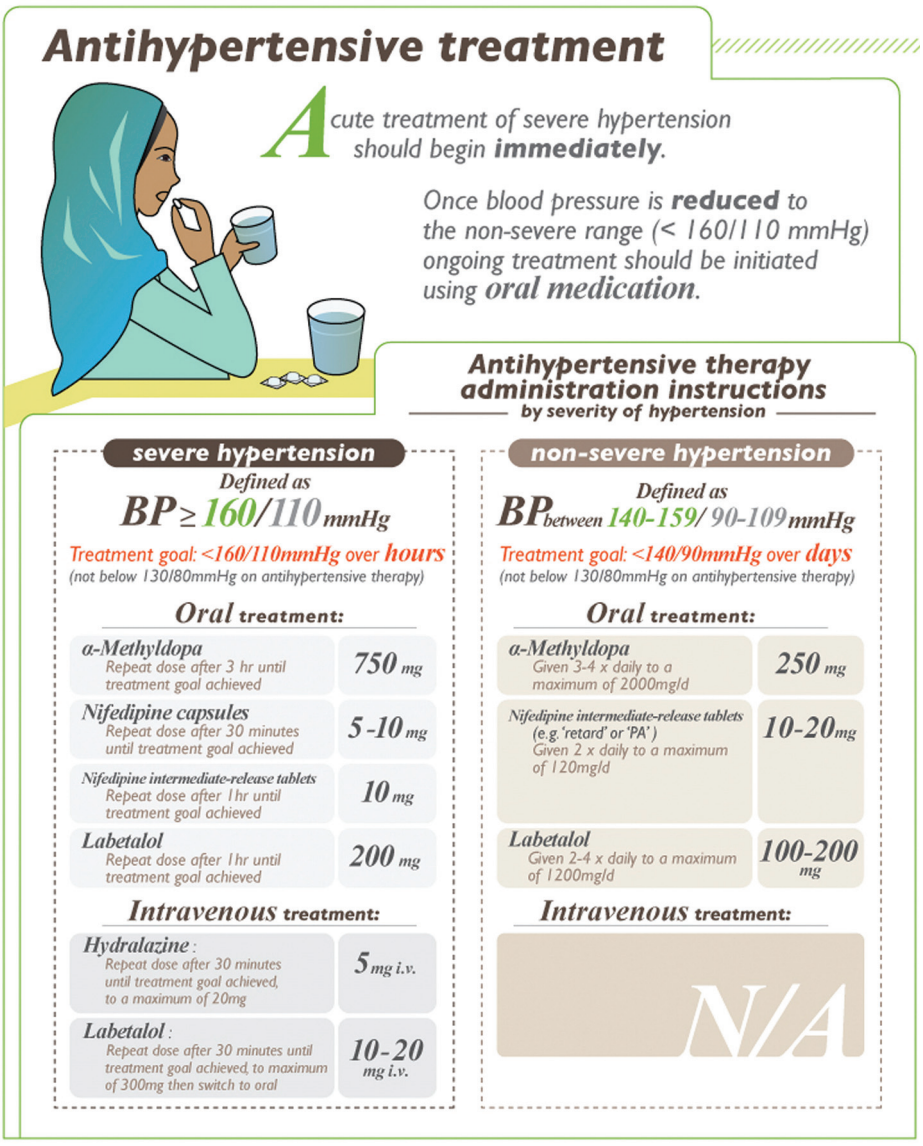


Figure S8.1 Wall chart for treatment of hypertension

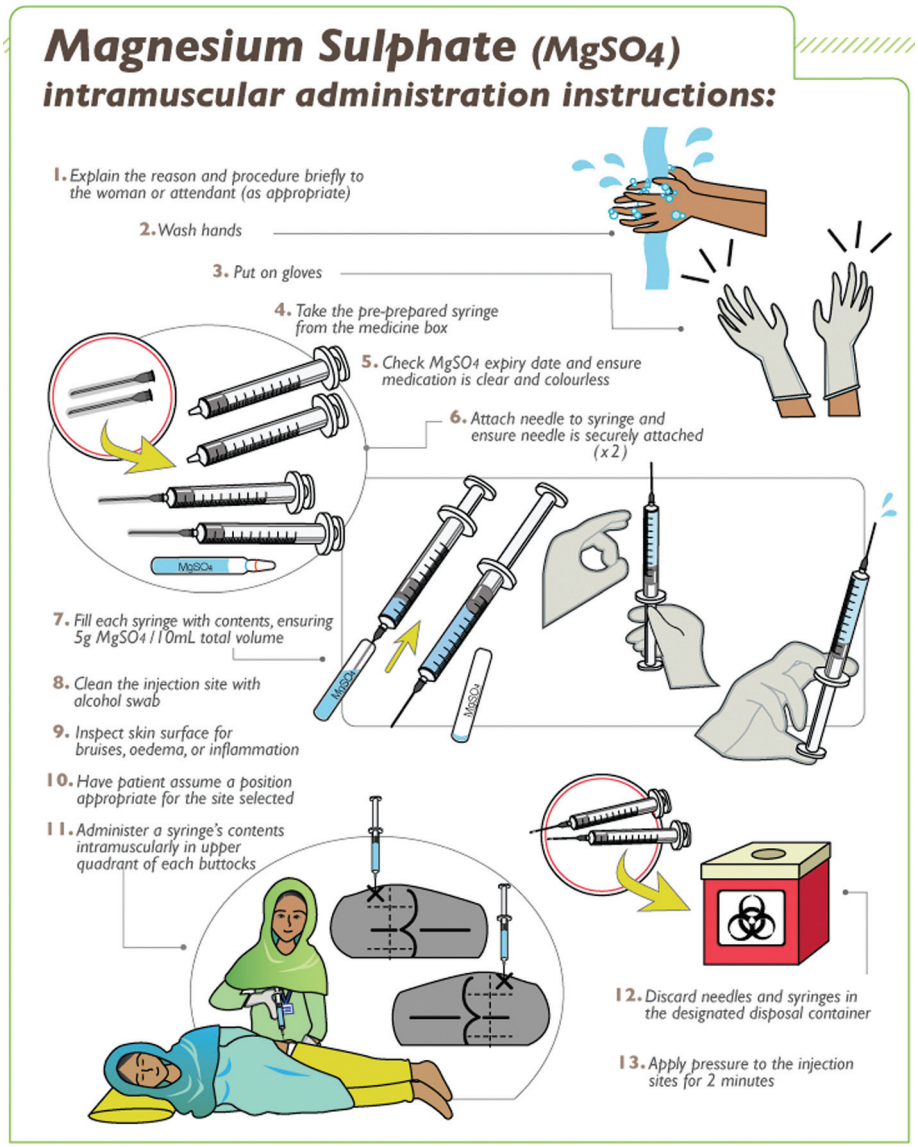


Figure S8.2 Wall chart for intramuscular administration of magnesium sulphate ($MgSO_4$)

Appendix 8.2

Essential Steps in Managing Obstetric Emergencies (ESMOE) – Emergency Obstetric Simulation Training (EOST)

The three drills listed here for eclampsia/pre-eclampsia are part of a more comprehensive set of drills designed for training in South Africa for a variety of obstetric emergencies, both maternal and neonatal. The instructions listed for these drills were adapted, with permission, from the ESMOE-EOST training manual.

Emergency drills (also known as 'fire drills') provide a simulated experience for participants to practice problem-solving and decision-making skills in the management of an obstetric or newborn emergency, with emphasis on thinking quickly, reacting (intervening) rapidly, and working as a team. Also, they provide opportunities to both revise essential skills and develop confidence in dealing with emergencies that do not occur frequently. Enquiries into poor outcomes from obstetric emergencies revealed the following common errors:

- Confusion in roles and responsibilities
- Failure to prioritise
- Failure to perform clinical tasks in a structured coordinated manner
- Poor communication
- Lack of organisational support?

Emergency drills should be carried out in the most realistic setting possible, such as the labour and delivery area of a hospital, clinic or maternity centre, where equipment and supplies are available for emergency interventions.

Drills should occur every 3 or 6 months. Try to avoid postponing a drill. The same drills should be repeated regularly to help health care workers to 'keep on their toes'. Ask yourself the following questions when you prepare your schedule:

- How will I/we ensure that all the emergency drills take place on time?
- How will I/we ensure that all staff are covered for each topic?
  - Day staff?
  - Night staff?
- Which skills do I/we not feel confident enough about?
- What will I/we do to improve my/our skills before doing the relevant emergency drill with the rest of the staff?
- How am I/are we going to improve the skills of staff members not feeling comfortable with certain skills after an emergency drill has been conducted?

The drills provided here cover eclampsia and pre-eclampsia.

- Scenario 1 (Eclampsia), version 1.2
- Scenario 2 (Pre-eclampsia), version 1.2
- Scenario 3 (Pre-eclampsia)

Start with Scenario 1 and proceed in order. Complete one scenario sheet for EVERY emergency drill. Please ensure that you complete the back page of the sheet where all participants should sign the attendance register.

Start a file for each scenario. Each time you have completed a drill, add that scenario sheet on top of the others in that file. Complete the summary sheets that should be kept in the front of this file.

Prepare for the drill by:

- Familiarising yourself with the requirements in terms of skills to demonstrate and materials to prepare for each scenario.
- Read the scenarios carefully before conducting the emergency drills. You must be comfortable and familiar with the different scenarios.
- Prepare all materials, medications, equipment, and manikins. Each scenario sheet has a list of materials needed for that drill on the first page.

Conducting an emergency drill: You or someone else should act as the "director" or "conductor" who facilitates the drill (10–15 min). The different roles for participants are illustrated on the diagram found on the first page of each scenario sheet.

Before beginning the drill, instruct the participants on which role they will play: (1) Team leader, (2) Helper 1, (3) Helper 2, or (4) Helper 3. The discoverer can become the team leader or a helper.

- One participant plays the role of patient.
- Invasive procedures are practised on the manikin/model that serves as the patient's "body".
- Procedures such as starting an IV and giving oxygen should be role played, using the appropriate equipment.
- A second participant plays the role of the "discoverer", while other participants are called on to assist the provider. It is important that during different drills, participants change their roles.
- The idea is to create a simulation that is as near as possible to a real emergency. Do not prompt participants as they participate in the drill and do not interrupt the drill with any discussion. However, throughout, participants should demonstrate what they would do and explain what they are doing and why they are doing it.

The facilitator/director/conductor uses the scenario sheet to orchestrate the drill. For information on how to do this and how to score the drill, see the instructions below under the heading "How to use the scenario sheets".

After the drill has been completed, give feedback (5–10 minutes) about how the team carried out the emergency drill (clinical skills and skills in conducting the drill). Facilitate an interactive discussion with participants who "acted" in the drill by asking them to:

- Comment on their performance, starting with strengths and then working towards areas that need improvement. Include aspects relating to clinical skills and to teamwork. Ask questions and encourage participants to ask questions. Review roles of providers who assist with the emergency, discuss what order there was, how the order could be improved and get participants to understand how to work as a team.
- Then, calculate the score for the drill (see scenario sheet) and review strengths and areas needing improvement based on the scenario sheet (where the column is blank).

Demonstrate each clinical skill with which problems were identified (clinical and teamwork) (5–10 minutes). Give participants a chance to return and demonstrate the skill(s) (10–30 minutes). Identify participants who need additional time to practise specific skills and arrange time after the session to work with each one.

Repeat the same drill (10 minutes) to give participants a chance to put together all of the skills in a repeat simulation. If you still identify serious problems with the drill (especially teamwork), repeat it for a third time.

Participants are evaluated by their ability to respond to an emergency as a team. Ideally this score will be 80% or higher. If one member of the team does well, the whole team will do well. If one member of the team is not performing to standard, the entire team will not pass. Participants must understand that they have a responsibility to themselves, team members, and women and newborns.

How to use the scenario sheet

- At the top of each scenario sheet, complete the line that indicates the topic of the scenario. (The number of the Module relates only to the ESMOE-EOST programme and can be ignored if not part of that programme in South Africa.)
- Complete the page of the sheet which is your summary record of what has happened in the drill, with space provided for: the before- and after-scores; observations and remarks on follow-up needed (e.g. for improvement of skills); and an attendance list to be signed by each participant.
- The scenarios are presented in a table with four columns:
  1. Information provided and questions asked
     - The scenario starts with *information about the patient's condition* written in italics across the first two columns. Give the information in the first block in italics to the participant who will act as "discoverer" (in front of the other participants) and ask him/her to repeat the information before starting with the drill. Provide the rest of the information in the blocks in italics as the drill progresses.
     - Each block with information in italics is followed by a question in bold that you should ask the participants. There are also discussion questions to use during feedback on the initial drill to push participants to problem-solve and give you an opportunity

to provide additional information about the condition and/or care provision.

2. Key reactions/responses expected from participants
   - Key reactions/responses expected from participants are provided in the second column of each scenario. The participant should demonstrate and explain what he/she is doing and also talk to the patient/family member of the patient.
   - Participants are expected to think quickly and react (intervene) rapidly when you provide information and ask questions.
3. Before (B)
   - Complete this during the initial drill.
   - Put a "Y" or "√" beside each step or task that the team performed correctly. If the team did NOT perform the step/task or did not perform it correctly, leave that space blank.
   - After the drill is complete, add up the number of "Y"s or "√"s and calculate the score for the drill.
4. After (A)
   - Complete this during the repeat drill.
   - Put a "Y" or "√" beside each step or task that the team performed correctly. If the team did NOT perform the step/task or did not perform it correctly, leave that space blank.
   - After the drill is complete, add up the number of "Y"s or "√"s and calculate the score for the drill.

Table S8.1 contains a fictitious example of a template for scoring a drill. Overall, the evaluation

Table S8.1 Example of how to score a drill

	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	*43*	*43*
CLINICAL SCORE: Total number of boxes ticked above	23	32
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)	√	√
2. Discoverer exchanges information with team leader and helpers using SBAR approach		√
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)	√	√
4. Team leader addresses team members by name		√
5. All observations are communicated clearly and loudly	√	√
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		√
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions	√	√
9. Team members cooperate with each other		√
10. The team determines the disposition of the patient (transfer, plan for further management)	√	√
C. Sign out/Documentation		
11. Person allocated to do documentation	√	√
12. Care (actions) completely documented (timing of intervention and administration of drugs)		√
D. Sequence of activities		
13. Activities performed in the correct order of priority		√
EXECUTION OF DRILL SCORE (A-D above)	*13*	*13*
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked	6	12
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)	29	44
Out of a possible score of	*56*	*56*

of the response to an emergency is graded according to the sum of two sub-scores: a 'clinical score' and 'execution of drill score' (made up of scores for A. Activation/communication skills, B. Response/ team work, C. Sign-out/documentation, and D. Sequence of activities). To calculate the score, add the two subs-cores together to get the total score. You can get the percentage by dividing the score received by the possible score and then multiplying by 100. In the example in Table S8.1, the "before" drill was scored as follows: total score: $23 + 6 = 29$ (for clinical + execution) out of a possible total of $43 + 13 = 56$ points, giving a percentage score of $(29/56) \times 100 = 52\%$. The "after" drill was scored as $32 + 13 = 45$ points out of a possible 56 points, giving a percentage score of $(45/56) \times 100 = 80\%$, a passing score.

Date: …… Name of health facility: ……

Name(s) of evaluator(s): Signature(s):

…… ……

…… ……

SCORE:

BEFORE	AFTER

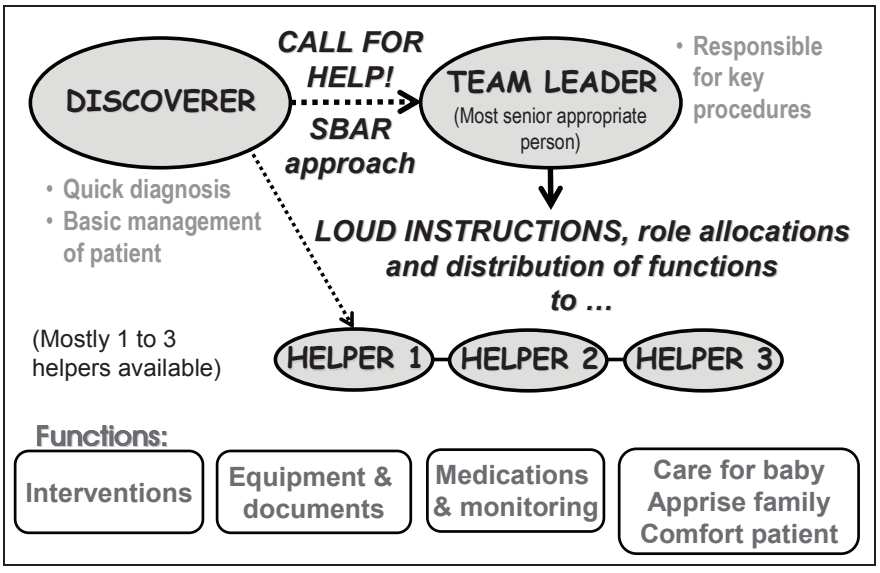
NOTES AND FOLLOW-UP

ATTENDANCE

	Name	Rank	Ward	Signature
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

PRE-ECLAMPSIA AND ECLAMPSIA
Scenario 1 (Eclampsia)

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • Ask one of the participants to be the patient. Brief the "patient" on the scenario. • Blank clinical notes sheet • Clock **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate **Learning materials** • Flip charts Module 4	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Ambu bag and mask • Oxygen mask Oxygen tubing • Oropharyngeal airway • Yankauer sucker • Pinardfetal stethoscope • Patellar hammer



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it.

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 1 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Ms X is 16 years old and is 37 weeks pregnant. This is her first pregnancy. She has presented to the labour unit with contractions and says that she has had a bad headache all day. She also says that she cannot see properly. While she is getting up from the examination table, she falls back onto the pillow and begins to have a convulsion.			
1. What will you do?	Call for HELP! Mobilise all available personnel!!		
	Checks airway to ensure that it is open, and turns Ms X onto her left side		
	Secure circulation, airway, and breathing (CAB), if needed		
	Protect her from injuries (fall) but do not attempt to restrain her		
	While caring for the woman, find out the history of the woman's present and past illnesses from her relatives. Ask if she has epilepsy, history of previous convulsions, other signs and symptoms (fever, vaginal bleeding, severe headache/blurred vision, epigastric pain, severe abdominal pain)		
Ms X has stopped fitting.			
2. What will you do now?	Ensure the woman's airway is open: aspirate the mouth and throat as necessary. Observe colour for cyanosis and need for oxygen (if available, place a pulse oximeter).		
	Keep the woman on her side or place a wedge under the woman's right side so she tilts toward her left side to reduce the risk of aspiration of secretions, vomit and blood.		
	Check lungs for aspiration: Lungs should always be auscultated after the convulsion has ended.		
	Give oxygen at 4-6L per minute by mask or nasal cannulae, if available.		
	Put in a large bore IV (16 gauge or largest available) cannulae or needle with Ringer's Lactate		
	Obtain blood for the laboratory before infusing IV fluids (haematocrit, clotting profile, creatinine, AST, liver function tests) [Do bedside Hb]		
	Prepare and give magnesium sulfate IV 4g (20% solution) made up to 200mls (normal saline for injection) over 20 mins followed by 100 ml RL		
	Follow promptly with 10 g of 50% magnesium sulfate solution, 5 g in each buttock deep IM injection with 1 mL of 2% lignocaine in the same syringe		
	Infuse IV fluids (Ringer's Lactate) at 125 ml/hour when patient is ready for transfer to prevent accidental fluid overload en route to next level of care.		
	Catheterise the bladder and monitor fluid intake and output, test urine for proteinuria		
	Listen for fetal heart		
	At the same time, tells Ms X (and family members) what is going to be done, listens to her and responds attentively to her questions and concerns		
	Plan for transfer to a level 2 or 3 hospital if in a PHC, CHC, or Level 1 Hospital.		
Discussion Question 1			
Ms X's airway is clear, pulse is 110 bpm, BP 170/90 mmHg, AVPU = V, colour is pink. Breathing is shallow, lung sounds are clear, RR 28 breaths / minute. Urine protein is 3+, Hb is 9 g/dL, glucose if 4.5mmol/l.			
3. What will you do now?	This BP is dangerously high and needs management. Depends on drugs available in the clinic and presence of contraindications in the woman: • Labetalol, as stat IV doses 20 mg stat (increasing by 40, 80, 80 80mg every 20 minutes to achieve hypertension control or to a maximum of 300 mg in 24 hours. • An alternative if Labetalol is not available: give nifedipine 10 mg orally swallowed (not chewed, sublingual or buccal) stat; repeat @15 min x 3 or until BP less than 160/110		
	Conduct a **targeted history and physical examination.** Perform a secondary survey (Big 5, Forgotten 4, Core 1)		
	Plan to monitor lung sounds, BP, respirations, reflexes, oxygenation, colour, level of consciousness, maternal pulse, urine output, and fetal heart rate, temperature, liver tenderness, and labour signs		
Discussion Question 2			
It is now 1 hour since Ms X received MgSO4 following her convulsion. Her airway is clear, pulse is 110 bpm, BP 150/90 mmHg, AVPU = V, colour is pink. Breathing is shallow, you note creps in the lung bases, RR 32 breaths / minute. Urine output was 40 mL over the past hour. Reflexes are hyper-reactive. Her cervix is closed and she has no uterine contractions. (You are in an institution with safe C/S facilities).			
4. What will you do now?	Diagnose pulmonary oedema; give furosemide 40 mg IV once, reduce fluids but keep line open. (She is already on oxygen).		
	Plan for delivery. (Either induction or C/S depending on blood results and fetal condition)		
	Monitor level of consciousness. reflexes, BP, maternal pulse, lung sounds, respiratory rate, oxygenation, (Saturation if possible) liver tenderness (and AST), urine output (and urea and creatinine), Haemoglobin and platelets, temperature, and fetal heart rate and labour signs		
CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE			

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 1 Version 1.2

	B = Before / A = After	B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
DISCUSSION QUESTIONS			
1. What would you do if there was no magnesium sulfate?	*If cannot give magnesium because it is unavailable drug of choice is lorazepam (Ativan) 1-2mg IV (max= 4mg/24 hours) or clonezepam (Rivotril) 1mg IV repeated in 30 minutes if required (beware respiratory depression) If not available prescribe valium 10mg IV slowly and further 10mg IV slowly if convulsions recur.*		
2. What other diagnoses must you rule out?	*Epilepsy, meningitis, encephalitis, tetanus, severe/complicated malaria.*		

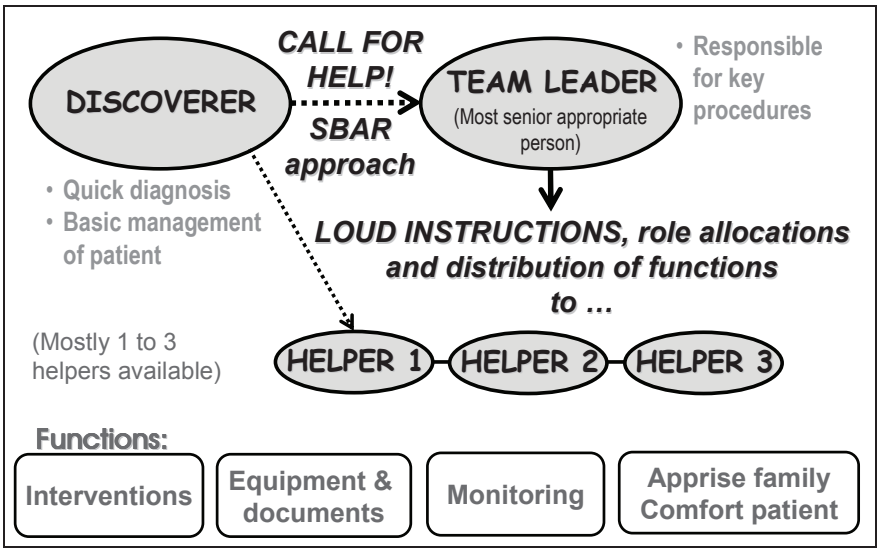
	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	***24***	***24***
CLINICAL SCORE: Total number of boxes ticked above		
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (eclampsia box; emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***37***	***37***

DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

PRE-ECLAMPSIA AND ECLAMPSIA
Scenario 2 (Pre-eclampsia)

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • Request colleague to be the patient **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate • Magnesium sulphate **Learning materials** • Flip charts Module 4	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Oxygen mask • Pinard fetal stethoscope • Patellar hammer



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it.

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 2 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Mrs P is aged 19, P2, who is 36/40 pregnant has presented to the antenatal clinic. She complains of headache, blurred vision and had some epigastric pain this morning.			
1. What will you do?	Call for HELP! Mobilise all available personnel!!		
	Place the patient on the examination table with left lateral tilt		
	Perform a rapid evaluation of the general condition of the woman, including circulation (pulse, BP), airway, breathing, oxygenation, level of consciousness (AVPU), skin colour, presence of anxiety and/or confusion, blood loss, and skin temperature		
	Check patellar reflexes		
	Simultaneously ask about the history of Ms P's present illness		
The nurse reports that her BP is 148/96 mmHg, pulse is 100 bpm, respirations 20 breaths per minute, temperature is 37.2 ℃, and 2+ proteinuria is present. On examination, you find her to have hyper-reflexia, clonus and to be jittery. AVPU = A. The FHR is 120/min and regular.			
Discussion Question 1			
3. What will you do now?	Give oxygen at 4-6L per minute by mask or nasal cannulae, if available		
	Put in a large bore IV (16 gauge or largest available) cannulae or needle		
	Prepare and give magnesium sulfate IV 4g (20% solution) made up to 200mls (normal saline for injection) over 20 mins followed by 100 ml RL		
	Follow promptly with 10 g of 50% magnesium sulfate solution, 5 g in each buttock deep IM injection with 1 mL of 2% lignocaine in the same syringe		
	Infuse IV fluids (normal saline or Ringer's Lactate) at 80 ml/hour when patient is ready for transfer to prevent accidental fluid overload en route to next level of care		
	Listen to the fetal heart		
	Catheterise the bladder and monitor fluid intake and output		
	At the same time, tells Ms P (and family members) what is going to be done, listens to her and responds attentively to her questions and concerns		
	Check the BP every 15 minutes until ambulance arrives. Give nifedipine if BP systolic >160mmHg or diastolic >110mmHg		
	Plan for transfer to a level 2 or 3 hospital if in a PHC, CHC, or Level 1 Hospital and complete SBAR form		
Discussion Question 2			
3. What will happen once Ms P arrives as the referral hospital?	Conduct a **targeted history and physical examination.** Perform a secondary survey (Big 5, Forgotten 4, Core 1)		
	Obtain blood for laboratory investigations: haematocrit, clotting profile, creatinine, AST, liver function tests		
After 15 minutes at the referral hospital, Ms P is resting quietly. She still has a headache and hyper-reflexia.			
4. How will you plan to monitor her condition?	Check respirations, reflexes, oxygenation, colour, level of consciousness, maternal pulse,urine output, and fetal heart rate (FHR) at least hourly, or more frequently as needed		
	Check BP every 15 minutes for the first hour, and decide if antihypertensive medications are needed		
	Check temperature every four hours (hyperpyrexia may occur)		
	Check for liver tenderness		
	Check for signs of labour		
Discussion Question 3			
Her pulse is now 98 bpm, BP 156/110 mm Hg, respiration rate 20 breaths/minute, and urine output was 40 mL since catheterization at the clinic. She still has hyper-reflexia. You detect that the fetal heart rate is 120 bpm, slowing to 100 bpm after a contraction.			
5. What will you do now?	This BP is dangerously high and needs management. Depends on drugs available in the clinic and presence of contraindications in the woman: • Give nifedipine 10 mg orally swallowed (not chewed, sublingual or buccal) stat; repeat @15 min x 3 or until BP less than 160/110 • [An alternative is labetalol, as an IV infusion at 20 mg/hour (200 mg in 200 mL of normal saline, run at 20 mL/hour), increasing by 20 mg/hour every 20 minutes to achieve hypertension control or to a maximum of 300 mg in 24 hours].		
	Continue monitoring the woman and fetus.		
	Plan to keep the BP between dBP 90 and 100 mmHg		
Discussion Question 4			
6. What is your further plan of action?	Ms P needs delivery .The main concern now is fetal heart abnormality		
	Ms P should be prepared to go to the operating room for cesarean section. Only once stable, position Ms P on her side		
	Tells Ms P (and family members) what is happening, listens to her concerns and provides reassurance		
Discussion Question 5			

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 2 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
	CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE		
DISCUSSION QUESTIONS			
1. What is Ms P's problem?	*Ms P's symptoms and signs are consistent with severe pre-eclampsia*		
2. What is your main concern at the moment?	*The main concern at the moment is to prevent Ms P from convulsing*		
3. What are signs of magnesium toxicity that you should check for before giving an additional dose?	• *Respiratory rate falls below 16 per minute.* • *Patellar reflexes are absent.* • *Urinary output falls below 30 mL per hour over preceding 4 hours.*		
4. What counselling will you give the woman and her family?	*Explain the severity of the illness, the necessity for organ system evaluation and then delivery. Reassure at this pregnancy duration there should not be any problems with the baby*		
5. What is the appropriate time for delivery?	*Mother must be fully resuscitated before a caesarean section is performed for fetal distress*		

	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	***28***	***28***
CLINICAL SCORE: Total number of boxes ticked above		
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***40***	***40***

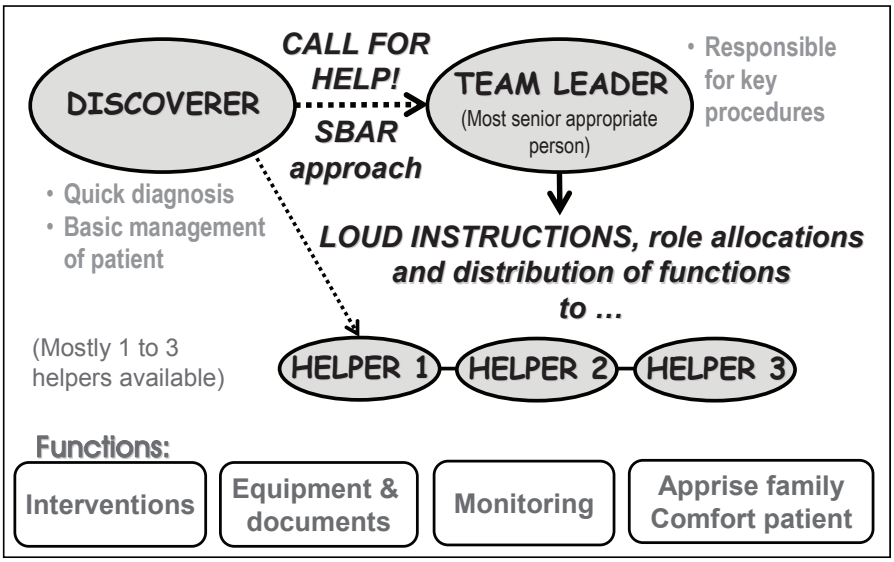
DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

ESMOE-EOST: Preeclampsia. Module , Scenario 3

PRE-ECLAMPSIA
Scenario 3

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • "Actor" • Blank clinical notes sheet • Clock **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate **Learning materials** • Flip charts Module	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Ambu bag and mask • Oxygen mask • Oxygen tubing • Oropharyngeal airway • Yankauer sucker • Model of larynx • Defibrillator if available



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it. As you perform each step the facilitator will give you the results of your actions

ESMOE-EOST: Preeclampsia. Module , Scenario 3

	B = Before / A = After	B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Mrs C a 25 year old Gravida 1, para 0, presents at casualty complaining she is feeling nauseaous. She is 31 weeks pregnant by early ultrasound done by her family physician. ***What will you do?***			
1. Shake and Shout	Responds appropriately to your greeting		
2. Call a CAB	*Assess circulation; pulse 120 beats per minute, blood pressure 205/118mmHg*		
	Assess Airway: Clear		
	Assess Breathing: Respiratory rate 24		
	Call for Help		
	Lie on bed in left lateral position		
The doctor/ senior sister and two other nurses arrive **(What must be done now?)**			
	Insert a IV line and obtain blood for Hb, platelets, AST, U&E		
	Run IV line of ringers lactate at 100ml/minute		
	Put 4g MgSO4 into 200ml normal saline and run in as a side drip over 20 minutes		
	Put up oxygen mask		
	Insert catheter		
	Repeat observations		
More information **(What must be done now?)**			
3. Big 5, Forgotten 4, Core 1 (Secondary survey)	*Further History: Ask about symptoms, etc.: No headache, blurred vision or epigastric pain*		
	CNS: Very brisk reflexes		
	CVS: Pulse 110 after, BP 170/115 mmHg after 10 minutes; heart sounds normal; repeat BP every 5 minutes		
	Resp: RR 20 breaths per minute; saturation 98% on oxygen mask; lung bases clear		
	Liver and GIT; Not tender, no jaundice		
	Renal: Catheter drains 20 mls concentrated urine, 3+ proteinuria		
	Heamatological: Not pale, no signs ecchymosis		
	Endocrine: Breast, thyroid normal; Glucose 5.1mmol/l		
	Musculo-skeletal: No DVTs		
	Immune: HIV neg, Temp. 36.4^{0}C		
	Core 1:, SF measurement 23 cm, Uterus not tender but irritable, Cephalic presentation, oligohydramnios, FH beat present,		
	Core 2: No vaginal bleeding (vaginal examination not done)		
4. Diagnosis	*Severe Pre-eclampsia at 31 weeks gestation*		
5. Further management	*Repeat observations At 20 minutes BP175/115mmhg, pulse 110, RR 18 breaths/min.*		
	Give labetalolol if available, or nifedipine		
	Give corticosteroids		
	Run fluids in at 100ml/hour		
Blood results: Hb 14g%, Platelets 120, AST 40, Urea 4.2, Creatinine 110, Sonar examination: 930gm, AEDF, AFI 3 **(What must be done now? Discussion)**			
	CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE		
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management		***23***	***23***

DISCUSSION QUESTIONS	
1. Should the baby be monitored	*Discuss management at every level of care; if cannot refer what actions should be taken.*
2. What is the place of expectant management	*Only in tertiary units*

ESMOE-EOST: Preeclampsia. Module , Scenario 3

EXECUTION OF DRILL SCORE:	Before (B)	After (A)
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***36***	***36***

DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

Appendix 8.3

GRADE evaluation of best practice points regarding fluids, drugs and transfusion

	*Quality of evidence**	*Strength of recommendation†*
Fluid therapy		
1. Plasma volume expansion is not recommended for women with pre-eclampsia.	Moderate	Strong
2. IV fluid intake should be minimized to 80 mL/h in women with pre-eclampsia to avoid pulmonary oedema.	Low	Strong
3. Fluid should not be routinely administered to treat oliguria (<15 mL/h for 6 consecutive hours) for the sole purpose of increasing urine output.	Very low	Weak
4. For treatment of persistent oliguria, neither dopamine nor furosemide is recommended.	Moderate	Strong
Antihypertensive therapy for severe hypertension		
1. BP should be lowered to <160 mmHg systolic and <110 mmHg diastolic.	Low	Strong
2. Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting (capsules), parenteral hydralazine, or parenteral labetalol	High	Strong
3. Alternative antihypertensive medications include oral methyldopa, oral labetalol, oral clonidine, oral captopril (only postpartum), or a nitroglycerin infusion	Moderate (labetalol, nitroglycerin) Low (clonidine, captopril postpartum) Very low (methyldopa)	Weak
4. Refractory hypertension may be treated with sodium nitroprusside	Low	Weak
5. Nifedipine and $MgSO_4$ can be used contemporaneously	Moderate	Weak
6. $MgSO_4$ is not recommended solely as an antihypertensive agent.	High	Strong
7. Continuous FHR monitoring is advised until BP is stable.	Very low	Weak
Antihypertensive therapy for non-severe hypertension		
1. Antihypertensive drug therapy should aim for a dBP of 85 mmHg.	High	Strong
2. The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.	Very low	Weak
3. Initial therapy in pregnancy can be with one of a variety of antihypertensive agents methyldopa, labetalol, other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol and calcium channel blockers (nifedipine).	High (methyldopa, labetalol, nifedipine), moderate (other beta-blockers)	Strong

continued

Appendix 8.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Antihypertensive therapy for non-severe hypertension		
4. ACE inhibitors and ARBs should not be used during pregnancy.	Moderate	Strong
5. Atenolol and prazosin are not recommended prior to delivery.	Low	Weak
6. Captopril, enalapril, or quinapril may be used postpartum, even during breastfeeding.	Low	Weak
7. There is no compelling evidence that antihypertensive treatment of hypertension (with labetalol, nifedipine, and probably methyldopa) is associated with adverse effects on child development.	Low	Weak
8. Gestational hypertension and pre-eclampsia may each be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalising behaviours.	Very low	Weak
$MgSO_4$		
1. $MgSO_4$ is recommended for first-line treatment of eclampsia.	High	Strong
2. $MgSO_4$ is recommended for eclampsia prevention in women with severe pre-eclampsia.	High	Strong
3. $MgSO_4$ may be considered for eclampsia prevention in women with non-severe pre-eclampsia based on cost considerations.	Moderate (based on effectiveness; cost from only one trial)	Strong
4. $MgSO_4$ should be used in standard dosing, usually 4 g IV loading dose followed by 1 g/h	Moderate	Strong
5. Routine monitoring of serum Mg levels is not recommended.	Low	Strong
6. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to $MgSO_4$ or it is ineffective.	High (phenytoin) Moderate (diazepam)	Strong
7. In women with pre-existing or gestational hypertension, $MgSO_4$ should be considered for fetal neuroprotection in the setting of imminent preterm birth within the next 24 hours at $\leq 33^{+6}$ weeks.	Moderate (extrapolating from preterm labour)	Strong
Therapies for HELLP syndrome		
1. Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units	Very low	Strong
2. For a platelet count $<20 \times 10^9$/L, platelet transfusion is recommended, regardless of mode of delivery.	Low	Strong
3. For a platelet count $20–49 \times 10^9$/L platelet transfusion is recommended prior to Caesarean delivery.	Low	Strong
4. For a platelet count $20–49 \times 10^9$/L, platelet transfusion should be considered prior to vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy.	Low	Weak

continued

Appendix 8.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Therapies for HELLP syndrome		
5. For a platelet count of $\geq 50 \times 10^9$/L, platelet transfusion should be considered prior to either Caesarean or vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy.	Low	Weak
6. We do not recommend corticosteroids for treatment of HELLP until they have been proven to decrease maternal morbidity	Moderate/Low (RCTs did not show change in hard outcomes but underpowered)	Weak
7. We recommend against plasma exchange or plasmapheresis for HELLP, particularly within the first 4 days postpartum.	Low	Strong
Other therapies for treatment of pre-eclampsia (from 2008 document)		
1. Women with pre-eclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity.	High	Strong
2. Thromboprophylaxis may be considered antenatally among women with pre-eclampsia who have two or more additional thromboembolic risk markers, postnatally among women with pre-eclampsia who have at least one additional thromboembolic risk marker, or postnatally among women any HDP who were on antenatal bed rest for at least 7 days	Low	Weak

FHR, fetal heart rate; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, Haemolysis, Elevated Liver enzyme, Low Platelet syndrome; $MgSO_4$, magnesium sulphate

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 8.4

Sample policy briefs

ANTIHYPERTENSIVE THERAPY– Policy brief

"… the report of the 'Confidential Enquiries into Maternal Deaths in the UK' that covered the hypertensive disorders of pregnancy (2005-8) identified the **failure to treat** the **severe** (particularly systolic) **hypertension** of pre-eclampsia as the **single most serious failing** in the clinical care of these women who died."

WHY IS ANTIHYPERTENSIVE THERAPY IMPORTANT?

Women with severe hypertension, defined as BP of ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic in pregnancy (or postpartum), should be treated with antihypertensive therapy. The World Health Organization (WHO) 'Prevention and Treatment of Pre-eclampsia and Eclampsia' recommendations strongly recommend use of antihypertensive therapy for treatment of severe hypertension during pregnancy, because treatment of severe hypertension in pregnancy or postpartum decreases maternal risk, particular that of stroke. This has been demonstrated in the 'Confidential Enquiries into Maternal Deaths in the UK (2009-12) and through a similar process in South Africa.

Antihypertensive therapy for **non-severe** pregnancy hypertension decreases the risk of severe hypertension and the associated risks.

WHICH ANTIHYPERTENSIVE SHOULD BE USED?

The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.

Severe hypertension

The antihypertensive agents used most commonly are oral nifedipine (capsules or tablets) or intravenous labetalol or hydralazine. Hydralazine is on the WHO Model List of Essential Medicines (2015) for treatment of severe hypertension, although nifedipine capsules (10mg) are listed as a tocolytic. Both of these medications are on the essential medicines lists of most LMICs.

Oral agents (such as methyldopa or labetalol) are far better-suited to management of severe hypertension than are parenteral agents, especially in resource-limited settings, as they do not require an investment in either physical resources (i.e. intravenous tubing, syringes and needles) or human resources (as administration of parenteral agents is by nurses or often, doctors). Also, oral antihypertensive agents do not mandate the same level of monitoring given a lower risk of dropping the blood pressure quickly and causing fetal compromise.

Non-severe hypertension

Oral methyldopa and oral labetalol are used most frequently for treatment of non-severe hypertension, but there are a wide variety of agents that can be used. Only methyldopa is on the WHO Model List of Essential Medicines (2015) for non-severe pregnancy hypertension.

Above: An instructional chart for Mozambique health workers showing the administration of methyldopa to a woman who has non-severe hypertension in pregnancy

ACTIONS

- **Create regulatory efficiency by** updating the National Essential Medicines List to include antihypertensive agents for treatment of severe and non-severe hypertension.
- **Identify and promote opportunities** where maternal health commodities can be integrated into the broader Health Management Information System.
- **Task-shift** to enable midwives, nurses, and lower-level providers to prescribe and safely administer the appropriate antihypertensive agent.
- **Strengthen the treatment at the community level** where few centers initiate treatment for pre-eclampsia and eclampsia. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome.
- **Update national protocols and clinical guidelines** to facilitate education, training and proper use of antihypertensive therapy among health care workers, particularly those in the community Materials should include a standardised toolkit that includes treatment guidance such as a visual record of monitoring and treatment, as well as other drugs needed for women with severe pre-eclampsia/eclampsia.

MAGNESIUM SULFATE ($MgSO_4$) – Policy brief

WHY USE MAGNESIUM SULFATE?

Magnesium sulfate ($MgSO_4$) has been on the World Health Organization(WHO) Model List of Essential Medicines since 1996. $MgSO_4$ is recommended by the WHO as the most effective, safe, and low-cost treatment for eclampsia prevention and treatment.

"…(F)ewer than half of centres initiated treatment for pre-eclampsia (40.0%) or eclampsia (28.0%) prior to transfer to facility (rural Nigeria). Taken in the context of the 'three delays' model of maternal mortality (delays in triage, **treatment,** transport), this represents a **lost opportunity** for improving maternal outcome"

- **First-line treatment of eclampsia**
  $MgSO_4$ more than halves the risk of recurrent eclampsia compared with other agents. Also, $MgSO_4$ is associated with a lower risk of both maternal death (compared with either diazepam or a lytic cocktail) and maternal pneumonia and respiratory support (compared with either phenytoin or a lytic cocktail). Although the WHO Model List of Essential Medicines (2015) also lists benzodiazepines as anticonvulsants, they are not recommended for eclampsia treatment.
- **First-line therapy for eclampsia prevention in severe pre-eclampsia**
  Compared with placebo or no treatment, $MgSO_4$ more than halves the risk of eclampsia among women with pre-eclampsia. $MgSO_4$ may be considered for eclampsia prevention in women with non-severe pre-eclampsia based on cost considerations. In under-resourced settings, 43 women with pre-eclampsia need to be treated to prevent one case of eclampsia, for a cost (in 2001 US dollars) of $456.
- **Prevention of cerebral palsy in infants born before 34 weeks' gestation**
  $MgSO_4$ decreases the risk of cerebral palsy by 30% when infants are born before 34 weeks' gestation, based on the results of four trials and over 4,000 babies. $MgSO_4$ may be administered before delivery in the same way as for eclampsia prevention.

ACTIONS

Above: An instructional chart showing the procedure of im $MgSO_4$ administration.

© PRE-EMPT Project

- **Standardise MgSO4 concentrations** in order to address complicated dosage preparations and variations in dosing regimens that are among the major barriers to use of $MgSO_4$ according to the Maternal Health Technical Resource Team of the UN Commission on Life-Saving Commodities. The WHO is advocating use of a 50% solution, equivalent to 50 g of $MgSO_4$ in 100mL of solution; as each ampule contains 10mL of solution, each vial contains 5 g of $MgSO_4$. National or institutional essential medicine lists (EMLs) should be updated to include this standardised concentration (50%) of $MgSO_4$.
- **Strengthen supply chains** by offering results-based financing of maternal health commodities that rewards providers when they meet performance standards for $MgSO_4$ administration.
- **Ensure procurement** by providing advanced market commitments or pooled procurements at the regional/central level to incentivise manufacturers to supply $MgSO_4$ and create a more sustainable market
- **Update national protocols** to facilitate education, training and proper use of $MgSO_4$ among health care workers, including community midwives and health care workers. Materials should include a standardised toolkit which includes treatment guidance such as visual record of monitoring and treatment, as well as other drugs needed for women with severe pre-eclampsia/eclampsia.
- **Strengthen the treatment at the community level** where few centres initiate treatment for pre-eclampsia and eclampsia. Ready-to-use packs comprising a loading dose pack, a maintenance dose pack, of appropriate strengths of $MgSO_4$, in addition to critical items such as lidocaine and a 20mL syringe, could enhance the use of MgSO4 at the community level. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome
- **Dispel myths about the safety of $MgSO_4$**. $MgSO_4$ is a safe drug with a very low incidence of severe side effects (1-2%). These are usually attributable to medication errors that would be addressed by standardising use of 50% $MgSO_4$, as discussed above. Even when adverse effects occur, delaying the next scheduled dose is generally sufficient to mitigate the effect.

Appendix 8.5

Recommendations for fluids, drugs and transfusion from international clinical guidelines*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antihypertensive therapy (antenatally or postnatally)			
Antihypertensive therapy for severe Hypertension (defined)	(≥160/110 mmHg)	(≥160/110 mmHg)	
Treatment recommended	For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension (immediately) during pregnancy or postpartum	For women with any HDP, treat severe hypertension
Target BP level (level at which treatment may be unchanged; level above which treatment should be started; below which treatment should be decreased if on antihypertensive therapy)	For women with any HDP, goal of ≤160/100 mmHg	For women with any HDP (in critical care), goal of <150/80–100 mmHg is recommended	
Initial antihypertensive therapy/first choice	Initial anti-hypertensive therapy can be with one of a variety of antihypertensive drugs	Labetalol (oral or IV, hydralazine (IV) or nifedipine (oral) are recommended for women in a critical care setting Consider administration of up to 500 mL of crystalloid before or with the first dose of hydralazine IV	Should be based on clinician's experience, cost and local availability
Alternative antihypertensives			
Antihypertensives NOT to use			
Other considerations		For women with PET, consider side-effect profiles if giving treatment other than labetalol For women with severe hypertension treated in critical care setting, monitor response to treatment, ensure BP falls, identify adverse effects, and modify treatment according to response	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
(≥160/110 mmHg)	(≥160/110 mmHg)	(≥160/110 mmHg)	(≥160/110 mmHg)
For women with any HDP, treat severe hypertension		For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension
		For women with chronic hypertension, goal of <160/105 mmHg is recommended For women with PET, goal of <160/110 mmHg	For women with any HDP, goal of <160/110 mmHg is recommended
Methyldopa, labetalol and nifedipine			Labetalol (IV), hydralazine (IV) or nifedipine (oral capsules) recommended Nifedipine and $MgSO_4$ can be used contemporaneously
			Alternatives are nitroglycerin (IV) methyldopa (oral), labetalol (oral), clonidine (oral), or captopril (oral) only postpartum Sodium nitroprusside recommended for refractory hypertension
ACE inhibitors, ARBs and direct renin inhibitors during pregnancy			$MgSO_4$ as an antihypertensive
			FHR monitoring (until stable BP) recommended

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
For non-severe hypertension			
Target BP level (level at which treatment may be unchanged; level above which treatment should be started or increased; level below which any antihypertensive therapy should be decreased)		For women with uncomplicated chronic hypertension, goal of <150/100 mmHg (without lowering dBP to <80 mmHg) is recommended For women with chronic hypertension and target organ damage, goal of <140/90 mmHg recommended	
Antihypertensives to use		For women with chronic hypertension, choose an agent(s) based on pre-existing treatment, side-effect profiles and teratogenicity For women with GH, offer antihypertensive medication (other than labetalol) ONLY after considering side-effect profiles Alternatives include methyldopa† and nifedipine	
Antihypertensives NOT to use during pregnancy (and should be stopped)		For women with any HDP, ACE, ARBs or chlorothiazide (as they are associated with an increased risk of major malformations) For women with chronic hypertension, stop ACE inhibitors or ARBs in pregnancy (preferably within 2 working days of notification of pregnancy) and offer alternatives Tell women who took ACE inhibitors or ARBs "during pregnancy" that these medications increase the risk of congenital abnormalities Tell women who took chlorothiazide "during pregnancy" that this medication may increase the risk of congenital abnormalities and neonatal complications	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For any HDP, goal of <160/110 mmHg is recommended		For women with uncomplicated chronic hypertension, goal of 120–159/80–104 mmHg is recommended For women with mild GH or PET, goal of <160/110 mmHg is recommended	For any HDP, goal of 130–155/80–105 mmHg is recommended For women with any HDP and a comorbid condition(s), goal of <140/90 mmHg is recommended
For women with any HDP, methyldopa, labetalol, and nifedipine recommended as agents of first choice		For women with chronic hypertension, methyldopa, labetalol, and nifedipine recommended as agents of first choice	For women with any HDP, the choice of antihypertensive agent should be based on patient characteristics, contraindications and physician and patient preference For women with any HDP, methyldopa, labetalol, nifedipine, other beta-blockers, or other calcium channel blockers are reasonable as agents of first choice Methyldopa, labetalol and nifedipine are acceptable choices in the 1st trimester of pregnancy
For women with any HDP, ACE inhibitors, ARBs, and direct renin inhibitors		For women with uncomplicated chronic hypertension, ACE inhibitors, ARBs, renin inhibitors, and mineralcorticoid receptor antagonists are NOT recommended	For women with any HDP, atenolol and prazosin are not acceptable for use For women with any HDP, ACE inhibitors and ARBs (which should be stopped) – not acceptable for use

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antenatal corticosteroids			
"≤34 weeks" – FIRST dose		"Between 24 and 34 weeks" For women with PET who are likely to deliver within 7 days	
REPEAT dosing			
"35–36 weeks"		"35–36 weeks" For women with PET who are likely to deliver within 7 days	
≤38^{+6} weeks gestation and elective Caesarean			

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
"Before 34 weeks" For women with any HDP who are likely to delivery within 2-10 days		"At ≤34^{+0} weeks" For women with severe PET or superimposed PET who are receiving expectant care "≤$33^{+6/7}$ weeks" For women with severe PET who require delivery, without delivery being delayed NOTE: Listed were: uncontrollable severe hypertension, eclampsia, pulmonary oedema, abruption placentae, disseminated intravascular coagulation, evidence of non-reassuring feta status, intrapartum fetal demise "≤$33^{+6/7}$ weeks" For women with severe PET who are stable enough to have delivery delayed by 48 h NOTE: Criteria specified were: low platelet count (<100,000/mL), persistently abnormal hepatic enzyme concentrations (twice or more the upper normal values), fetal growth restriction (less than the fifth percentile), severe oligohydramnios (amniotic fluid index <5 cm), reversed end-diastolic flow on umbilical artery Doppler studies, new-onset renal dysfunction or increasing renal dysfunction	"At ≤34^{+6} weeks" For women with PET "≤34^{+6} weeks" For women with GH who may deliver within the next 7 days
"Before 33 weeks" For women with any HDP, ONLY if first does were given at <30 weeks and >14 days prior			"≤34^{+6} weeks" For women with any HDP, if first dose ≥7 days prior
			"≤38^{+6} weeks" May consider for women with any HDP who are delivered by elective Caesarean

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antenatal corticosteroids			
Fluid administration (including management of oliguria)		For women with severe PET, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial analgesia For women with severe PET, limit ongoing fluid administration to 80 mL/h (unless ongoing fluid losses)	
Treatment of oliguria			
Aspects of care for women with pre-existing hypertension			
General considerations		Advice and treatment should be in line with 'Hypertension: the management of hypertension in adults in primary care' (NICE clinical guideline 34), unless it specifically differs from recommendations in this guideline Schedule additional antenatal consultations based on needs of woman and baby	
Specialist referral		(Specialist in hypertensive disorders) For women with secondary chronic hypertension	
Antihypertensive therapy – BEFORE pregnancy	For women with any prior HDP, preconceptional advice should be offered at a formal postnatal review	Tell women of reproductive age who take ACE inhibitors or ARBs that these medications increase the risk of congenital abnormalities if they are taken "during pregnancy" Tell women who take chlorothiazide that this medication may increase the risk of congenital abnormalities and neonatal complications if the drug is taken "during pregnancy" Discuss alternatives to ACE inhibitors, ARBs, and chlorothiazide for women planning pregnancy	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			For women with any HDP, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial anaesthesia For women with PET, minimise IV and oral fluid intake
			For women with any HDP, do NOT routinely administer fluid to treat oligura (<15 mL/h for 6 consecutive hours) For women with any HDP, do NOT treat oliguria with dopamine or furosemide
Discuss alternatives to ACE inhibitors, ARBs and direct renin inhibitors for women planning pregnancy		Women of reproductive age should not be prescribed ACE inhibitors, ARBs, renin inhibitors, and/or mineralocorticoid receptor antagonists unless there is a compelling indication	Pre-conceptional counselling is recommended Discuss alternatives to ACE inhibitors and ARBs for women planning pregnancy Changes to antihypertensive therapy should be made when planning pregnancy

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Aspects of care for women with pre-eclampsia			
$MgSO_4$			
Indications	Eclampsia (drug of first choice)	Eclampsia Previous eclampsia in women with severe hypertension or severe PET in a critical care setting Severe PET in a critical care setting when birth is planned within 24 h Severe PET NOTE: features listed: severe hypertension and proteinuria or mild or moderate hypertension and proteinuria with one or more of the following: symptoms of severe headache, problems with vision, such as blurring or flashing before the eyes, severe pain just below the ribs or vomiting, papilloedema, signs of clonus (≥3 beats), liver tenderness, HELLP syndrome, platelet count falling to below 100×10^9/L, abnormal liver enzymes (ALT or AST rising to above 70 IU/L)	Eclampsia (drug of first choice) Severe PET
Dosage		Loading dose: 4 g IV over 5 min Maintenance dose: 1 g/h for 24 h Recurrent seizure dose: 2–4 g IV over 5 min	"Full IV or IM" regimens When full IV or IM regimens cannot be administered, administer loading dose and transfer immediately to a higher level health care facility
Monitoring			
Alternatives to $MgSO_4$		Do NOT use diazepam, phenytoin or lytic cocktail in preference to $MgSO_4$ in women with eclampsia	Do NOT use diazepam, phenytoin or lytic cocktail in preference to $MgSO_4$ in women with eclampsia or severe PET

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Eclampsia (drug of first choice) Severe PET Mild/moderate PET ("can be considered")		Eclampsia (drug of first choice) Severe PET and superimposed PET with severe features, intrapartum and postpartum for severe PET for superimposed PET with severe features NOT routinely for PET with BP <160/110 mmHg and no symptoms Any PET intraoperatively during Caesarean delivery Postpartum, PET with severe hypertension or new-onset hypertension with headaches/ blurred vision	Eclampsia (drug of first choice) "Severe PET" "Non-severe PET" ("can be considered based on cost considerations") Fetal neuroprotection for women with any HDP when imminent preterm birth at $\leq 31^{+6}$ weeks
			Loading dose: "standard dosing", usually 4 mg IV Maintenance dose: "standard dosing", usually 1 g/h
Monitor mothers according to local protocol			Do NOT routinely monitor serum Mg levels
			Do NOT use diazepam or phenytoin in preference to $MgSO_4$ in women with eclampsia or PET

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Plasma volume expansion			
Pre-eclampsia		NOT recommended for women with severe PET (unless hydralazine is the antenatal antihypertensive)	
Therapies for HELLP			
Platelet transfusion			
Corticosteroids		NOT recommended	NOT recommended
Plasma exchange or plasmapheresis			

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon[187]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			NOT recommended for women with PET
			Platelet count $<20\times10^9$/L Platelet count 20–49×10^9/L prior to Caesarean Platelet count 20–49×10^9/L prior to vaginal delivery if there is: excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy Platelet count $\geq50\times10^9$/L if there is: excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units
		NOT recommended to improve clinical outcomes (footnote) Can be considered if improvement in platelet count would be useful (footnote)	NOT recommended
			NOT recommended

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 9.1

GRADE evaluation of best practice points regarding timing and mode of delivery

	*Quality of evidence**	*Strength of recommendation†*
Place of delivery		
1. All women with a HDP of any type require delivery in a centre that can provide EmONC	Low	Strong
2. Women with a HDP and serious maternal complications require delivery in a centre capable of providing CEmONC	Low	Strong
Timing of delivery		
Women with pre-eclampsia		
1. Consultation with an obstetrician is advised in women with pre-eclampsia. (If an obstetrician is not available in under-resourced settings, consultation with at least a physician is recommended.)	Low	Strong
2. All women with severe pre-eclampsia as defined by the SOGC should be delivered immediately (either vaginally or by Caesarean), regardless of gestational age‡	Low	Strong
3. For women with non-severe pre-eclampsia at $<24^{+0}$ weeks' gestation, counselling should include information about delivery within days as an option	Low	Weak
4. For women with non-severe pre-eclampsia at 24^{+0}–33^{+6} weeks' gestation, expectant management should be considered, but only in perinatal centres capable of caring for very preterm infants	Moderate	Weak
5. For women with non-severe pre-eclampsia at 34^{+0}–36^{+6} weeks' gestation, expectant management is advised	High	Strong
6. For women with pre-eclampsia at $\geq 37^{+0}$ weeks' gestation, immediate delivery is recommended	High	Strong
7. For women with non-severe pre-eclampsia complicated by HELLP syndrome at 24^{+0}–34^{+6} weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity if there is temporary improvement in maternal laboratory testing (II-2B)	Low	Weak
8. All women with HELLP syndrome at $\geq 35^{+0}$ weeks' gestation should be considered for delivery within 24 hours	Moderate	Strong
Women with gestational hypertension without pre-eclampsia		
1. For women with gestational hypertension at $<34^{+0}$ weeks, expectant management is advised	Low	Weak
2. For women with gestational hypertension at 34–36^{+6} weeks, expectant management is advised	Low	Weak
3. For women with gestational hypertension at $\geq 37^{+0}$ weeks', childbirth within days should be discussed	Low	Weak

continued

Appendix 9.1 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Timing of delivery		
Women with pre-existing hypertension		
1. For women with pre-existing hypertension at $<34^{+0}$ weeks, expectant management is advised	Low	Weak
2. For women with pre-existing hypertension at $34–36^{+6}$ weeks, expectant management is advised, even if women require antihypertensive therapy	Low	Weak
3. For women with uncomplicated pre-existing hypertension who are otherwise well at $\geq 37^{+0}$ weeks' gestation, delivery should be considered at $38^{+0}–39^{+6}$ weeks' gestation.	Low	Weak
Mode of delivery		
1. For women with any HDP, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications	Low	Strong
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery	Moderate	Strong
3. At a gestational age remote from term, women with HDP with evidence of fetal compromise may benefit from delivery by emergent Caesarean	Low	Strong
4. Antihypertensive treatment should be continued throughout labour and delivery to maintain sBP at <160 mmHg and dBP at <110 mmHg	Low	Strong
5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopaenia or coagulopathy	Moderate	Strong
6. Ergometrine maleate should not be administered to women with any HDP, particularly pre-eclampsia or gestational hypertension; alternative oxytocics should be considered	Low	Strong

CEmONC, comprehensive emergency obstetric and neonatal care; BPP, biophysical profile; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, haemolysis, elevated liver enzymes, low platelet; HDP, hypertensive disorder of pregnancy

* The judgements about the quality of evidence are based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there are a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

‡ Severe pre-eclampsia is defined according to Canadian criteria of potentially life-altering complications included within all other definitions of severe pre-eclampsia. There is consensus that these represent indications for delivery: (1) uncontrolled severe maternal hypertension; (2) maternal end-organ complications of the central nervous, cardiorespiratory, haematological, renal, or hepatic systems; or (3) stillbirth or substantial fetal compromise of abruption with maternal/fetal compromise or reversed ductus venosus A wave. Although these conditions are included in the WHO definition of severe pre-eclampsia, WHO also includes other criteria for severe pre-eclampsia that are not clear indications for delivery: heavy proteinuria, gestational age <34 weeks, and evidence of any 'fetal morbidity'.

Appendix 9.2

Timing and mode of delivery according to international clinical practice guidelines*

See next page – this appendix requires a double-page layout

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Timing of delivery				
General comments			For women with PET at "before 34 weeks", consultant obstetric staff should document maternal and fetal indications for elective birth	
Delivery indicated (indications)			For women with any HDP (regardless of GA) who have refractory severe hypertension after BP has been controlled and a course of antenatal corticosteroids has been completed (if appropriate) For women with PET "before 34 weeks" who have a maternal or fetal indication for delivery (as specified by the care plan), after discussion with neonatal and anaesthetic teams, and after a course of antenatal corticosteroids has been "given" For women with PET "after 37+0 wks" who have mild to moderate hypertension	For women with severe PET before fetal viability (and at a GA at which fetus not viable or unlikely to achieve viability in 1–2 weeks) For women with severe PET "before 34 weeks" or "between 34 and 36 (+6 days) weeks" who cannot be monitored or who have uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress In women with mild GH or mild PET "at term" For women with severe PET "at term"
Expectant care ONLY until steroids have been administered				For women with HELLP syndrome "from fetal viability to $33^{+6/7}$ weeks" with stable maternal and fetal conditions

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For women with any HDP, indications should be based on care provider's own knowledge and experience			For women with "severe PET", consultation must be undertaken (by telephone is necessary) with an obstetrician
For women with severe PET (including HELLP) or any HDP with an abnormal Doppler		For women with severe PET or HELLP syndrome before fetal viability (after maternal stabilisation) for severe PET for HELLP For women with PET or superimposed PET at any GA who have unstable maternal or fetal conditions (after maternal stabilisation) NOTE: Listed were uncontrollable severe hypertension, eclampsia, pulmonary edema, abruption placentae, disseminated intravascular coagulation, non-reassuring fetal status For women with severe PET or HELLP syndrome "≥34 0/7 wks", or superimposed PET with severe features "beyond 34 0/7 wks" (after maternal stabilisation) For women with mild GH or mild PET at "≥37 0/7 wks" who have no severe features	For women with uncomplicated chronic hypertension, consider delivery at $38^{+0/7}$ to $39^{+6/7}$ weeks For women with GH at ≥37 weeks, delivery within days should be discussed For women with PET at $<24^{+0}$ weeks, delivery should be discussed as an option For women with "severe PET" regardless of GA For women with PET at ≥37 weeks For women with HELLP at $≥35^{0}$ wks
			For women with HELLP syndrome at 24^{+0}–34^{+6} weeks If there is temporary improvement in maternal laboratory testing

continued

Appendix 9.2 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Timing of delivery				
Expectant care			For women with PET "until 34 weeks" For women with chronic hypertension at <37 weeks and BP <160/110mmHg For women with GH "before 37 wks" who have BP <160/110 mmHg (even on antihypertensive treatment) For women with PET at 34^{+0} to 36^{+6} weeks who have mild or moderate hypertension, depending on maternal and fetal condition, risk factors and availability of neonatal intensive care	For women with severe PET "before 34 weeks" who have a viable fetus and can be monitored For women with severe PE "between 34 and 36 weeks (+6 days)" who have a viable fetus and can be monitored
Care plan			For women with severe GH or PET, write a care plan that includes: timing and mode of delivery, indications for delivery, timing of antenatal corticosteroids, and when discussion should take place with neonatology and obstetric anaesthesia	
Evidence insufficient to make a recommendation about delivery or expectant care			For women with chronic hypertension at ≥37 weeks and BP <160/110 mmHg ("timing of birth and indications for birth to be agreed upon between woman and specialist") For women with GH "after 37 weeks" who have BP <160/110 mmHg (even on antihypertensive therapy) ("timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician")	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
		For women with severe PET or severe superimposed PET at $<34^{+0/7}$ weeks who have stable maternal and fetal conditions and who can be monitored at facilities with adequate intensive care resources(Moderate, Strong) for PET For women with superimposed PET "at $<37^{+0/7}$ weeks" who have no severe features and stable maternal and fetal conditions For women with mild GH or PET at "$<37^{+0/7}$ weeks" who have no severe features or indication for delivery, and can be monitored For women with uncomplicated chronic hypertension at <38 weeks For women with PET regardless of the amount or change in proteinuria	For women with non-severe PET at 24^{+0}–33^{+6} weeks, at centres capable of caring for very preterm infants
			For women with non-severe PET at 34^{+0}–36^{+6} weeks For women with GH at <37 weeks

continued

Appendix 9.2 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Labour and delivery				
Intrapartum care			Advice and treatment should be in line with 'Intrapartum care: management and delivery of care to women in labour' (NICE clinical guideline 55), unless it specifically differs from recommendations in this guideline	
BP management			For women with any HDP, continue antihypertensive therapy For women any HDP, monitor BP continuously in women who have severe hypertension, and hourly in women who have non-severe hypertension	
Investigations (for PET)			For women with any HDP and non-severe hypertension, perform haematological and biochemical tests using the same criteria as those used antenatally, whether regional anaesthesia is being considered	
Vaginal or Caesarean delivery		For women with any HDP, Caesarean should be reserved for the usual obstetric indications If vaginal birth is planned and the cervix is unfavourable, cervical ripening is recommended	For women with any HDP and severe hypertenison, severe PET, or eclampsia, choice should be based on clinical circumstances and woman's preference	
Second stage (of labour)			For women with any HDP with severe hypertension whose BP is not meeting treatment targets, recommend operative birth. Otherwise, do NOT limit second stage of labour	
Third stage				

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			For women with any HDP, continue antihypertensive therapy
			For women with PET, platelet count should be done upon admission to delivery suite
		For women with any HDP, Caesarean need not be the mode of delivery, depending on the GA, fetal presentation, cervical status and maternal and fetal conditions	For women with any HDP and evidence of fetal compromise, Caesarean delivery may be beneficial For women with any HDP without fetal compromise, Caesarean should be reserved for the usual obstetric indications If vaginal birth is planned and the cervix is unfavourable, cervical ripening is recommended
	For women with any HDP, active management with oxytocin recommender Ergonovine maleate should NOT be used to prevent/ treat PPH if other suitable uterotonic drugs are available		For women with any HDP, active management with oxytocin (5 units IV or 10 units IM) recommended Ergonovine maleate NOT be used to prevent/treat PPH

continued

Appendix 9.2 *continued*

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[80]

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 10.1

Randomised controlled trials (RCTs) of prevention of the hypertensive response to intubation in women with pre-eclampsia

Author	*Study type*	*Population*	*N*	*Methods (n women)*	*Results*	*Other*
Rout & Rocke 1990[54]	RCT	'Severe' pre-eclampsia	40	Alfentanil 10 μg/kg 3 min before induction (N = 20) Fentanyl 2.5 μg/kg 1 min before induction (N = 20) All induced with lidocaine, etomidate 0.3 mg/kg, succinylcholine	Both groups had ↑ HR after intubation. No significant difference MAP before induction and after intubation	9 fentanyl, 8 alfentanil received magnesium 2 alfentanil group had no treatment for hypertension, rest had various anti-hypertensives
Hood *et al.* 1985[57]	RCT	'Severe' pre-eclampsia	19	Nitroglycerin infusion 200 μg/mL (N = 9) Control (N = 10) Induction: thiopental 4 mg/kg, succinylcholine	Maximum HR occurred 2 min after intubation in both groups Nitroglycerin: MAP ↓ 20% before induction – ↑ 2 min after intubation but significantly more in control group	All received magnesium preoperatively No information re anti-hypertensive medication
Ramanathan *et al.* 1988[58]	RCT	'Mild-moderate' pre-eclampsia	25	Labetalol 20 mg – then 10 mg increments to total 1 mg/kg (N = 15) – administered until DBP<100 or MAP ↓ 20% from baseline Control (N = 10) Induced 10 min after BP stabilised Induction: thiopental 4 mg/kg, succinylcholine	Baseline values similar Labetalol ↓ mean MAP & HR before induction After intubation MAP ↑ significantly both groups but significantly > control Mean HR ↑ significantly more in control group	All received magnesium pre-operatively No antihypertensive medication 3 subjects in labetalol group did not achieve BP goals in spite of maximum dose
Allen *et al.* 1991[53]	RCT	'Moderate' (N = 5) to 'severe' (N = 64) pre-eclampsia	69	Lidocaine 1.5 mg/kg (N = 21) Magnesium 40 mg/kg (N = 24) Alfentanil 10 μg/kg (N = 24) Study drug given after induction with thiopental 5 mg/kg. Succinylcholine given after study drug	↑ SBP, dBP, MAP post intubation > lidocaine group compared to other 2 groups	10 subjects did not receive antihypertensive therapy – various antihypertensives used in other 59 – many in combination Some in other groups received magnesium No control group so difficult to determine effect of lidocaine but authors felt should not be used alone

continued

Appendix 10.1 *continued*

Author	*Study Type*	*Population*	*N*	*Methods (n women)*	*Results*	*Other*
Ashton *et al.* 1991[56]	RCT	'Moderate' and severe pre-eclampsia	38	Magnesium 40 mg/kg (N = 19) Magnesium 30 mg/kg + alfentanil 7.5 μg/kg (N = 19) Study drug given after induction with thiopental 5 mg/kg. Succinylcholine given after study drug	sBP, dBP, MAP ↓ after induction both groups No statistically significant ↑ in BP at intubation – better control sBP in magnesium + alfentanil group	Use of antihypertensives same in both groups
Kumar *et al.* 1993[59]	RCT	Pre-eclampsia	30	Nifedipine 10 mg sublingual (15) Control (15) Study drug given 20 min before induction Induction: thiopental 5 mg/kg, succinylcholine	↓ MAP after nifedipine ↑ MAP during laryngoscopy & intubation both groups but more in control	All patients received antihypertensive medication No information re. magnesium
Yoo *et al.* 2009[50]	RCT	'Severe' pre-eclampsia	42	Remifentanil 1 μg/kg (N = 21) Control (N = 21) Study drug given over 30 s immediately before induction Induction: thiopental 4 mg/kg, succinylcholine Also, looked at BIS	Baseline BP & HR similar Arterial BP ↑ significantly after intubation in both groups but was significantly lower in remifentanil group Transient newborn respiratory depression in remifentanil group	All received magnesium pre-operatively Some received hydralazine 2 in remifentanil group required ephedrine for hypotension
Park 2011[51]	RCT	'Severe' pre-eclampsia	48	Remifentanil 0.5 μg/kg (N = 24) Remifentanil 1.0 μg/kg (N = 24) Study drug prior to induction thiopental 5 mg/kg, succinylcholine	Both effectively attenuated haemodynamic response Transient neonatal respiratory depression	3 subjects in 1.0 μg/kg dose had hypotension
Pournajafian *et al.* 2012[52]	RCT	Pre-eclampsia	38	Fentanyl 50 μg (N = 18) Remifentanil infusion 0.05 μg/kg/min for 3 min (N = 20) Induction: thiopental 5 mg/kg, succinylcholine	Fentanyl group: HR, dBP significantly different pre & post intubation Remifentanil: HR ↑, SBP & DBP ↓ after intubation	Authors suggest study favours remifentanil Nothing about severity of pre-eclampsia or use of magnesium or antihypertensives
Yoo 2013[55]	RCT	'Severe' pre-eclampsia	75	Dose study for remifentanil Doses: 0.25, 0.5, 0.75, 1.0, 1.25 μg/kg before induction with thiopental 5 mg/kg + succinylcholine	Baseline sBP and HR similar among groups ↑ HR & BP attenuated dose-dependent manner ED95 was 1.34 μg/kg Majority of newborns required assisted ventilation	Need to have neonatal resuscitation available.

BIS, bispectral index; dBP, diastolic blood pressure; ED, effective dose; HR, heart rate; MAP, mean arterial pressure; RCT, randomised controlled trial; sBP, systolic blood pressure

Appendix 10.2

Anaesthesia for Caesarean delivery in women with pre-eclampsia

See next page – this appendix requires a double-page layout

Author & date	*Study type*	*Study subjects*	*Number*
Wallace 1995[80]	Prospective, randomised	Severe pre-eclampsia	80
Sharwood-Smith 1999[77]	Prospective, randomised	Severe pre-eclampsia	11 S 10 EA
Dyer 2003[81]	Prospective, randomised	Pre-eclampsia	35 S 35 GA
Visalyaputra 2005[76]	Prospective, randomised	Severe pre-eclampsia	47 EA 53 S
Berends 2005[85]	Prospective, randomised	Severe pre-eclampsia Not in labour	Total 30 10 EA 20 CSE
Aya 2003[73]	Prospective cohort	Severe pre-eclampsia	PE (N = 30) Healthy (N = 30) All had S

Methods	*Results*
3 groups – GA (N = 26), EA (N = 27), CSE (N = 27) All received magnesium, intermittent IV hydralazine as needed IV fluid limited to 60 mL/h but did preload GA: IV hydralazine – dBP 100 mmHg preintubation; lidocaine, NTG; RSI: thiopental 4–5 mg/kg, succinylcholine – nitrous oxide, oxygen, isoflurane EA: preload 1000 mL LR; incremental 2% lidocaine or 3% chloroprocaine CSE: preload 1000 mL LR; hyperbaric 0.75% bupivacaine; epidural supplements 3 mL boluses 0.5% bupivacaine Ephedrine 5 mg doses for hypotension S & EA groups	GA: shortest induction to skin incision time (3 min vs. 25–35 min) Hypotension requiring ephedrine similar in CSE and EA BP ↓ significantly over time in all groups IV fluids > EA & CSE groups than GA group Concluded: all techniques acceptable for CS
All required antihypertensive therapy S: 2.75 mL hyperbaric 0.5% bupivacaine EA: 4 mL + 16 mL 0.5% bupivacaine Preload 250 mL LR, otherwise fluids restricted to 80 mL/h + losses Ephedrine – 6 mg increments if hypotension	Poor anaesthesia in EA group Ephedrine use similar
All had non-reassuring FHR trace Severe PE had magnesium sulphate Dihydralazine IV used for BP control GA: Preload <750 mL LR; thiopental 5 mg/kg then 30–45 mg/kg magnesium sulphate to ablate hypertensive response to intubation, followed by succinylcholine; nitrous oxide, oxygen isoflurane S: Preload <750 mL LR; 1.8 mL hyperbaric 0.5% bupivacaine + 10 μg fentanyl	Groups similar at baseline HR, sBP, dBP, MAP significantly lower in S group > umbilical arterial base deficit & lower median umbilical arterial pH in S group More ephedrine used in S group Questioned the clinical significance of this
EA: 18–23 mL 2% lidocaine with epinephrine S: 2.2 mL 0.5% hyperbaric bupivacaine + morphine Hypothesis MAP 10 mm < S group during delivery	Hypotension > S than EA (51% vs. 23%) Duration short both groups More ephedrine in spinal group
Compared EA vs. CSE with 2 prophylactic regimens EA + fluid preload (N = 10) – preload 10 mL/kg RL CSE + fluid preload (N = 10) – preload 10 mL/kg RL CSE prophylactic ephedrine (N = 10) 15 mg ephedrine in 150 mL LR given over 5 min Primary outcome: incidence hypotension	Shorter time induction to surgery both CSE groups 7 EA group needed supplemental analgesics – only 2 CSE groups MAP similar between groups during surgery More ephedrine, < LR in CSE prophylactic ephedrine group No hypertension
All had magnesium After each PE enrolled the next normotensive was the control Preload 1500–2000 mL LR S: hyperbaric 0.5% bupivacaine 8–12 mg + sufentanil/morphine Hypotension treated with ephedrine	PE group – more nulliparas, younger gestational age, less IV fluid, 12 had magnesium, 11 had nicardipine, 2 urapidil, 8 had both magnesium & nicardipine Bupivacaine > PE group; ↓ in dBP, MAP < PE group; ↓ sBP similar both groups Ephedrine 16.6% PE vs. 53.3% control

continued

Appendix 10.2 *continued*

Author & date	*Study type*	*Study subjects*	*Number*
Aya 2005[83]	Case–controlled study	Severe pre-eclampsia Healthy controls	PE 65 Control 71
Tihtonen 2006[75]	Prospective	Pre-eclampsia Healthy	6 severe, 4 mild or moderate PE 10 healthy
Clark 2005[74]	Observational	Normotensive Severe pre-eclampsia	40–20/group
Dyer 2008[65]	Observational	Severe pre-eclampsia	15 S
Hood 1999[78]	Retrospective	Severe pre-eclampsia Not in labour	103 S 35 EA
Chiu 2003[79]	Retrospective	Pre-eclampsia	70 S 51 EA

RCT, randomised controlled trial; GA, general anaesthesia; EA, epidural; CSE, combined spinal-epidural; IV, intravenous; dBP, diastolic BP; NTG, nitroglycerin; RSI, rapid sequence induction; LR, lactated Ringer's; CS, Caesarean delivery; S, spinal; OB, obstetrician; BP, blood pressure; MAP, mean arterial pressure; FHR, fetal heart rate; sBP, systolic BP; CO, cardiac output; HR, heart rate; bpm, beats per minute; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; SI, stroke index; CI, cardiac index

Methods	*Results*
All subjects were preterm (<35 weeks) patients Consecutive enrollment Pharmacologic treatment of BP before inclusion Nicardipine was 1st line antihypertensive All were on magnesium sulphate Neonatal weight 1100–1900 g Preload 1500–2000 mL LR over 20 min Spinal anaesthesia (8–12 mg hyperbaric bupivacaine, sufentanil, morphine) Primary outcome – 25% difference in hypotension	All had effective anaesthesia PE group: heavier, more nulliparas, 7 had only magnesium, 11 only nicardipine, 18 both drugs Hypotension treated with ephedrine < in PE group Magnitude ↓ sBP, dBP and MAP similar – time to nadir of MAP longer in PE group PE group less ephedrine Risk of hypotension almost 2 times < PE group
PE: 4 received labetalol All had whole-body impedance cardiography S = 2.4–2.7 mL 0.5% hyperbaric bupivacaine Hypotension treated with ephedrine infusion	Baseline: mean MAP and SVRI were significantly ↑ in PE, SI and CI significantly lower in PE S group: SVRI & MAP ↓ Hypotension: 30% PE vs. 80% controls Ephedrine ↑ MAP & SVRI both groups Concluded PE a state of low CO, high SVR. At delivery PE could not increase SI
All spinal anaesthesia: 2.5 mL hyperbaric 0.5% bupivacaine + fentanyl 12.5 μg Preload 250 mL Primary outcome: Difference in ephedrine use of 11 mg with more used in normotensives	All PE subjects were stabilised on antihypertensive drugs before study Mean ephedrine in normotensives 27.9 ± 11.6 mg vs. PE group 16.35 ± 15.0 mg ($p < 0.01$)
All received magnesium sulphate IV-300–500 mL hydroxyethyl starch before IV dihydralazine then crystalloid 120 mL/h Measured cardiac output with LiDCOplus S: co-hydration 10 mL/kg LR; 2.0 mL hyperbaric 0.5% bupivacaine + fentanyl 10 μg Hypotension: 50 μg phenylephrine every minute until within 20% baseline; if MAP ↓ 30% from baseline 100 μg phenylephrine given If CO didn't respond with target MAP then ephedrine 5 or 10 mg was given If HR ↓ <55 bpm + hypotension then 0.5 mg atropine and 10 mg ephedrine were given	All patients were haemodynamically stable Mean baseline SVR was above normal in spite of antihypertensive therapy Mean baseline CO was normal CO changes intraoperatively were clinically insignificant Induction of S was followed by significant ↓ in MAP and SVR Main effect of S was modest afterload reduction 7 did not require phenylephrine before delivery; only 1 required 100 μg before delivery, 7 received 50 μg Of the 8 who had phenylephrine pre-delivery, 4 also required it after delivery 5 required ephedrine pre-delivery
Database reviewed Ephedrine, IV fluids at discretion of anaesthetist Antihypertensive therapy discretion of OB or anaesthetist	EA more likely to receive antihypertensive therapy More IV fluids S group Ephedrine use similar BP ↓ similar both groups
5 year review: Mild, moderate, severe PE Not in labor having CS S = 1.7–2.5 mL 0.5% hyperbaric bupivacaine EA: Incremental boluses 3–10 mL 0.5% bupivacaine with 50–100 μg fentanyl	Labetalol most commonly used antihypertensive, then hydralazine No magnesium in mild or moderate group BP ↓ similarly S and EA Ephedrine use similar EA & S groups & in mild/moderate or severe PE

Appendix 10.3

GRADE evaluation of best practice points for anaesthesia

Recommendation	*Quality of evidence**	*Strength of recommendation†*
1. The anaesthetist should be informed when a woman with pre-eclampsia is admitted to the delivery suite (II-3B).	Low	Strong
2. Women with pre-eclampsia should have a platelet count on admission to the delivery suite. (III-C).	Low	Strong
3. Planning for the care of women with pre-eclampsia should include members of the multi-disciplinary team.	Low	Strong
4. The anaesthetist should assess the woman with pre-eclampsia from the standpoint of possible anaesthetic care and as her status may change, she should be reassessed.	Low	Strong
5. Arterial line insertion may be used for continuous arterial blood pressure monitoring when blood pressure control is difficult or there is severe bleeding. An arterial line also is useful when repetitive blood sampling is required e.g. in women with HELLP syndrome.	Very low	Strong
6. Central venous pressure monitoring is not routinely recommended and, if a central venous catheter is inserted, it should be used to monitor trends and not absolute values.	Very low/ low	Strong
7. Pulmonary artery catheterisation is not recommended unless there is a specific associated indication and then only in an intensive care setting.	Very low	Strong
8. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of labour pain.	Moderate/ strong	Strong
9. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean section: epidural, spinal, continuous spinal, combined spinal epidural and general anaesthesia.	Moderate/ strong	Strong
10. A routine, fixed intravenous fluid bolus should not be administered prior to neuraxial anaesthesia.	Low	Strong
11. Neuraxial analgesia and/or anaesthesia are appropriate in women with any hypertensive disorder of pregnancy provided there are no associated coagulation concerns (Table 6.6) or other specific contraindications.	Very low	Weak

continued

Appendix 10.3 *continued*

aPTT, activated partial thromboplastin time; ASA, aspirin; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, Haemolysis, Elevated Liver enzyme, Low Platelet syndrome; LMWH, low-molecular weight heparin; UFH, unfractionated heparin

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 10.4

Recommendations for anaesthesia from international guidelines[127]

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*
General principles					

AOM 2012	*ACOG 2013*	*SOGC 2014*
	For women with PET, neuraxial analgesia or anaesthesia (spinal or epidural) is recommended (Moderate, Strong)	For women with PET who are admitted to delivery suite, the anaesthesiologist should be informed (Low, Strong)
		Early insertion of an epidural catheter for analgesia is recommended (Moderate, Strong)
		Acceptable methods of anaesthesia include epidural, spinal, combined spinal-epidural and general anaesthesia (Moderate, Strong)
		For women with any HDP, neuraxial analgesia and/or anaesthesia are appropriate:
		a) With PET, provided there are no associated coagulation concerns. (Low, Strong);
		b) With a platelet count $\geq 75 \times 10^9$/L (Very low, Weak);
		c) Taking low-dose ASA in the presence of an adequate platelet count. (Moderate/High, Strong);
		d) Receiving UFH in a dose of ≤10,000 IU/d subcutaneously, 4 h after the last dose and possibly IV after the last dose without any delay (Very low, Weak);
		e) Receiving UFH in a dose of 10,000 IU/d subcutaneously if they have a normal aPTT 4 h after the last dose (Very low, Weak);
		f) Receiving IV heparin in a therapeutic dose if they have a normal aPTT 4 h after the last dose (Very low, Weak); or
		g) Receiving low-molecular weight heparin (LMWH) a minimum of 10–12 h after a prophylactic dose, or 24 h after a therapeutic dose (Very low, Weak)
		For women with any HDP, phenylephrine or ephedrine may be used to treat hypotension during neuraxial anaesthesia (Moderate, Strong)

continued

Appendix 10.4 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*
General principles					
Fluid administration (including management of oliguria)			For women with severe PET, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial analgesia For women with severe PET, limit ongoing fluid administration to 80 mL/h (unless ongoing fluid losses)		
Treatment of oliguria					
Anesthesia – monitoring					
Invasive haemodynamic monitoring					

ACOG, American College of Obstetricians and Gynecologists; ASA, aspirin; BP, blood pressure; GA, gestational age; GH, gestational hypertension; BPP, good practice point; HDP, hypertensive disorders of pregnancy; HELLP, haemolysis, elevated liver enzyme, low platelet syndrome; LMWH, low molecular weight heparin; $MgSO_4$, magnesium sulphate; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; SOGC, Society of Obstetricians and Gynaecologists of Canada; UFH, unfractionated heparin; WHO, World Health Organization

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

AOM 2012	*ACOG 2013*	*SOGC 2014*
		For women with any HDP, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial anaesthesia (Low, Strong)
		For women with PET, minimize iv and oral fluid intake (Low, Strong)
		For women with any HDP, do NOT routinely administer fluid to treat oligura (<15 mL/h for 6 consecutive hours) (Very low, Weak)
		For women with any HDP, do NOT treat oliguria with dopamine or furosemide (Moderate, Strong)
	For women with severe PET, do NOT routinely use invasive haemodynamic monitoring (Low, Qualified)	For women with any HDP, do NOT routinely use central venous pressure monitoring (Very low/Low, Strong)
		If a central venous monitoring is used, trends (and not absolute values) should be monitored (Very low/Low, Strong)
		For women with any HDP, an arterial line may be used when BP is difficult to control or there is severe bleeding (Very low, Strong)
		For women with any HDP, pulmonary artery catheterisation is NOT recommended unless there is a specific indication (Very low, Strong)
		If used, a pulmonary catheter should be used only in a critical care setting (Very low, Strong)

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 11.1

Training material for health care providers

MULTIPLE CHOICE QUESTIONS

1. When does blood pressure reach its peak during the postpartum period?
   a. Immediately after delivery
   b. Within the first 24 hours after delivery
   c. Days 3–6 postpartum
   d. Within 14 days postpartum
   e. Blood pressure remains the same throughout the postpartum period

2. Which of the following are acceptable antihypertensive choices during breastfeeding?
   a. Enalapril
   b. Labetalol
   c. Nifedipine
   d. Methyldopa
   e. All of the above

3. Of the following groups of women, which one has the highest risk for premature cardiovascular disease?
   a. A woman who develops gestational hypertension
   b. A woman who develops pre-eclampsia at 36 weeks' gestational age
   c. A woman who develops severe pre-eclampsia at 38 weeks' gestational age
   d. A woman who develops mild pre-eclampsia at 38 weeks' gestational age
   e. A woman with pre-existing hypertension who does not develop a hypertensive disorder of pregnancy

4. In which of the following scenarios, should a woman who developed pre-eclampsia be investigated for underlying renal disease?
   a. Persistent proteinuria at 6 months postpartum
   b. Urine analysis persistently showing leukocytes
   c. Hypertension at 4 weeks requiring 2 agents
   d. Ongoing hypertension at 6 weeks postpartum
   e. Delivery at 37 weeks' gestational age

5. In the postpartum cardiovascular evaluation of a woman with a history of pre-eclampsia, which of the following should be undertaken:
   a. Screening for traditional cardiovascular risk factors
   b. Counselling about a heart-healthy lifestyle
   c. Treating blood pressure, dyslipidaemia and blood sugar according to locally accepted guidelines
   d. Discussion about postpartum weight loss
   e. All of the above

Answers

1) c 2) e 3) b 4)a 5) e

CASE STUDY

A 34 year-old G1P1 previously healthy woman developed pre-eclampsia at 33 weeks' gestation. She developed severe hypertension, elevated liver enzymes and proteinuria with a protein to creatinine ratio of 257. She is now 3 months postpartum and has been referred for evaluation of ongoing postpartum hypertension. Her blood pressure is 135/85 mmHg on labetalol 200 mg TID.

1. The patient has been having difficulty taking antihypertensives three times a day and asks about other options that are dosed once daily and acceptable in breastfeeding.

Adalat and Enapril are two antihypertensives that are dosed daily and are acceptable in breastfeeding.

2. What would prompt you to screen this patient for underlying renal disease?

This patient should be screened for renal disease given that she developed severe pre-eclampsia and delivered before 34 weeks. Other factors that should prompt evaluation for underlying renal disease include proteinuria that persists beyond 3–6 months postpartum, glomerular filtration rate (GFR) <60 or abnormal urinary sediment.

3. How would you confirm that end organ dysfunction related to pre-eclampsia has resolved?

The patient had three manifestations of end organ dysfunction: hypertension, proteinuria and elevated liver enzymes. In women with severe pre-eclampsia, blood pressure may take about 3–6 months to resolves. Liver enzymes should normalise by 6 weeks. Proteinuria should resolve by 3–6 months postpartum and can be evaluated using albumin to creatinine ratio (ACR).

4. What are the long-term risks of pre-eclampsia?

Pre-eclampsia is associated with a number of long-term risks. These include cardiovascular disease (hypertension, ischaemic heart disease, stroke), end stage renal disease and diabetes.

5. What is her risk of developing ischaemic heart disease in the future?

Women who develop early onset pre-eclampsia are at the greatest risk of developing ischaemic heart disease in the future. The risk is almost 8 times higher than in women who developed pre-eclampsia after 37 weeks. She is at risk of developing premature disease as disease occurred as early as 12 years after the index pregnancy.

6. When should be screened and how should she be managed?

There are no specific guidelines for timing and type of screening for this group of high risk women. She should be screened for traditional cardiovascular risk factors according to local guidelines. There is also no evidence to suggest preventive therapies at an earlier age than usual. However, a heart-healthy lifestyle should be prescribed, as we know that there is evidence for lifestyle intervention for the prevention of cardiovascular disease. The postpartum period provides a unique window of opportunity to begin this important discussion.

Appendix 11.2

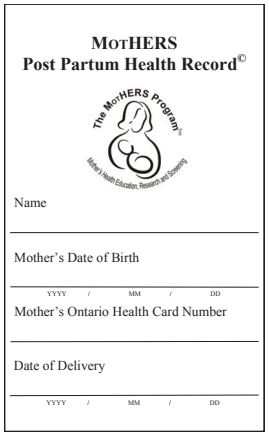
Knowledge translation tools

Patient resources

HH4M (Heart Health 4 Moms): a research study, designed for women with a recent pregnancy complicated by pre-eclampsia, to learn more about the best ways o reduce their risk of heart disease. [http://www.hh4m.org/]

Pre-eclampsia Registry: the first patient registry to focus on the HDPs and bring together those affected, their family members, and researchers to advance knowledge, and discover preventative approaches and treatments for the HDPs. Affected women can share their health and pregnancy histories and pose research questions. [http://preeclampsiaregistry.org/]

The Postpartum Mother's Health Record (see below): a record for the mother's use where the collection of information coincides with the baby's scheduled visits and immunisations. The card can help mothers to set goals and keep track of weight loss. [http://www.themothersprogram.ca/after-delivery/postpartum-health/maternal-health-clinic]


MOTHERS
Post Partum Health Record©
Name
Mother's Date of Birth
YYYY / MM / DD
Mother's Ontario Health Card Number
Date of Delivery
YYYY / MM / DD

Maternelle: an obstetrician-designed mobile application that focuses on the health of new mothers and their babies. Women can track weight, activity level, blood pressure and breast feeding. [http://www.mothersprogram.ca/apps/maternelle]

Virtual Care Program: online interactive health communication portal that will help women take control and manage their heart disease risk factors. This web-based platform will give women the latest medical information and lifestyle advice. It will encourage women to share information and experiences and help them navigate the spectrum of medical care for various aspects of heart disease. [http://cwhhc.ottawaheart.ca/changing-things/care]

Women@Heart Program: a peer support programme led by women with heart disease, for women with heart disease that aims to create a caring environment for women to learn from each other. The Women@Heart Program provides women with heart disease, with access to emotional support, educational support and a caring environment for a better recovery after a cardiac event. [http://cwhhc.ottawaheart.ca/changing-things/care]

Health care providers

The Maternal Health Follow Up Form: a form to record postpartum information and calculate a woman's lifetime risk for heart disease and stroke in order to help them improve their patients' long-term health. [http://www.themothersprogram.ca/after-delivery/postpartum-health/maternal-health-clinic]

The Postpartum Maternal Health Clinic Handbook: the handbook provides guidance on how to set up a postpartum cardiovascular health clinic. It provides information on the day-to-day management of the clinic including documents and the protocol followed by the Maternal Health Clinic at Kingston General Hospital. [http://www.themothersprogram.ca/after-delivery/postpartum-health/postpartum-maternal-health-clinic-handbook]

Appendix 11.3

GRADE evaluation of best practice points for postpartum care

	*Quality of evidence**	*Strength of recommendation†*
Care in the 6 weeks after birth		
1. Blood pressure should be measured during the time of peak postpartum blood pressure, at days 3–6 after delivery.	Low	Strong
2. Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising de novo or worsening from the antenatal period).	Low	Weak
3. Antihypertensive therapy may be continued postpartum, particularly in women with antenatal pre-eclampsia and those who delivered preterm.	Low	Weak
4. Severe postpartum hypertension must be treated with antihypertensive therapy, to keep systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.	Moderate	Strong
5. Antihypertensive therapy may be used to treat non-severe postpartum hypertension, to keep blood pressure at <140/90 mmHg for all but women with pre-gestational diabetes mellitus among whom the target should be <130/80 mmHg.	Very low	Weak
6. Antihypertensive agents acceptable for use in breastfeeding include nifedipine XL (slow-release), labetalol, methyldopa, captopril and enalapril.	Moderate	Weak
7. There should be confirmation that end-organ dysfunction of pre-eclampsia has resolved.	Very low	Strong
8. Non-steroidal anti-inflammatory drugs should not be given postpartum if hypertension is difficult to control, there is evidence of kidney injury (oliguria and/or an elevated creatinine) (≥90 μmol/L) or platelets are $<50 \times 10^9$/L.	Low	Weak
9. Postpartum thromboprophylaxis should be considered in women with pre-eclampsia who have other risk factors for thromboembolism.	Low	Weak
Care beyond the first 6 weeks after birth		
1. Women with a history of severe pre-eclampsia (particularly those who presented or delivered at <34 weeks) should be screened for pre-existing hypertension and underlying renal disease.	Low	Weak
2. Referral for internal medicine or nephrology consultation should be considered for women with postpartum hypertension that is difficult to control, or women who had pre-eclampsia and have at 3–6 months postpartum ongoing proteinuria, decreased eGFR (<60 mL/min), or another indication of renal disease (such as abnormal urinary sediment).	Low	Weak
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future and for long-term health.	Low/ moderate	Strong
4. Women with pre-existing hypertension or persistent postpartum hypertension should undergo the following investigations (if not done previously): urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting lipid profile; and standard 12-lead electrocardiography.	Low	Weak

continued

Appendix 11.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Care beyond the first 6 weeks after birth		
5. Women who are normotensive but who have had a hypertensive disorder of pregnancy, may benefit from assessment of traditional cardiovascular risk markers.	Low/ moderate	Weak
6. All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle.	Low	Strong

eGFR, estimated glomerular filtration rate

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 11.4

Postnatal care care – Policy brief

Postnatal care (PNC) is considered to be an essential intervention for reducing maternal mortality. In LMICs, almost 40% of women experience complications after delivery and in 15% of women, those complications are life-threatening. A 2013 WHO systematic analysis of the causes of maternal deaths (2003–09) determined that 480,000 or 19.7% of maternal deaths worldwide occurred postpartum. Most of those deaths occur in the first week postpartum.

Postpartum care has the potential to optimise future pregnancy outcomes and the long-term health of the mother. PNC affords the opportunity to counsel women about birth spacing and contraception. Also, the HDPs, and pre-eclampsia in particular, are associated with an increase in many adverse maternal health conditions, including hypertension, heart disease, stroke, renal disease, and diabetes mellitus. Postpartum care offers care providers the opportunity to educate women about these risks as well as changes in diet, lifestyle, and medical management that may modify them.

Postnatal period remains the most neglected period for provision of critical care for mothers and babies. In low-income countries, an estimated 70% of women do not receive any postnatal care.

Literature suggests that in sub Saharan Africa, 15.2% maternal deaths occurred in the postnatal period.

ACTIONS

Advancing PNC policy and implementing evidence-based programmatic changes in the national and state level health policies is crucial to improving access to care and reducing maternal mortality and morbidity.

- **Increase demand** for PNC care by engagement with women and communities
- **Engage relevant stakeholders** at the community and state levels in order to establish leadership for integration of a PNC package at the community level
- Develop a **local PNC package** adapted that includes all of the STRONG recommendations from the WHO 2013 Postnatal Care guidelines' recommendations (see Table S11.1 below), as follows:
  - PNC care beginning within 24 h of birth, consisting of at least three visits, and occurring ideally at home
  - Exclusive breastfeeding
  - Assessments of the mother that include physical and mental health evaluations, as well as targeted approaches for family planning needs. Providers need to be trained about the mental health implications of the HDPs, such as anxiety, depression, and post-traumatic stress disorder
- Engage **traditional birth attendants** in delivery of PNC

Table S11.1 Recommendations graded as STRONG in the WHO Postnatal Care Guidelines 2013[95]

Nature of recommendation	*Details*
Postnatal contact	
	Timing (as early as possible within 24 h)
	Number (3 visits)
	Place (home visits are recommended)
Exclusive breastfeeding of baby	
	Maternal counselling to encourage and support
Maternal assessment	
Physical	
Within 24 h of birth	*Starting shortly after birth and taken again at 6 h:* Blood pressure
	Starting from the first hour after birth and continuing routinely during the first 24 h: Assessment for vaginal bleeding, uterine contraction, fundal height, temperature and heart rate (pulse) routinely during the first 24 hours
Beyond 24 h of birth	*Ongoing assessment of:* general symptoms (headache, fatigue, back pain); uterine tenderness and lochia; voiding (i.e., micturition and urinary incontinence, bowel function); healing of any perineal wound, perineal pain, and perineal hygiene; breast pain and breastfeeding progress
	Counselling of mother on: warning signs and symptoms of PPH, infection, and pre-eclampsia/eclampsia; good nutrition, hygiene, especially hand washing; birth spacing and family planning; gentle exercise, iron and folic acid supplementation
Mental health	Emotional well-being
Psychosocial support	For women who have lost her baby
	Accounting for experiences in hospital

Appendix 11.5

Recommendations for partartum care of women with hypertensive disorders of pregnancy from international clinical guidelines*

	QLD	*NICE 2010*	*WHO 2011*
BP monitoring		For women with chronic hypertension or GH, measure BP daily for first 2 days, once/day on days 3–5, and as indicated if antihypertensive therapy is changed For women with PET, measure BP 4x/day in hospital, once/day on days 3–5, and if abnormal then, on alternate days (until normal) In women with PET who took antihypertensive therapy, measure BP 4x/day in hospital, then every 1–2 days for 2 weeks until off treatment and normotensive	
PET may appear or worsen	For women with pre-eclampsia, serial surveillance of maternal well-being is recommended	For women with severe PET, ask about severe headache and epigastric pain when BP is measured For women with PET with non-severe hypertension or those who have received critical care, measuring creatinine transaminases within 48–72 h If creatinine and transaminases are normal at 48–72 h after birth, they do NOT need to be retested For women with PET, repeat platelet count, transaminases and serum creatinine "as clinically indicated" and at the 6–8 weeks postnatal review For women with PET who have stepped down from critical care (level 2), do NOT measure fluid balance if creatinine is normal	
Continuation of antenatal antihypertensive therapy		For women with chronic hypertension, continue antenatal antihypertensive therapy In women with GH or PET who were taking antenatal antihypertensive therapy, continue therapy If methyldopa was the antenatal antihypertensive, stop it within 2 days of birth. For women with chronic hypertension, restart the antihypertensive agent that was taken before planning pregnancy	For women with any HDP, continue antenatal antihypertensive therapy
Treatment of severe hypertension		For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension with antihypertensive drugs

AOM 2012	*ACOG 2013*	*SOGC 2014*
Inform women with any HDP that elevated BP may take time to resolve Inform women with GH that hypertension may worsen "during the postpartum period"	For women with GH, PET, or superimposed PET, measure BP in hospital (or equivalent setting) for ≥72 h and at some point on days 7–10 or earlier if PET symptoms occur	For women with any HDP, measure BP at some point on days 3–6 postpartum
Inform women with any HDP to report any symptoms or signs of PET	Inform women with any HDP about symptoms and signs of PET which they should report immediately if they arise	Women with new/worsening postpartum hypertension should be evaluated for PET For women with PET, there should be confirmation that end-organ dysfunction has resolved
		For women with any HDP, especially with PET or preterm delivery, continue antihypertensive therapy
	For women with any HDP, treat severe hypertension (BP ≥160/110 mmHg) within 1 hour	For women with any HDP, treat severe hypertension with antihypertensive drugs For women with any HDP, goal of <160/110 mmHg

continued

Appendix 11.5 *continued*

QLD	*NICE 2010*	*WHO 2011*
Treatment of non-severe hypertension	For women with "chronic hypertension", goal of <140/90 mmHg In women with GH or PET goal of <150/100 mmHg In women with GH or PET consider a reduced dose if BP <140/90 mmHg. Reduce the dose if BP is <130/80 mmHg	
Antihypertensive agents and breastfeeding	Acceptable agents are nifedipine, labetalol, captopril, enalapril, atenolol and metoprolol Do NOT prescribe diuretics to women who are breastfeeding or expressing milk Insufficient evidence to comment on the neonatal safety of the following during breastfeeding: ACE inhibitors (other than enalapril and captopril), ARBs and amlodipine	
Discharge planning for community care	For women with chronic hypertension, review long-term antihypertensive treatment 2 weeks after the birth Offer women with PET transfer to community care if they have no symptoms, BP <150/100 mmHg, and laboratory abnormalities are stable/improving For women with GH or PET, write a detailed care plan before transfer to community care A care plan should include the following details: who will provide follow-up care, including medical review if needed, frequency of BP monitoring needed, thresholds for reducing or stopping treatment, indications for referral to primary care for BP review, and self-monitoring for symptoms	
At midwifery visits between discharge and formal 6–8 weeks postnatal review	Offer medical review (with the pre-pregnancy team) at the 6–8 weeks postnatal review for women with chronic hypertension Offer medical review at the 6–8 weeks postnatal review for women with GH or PET, especially if they are still on antihypertensive treatment 2 weeks after transfer to community care	
Formal medical postnatal review at 6–8 weeks after delivery	In women with PET, perform urinary reagent-strip testing. If proteinuria ≥1+, offer further review at 3 months postpartum If women with PET had improving but still abnormal haematological or biochemical indices at hospital discharge, repeat testing For women with PET, do NOT routinely perform thrombophilia screening	

AOM 2012	*ACOG 2013*	*SOGC 2014*
	For women with any HDP goal of <150/100 mmHg	For women with uncomplicated chronic hypertension, consider goal of <140/90 mmHg For women with chronic hypertension and comorbidities other than pre-gestational diabetes mellitus, consider goal of <140/90 mmHg For women with chronic hypertension and pre-gestational diabetes mellitus, goal of <130/80 mmHg
		Acceptable agents are nifedipine XL, labetalol, captopril and enalapril, and methyldopa For women with any HDP postpartum, captopril, enalapril or quinapril may be used
For women with any HDP, monitor BP at "all regular postpartum visits" in first 2 weeks postpartum, or until normal BP measured twice For women with any HDP who has an elevated BP upon discharge from hospital, ensure plan is in place for physician follow-up in the event that BP remains elevated (or increases further) Upon discharge from midwifery care, communicate information about any HDP to the primary care provider		For women with PET, there should be confirmation that end-organ dysfunction has resolved
		For women with chronic hypertension or any HDP with persistent postpartum hypertension, perform the following (if not done previously): urinalysis, serum Na/K and creatinine, fasting glucose and lipid profile and standard ECG recommended For women with severe PET (particularly with presentation at <34 weeks), screen for chronic hypertension and underlying renal disease) For women with any HDP, consider screening for traditional cardiovascular risk markers

continued

Appendix 11.5 *continued*

	QLD	*NICE 2010*	*WHO 2011*
Counselling about future pregnancy risks	For women with any HDP, offer preconceptual advice		
Counselling about long-term health risks	For women with any HDP, offer "screening" and lifestyle counselling	Advise women with GH or PET (and their primary care physicians) that they are at increased risk of future hypertension and cardiovascular disease in later life Advise women with PET with proteinuria (that has resolved) that they are still at increased risk kidney disease but the absolute risk is very low and follow-up is not necessary Advise women with PET to keep their BMI within healthy range (18.5–24.8 kg/m^2, NICE clinical guideline 43)	
Specialist referral (e.g., renal, etc.)		Hypertension specialist – for women with GH or PET who still need antihypertensive therapy 6–8 weeks after delivery Kidney specialist – for women with PET who have proteinuria ≥1+ at 6–8 weeks after delivery (although clinicians can reassess at 3 months post-delivery to confirm)	
NSAIDs			
Thromboprophylaxis			

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[98]. PRECOG II (2009) and NVOG (2011) did not provide postpartum guidance and are not included in this table

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

AOM 2012	*ACOG 2013*	*SOGC 2014*
		Advise women with any HDP to keep their BMI within healthy range to decrease risk in future pregnancy
Advise women with any HDP that they may be at increased risk of future hypertension and cardiovascular disease in later life Advise women with any HDP of the benefits of a heart healthy diet and lifestyle	For women with PET and preterm birth (<37 0/7 weeks) or recurrent PET, consider yearly assessment of BP, lipids, fasting blood glucose and BMI	Advise women with any HDP to pursue a healthy diet and lifestyle Advise women with any HDP to keep their BMI within healthy range for long-term health
		Offer in hospital specialist assessment with internal medicine – for women with any HDP when postpartum hypertension is difficult to control Offer outpatient renal assessment – for women who had PET who have proteinuiria, decreased eGFR (<60 mL/min) or another indication of renal disease at 3–6 months after delivery
For women with any HDP, limit use of NSAIDs and offer acetaminophen as an effective alternative (albeit with limited information about side-effects)		For women with any HDP, NSAIDs are NOT recommended if BP is difficult to control, there is kidney injury (oliguria and/or an elevated creatinine) (≥90 μM), or platelets are $<50 \times 10^9$/L
		Consider for women with PET, especially when there are other risk factors

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011