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Fluids, drugs and transfusion

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SYNOPSIS

The management of the hypertensive disorders of pregnancy encompasses far more than use of antihypertensive therapy. Women with pre-existing or gestational hypertension are at risk of it evolving into pre-eclampsia, a multisystem disorder of endothelial dysfunction. As such, attention must be paid to judicious fluid management, antihypertensive therapy of severe and non-severe hypertension with oral or parenteral agents, magnesium sulphate ($MgSO_4$) for eclampsia prevention and treatment as well as fetal neuroprotection with birth at <34 weeks, antenatal corticosteroids for acceleration of fetal pulmonary maturity, and various therapies for HELLP (haemolysis, elevated liver enzyme, low platelet) syndrome, including transfusion of blood products and, possibly, corticosteroids. The WHO Model List of Essential Medicines includes all of the aforementioned interventions other than fluid therapy for pregnant women. It is our responsibility to ensure that we advocate the use of effective interventions whether we practice in well- or under-resourced settings.

INTRODUCTION

At present, timed delivery of the placenta is the only cure for the hypertensive disorders of pregnancy. Care aims to optimise outcome for the fetus and reduce maternal risk related to end-organ complications (Table 8.1).

Fluid management

Plasma volume expansion

Plasma volume expansion is not recommended for women with pre-eclampsia. The rationale for this practice was that women with pre-eclampsia are intravascularly volume contracted and sympathetic tone is high. Observational studies suggested that plasma volume expansion (with crystalloid or colloid) improved maternal haemodynamics, umbilical blood flow velocities, fetal growth and perinatal mortality. However, trials (of colloid solution) demonstrated no improvement in maternal or perinatal outcomes (4 trials, 277 women)[2,3]. In the largest trial (216 women), plasma volume expansion was associated with harm – namely more Caesarean deliveries, a (non-significantly) shorter pregnancy prolongation, and a (non-significant) increase in pulmonary oedema[3]. Also, there was no evidence of benefit as measured by an increase in fetal middle cerebral or umbilical artery blood flow velocity[4], a decrease in sympathetic tone[5], or an improvement in neurodevelopmental outcomes at the age of 1 year[6].

KEY POINT

Use fluids judiciously in the hypertensive disorders of pregnancy, particularly pre-eclampsia

Table 8.1 Management of pre-eclampsia. (Adapted from Mol *et al.*, *Lancet* 2015 Sep 2. pii: S0140-6736(15)00070-7[1] with permission)

Antepartum (regardless of gestational age) and postpartum (unless otherwise specified)	
Place of care	**Inpatient** care when there is severe hypertension or maternal symptoms, signs, or abnormal laboratory tests
	Outpatient care can be considered, recognising that many women are not eligible and hospital re-admission rates are high following home care
Consultation	**Obstetrics** to ensure that pre-eclampsia risk is recognised and appropriate maternal and fetal surveillance is put in place
	Anaesthesia to plan maternal monitoring and plan neuraxial analgesia/anaesthesia in labour to assist with blood pressure control and facilitate Caesarean delivery (should it be necessary)
Fluid management	**Restrict** to a maximum of 80 mL/h when an IV is in place
Antihypertensive therapy	**Severe hypertension (blood pressure ≥160/110 mmHg):** Consider oral or parenteral agents that can be repeated in 30 min if blood pressure remains at ≥160 mmHg systolic or ≥110 mmHg diastolic: • Nifedpine capsule (10 mg orally without biting to a maximum of 30 mg) • Nifedipine tablet (10 mg orally to a maximum of 30 mg) • Hydralazine (5 mg IV bolus then if needed, 5–10 mg IV to a maximum of 45 mg) • Labetalol (20 mg IV then if needed, 40 mg then 80 mg to a maximum of 300 mg) Consider alternative oral agents that can be repeated in 1 h (supported by less evidence in pregnancy): • Labetalol (200 mg orally) • Clonidine (0.1–0.2 mg orally)*† • *Only postpartum* – Captopril (6.25–12.5 mg orally)*
	Non-severe hypertension • Methyldopa (500–2000 mg/d in 3 or 4 divided doses) • Labetalol (300–2400 mg/d in 3 or 4 divided doses) • Nifedipine (20–120 mg/d once daily)
$MgSO_4$	**Eclampsia *treatment*** • 4 g IV (over 5 min) then 1 g/h IV • If already on $MgSO_4$, administer another 2–4 g IV (over 5 min) and increase infusion to 2 g/h IV
	Eclampsia *prevention* among women with pre-eclampsia • 4 g IV (over 5 min) then 1 g/h IV
	Fetal neuroprotection 4 g IV (with/without 1 g/h until delivery or 24 h maximum) for women with imminent delivery at $<34^{+0}$ weeks who do not otherwise quality for eclampsia prevention or treatment
Corticosteroids	Antenatally only, for **fetal pulmonary maturity** when delivery is anticipated within the next 7 days and at $<34^{0-6}$ weeks
	HELLP syndrome (10 mg dexamethasone IV every 12 h for 48 h) if improvement in laboratory parameters alone will change management, such as eligibility for neuroaxial anaesthesia/analgesia or platelet transfusion
Platelet transfusion for HELLP syndrome	Recommended for counts: $<20 \times 10^9$/L, $20–49 \times 10^9$/L prior to Caesarean, or $\geq 50 \times 10^9$/L (± packed red blood cells) with excessive active bleeding, platelet dysfunction, a rapidly falling platelet count, or coagulopathy[2]

* Captopril (25 mg) and clonidine (0.1 mg) are being compared in a postpartum randomised controlled trial (NCT01761916) based on the effectiveness of these medications for severe hypertension treatment outside pregnancy

† Clonidine therapy is not recommended during breastfeeding (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)

Fluid restriction

Women with pre-eclampsia who are on delivery suite, for stabilisation or delivery, require IV access. In an international benchmarking study, restricting IV fluids was associated with lower rates of pulmonary oedema without an increase in acute renal failure[7]. As such, IV fluid of no more than 80 mL/h is recommended[8].

Oliguria (<15 mL of urine/h for 6 consecutive hours) is common in pre-eclampsia, particularly postpartum. Reasons include oxytocin administration and high levels of antidiuretic hormone following surgery. In the absence of pre-existing renal disease or a rising creatinine that mandate fluid challenge to rule out a component of pre-renal failure as a cause of renal dysfunction, oliguria should be tolerated and observed, at least over hours because fluid administration can precipitate pulmonary oedema in a dose-dependent fashion[3,7]. Furosemide should not be administered unless there is pulmonary oedema or the woman has oliguric renal failure (in which case increasing urine output simplifies management but does not improve prognosis in renal failure). 'Renal-dose' dopamine is not recommended; although it appears to increase postpartum urine output in women with pre-eclampsia; this is of uncertain clinical importance (1 trial, 40 women)[9].

Antihypertensive treatment of severe hypertension (blood pressure of ≥160 mmHg systolic or ≥110 mmHg diastolic)

The following discussion applies to women with either pre-existing or gestational hypertension, with or without evidence of pre-eclampsia.

In the WHO Prevention and Treatment of Pre-eclampsia and Eclampsia recommendations, antihypertensive treatment of severe hypertension during pregnancy was *strongly* recommended[10]. This seems very reasonable despite the fact that the quality of evidence on which the recommendation was based was graded as 'very low'. First, there are no relevant placebo-controlled randomised controlled trials that prove that women randomised to antihypertensive therapy more frequently have their blood pressure lowered compared with those randomised to placebo; however, such randomised controlled trials would be unethical and will never be done. Second, severe systolic hypertension is a independent risk marker for stroke in pregnancy[11]. Third, an individual short-acting antihypertensive agent is successful at lowering maternal blood pressure in at least 80% of women, based on randomised controlled trials of one antihypertensive drug versus another (as discussed below). Finally, a recent report of the Confidential Enquiries into Maternal Deaths in the UK that covered the hypertensive disorders of pregnancy (2005–2008) identified the failure to treat the severe (particularly systolic) hypertension of pre-eclampsia as the single most serious failing in the clinical care of the women who died[12,13]. It is of note that concerted efforts in the UK to address treatment of severe hypertension have been associated with a fall in the contribution of the hypertensive disorders of pregnancy to maternal mortality, based on 2009–2012 data[14]. Similarly, in South Africa that has a legislated Confidential Enquiries into Maternal Deaths process, maternal deaths owing to complications of hypertension have featured prominently, and recommendations for antihypertensive therapy have been associated with a reduction of deaths in this category[15].

In deciding on the need for treatment and the urgency with which blood pressure should be lowered, both the absolute level of blood pressure (i.e., severe or non-severe) and the rate with which it has risen should be considered. Experimental evidence from cats suggests that an abrupt (versus step-wise) increase in blood pressure is associated with more permeability of the cerebral vessels, taken as a measure of vascular injury[16]. Presumably, abrupt increases in intraluminal pressure may result in mechanical distension of the cerebral vessel wall which may adapt better to gradual or step-wise increases.

Women with a hypertensive 'urgency' (i.e., acute rise in blood pressure that is not associated with end-organ dysfunction) may be treated with oral antihypertensive agents that have peak drug effects in 1–2 hours (e.g., oral labetalol), recognising that gastric emptying may be delayed or unreliable among women in active labour. Choice of agents is discussed below.

In contrast to a hypertensive 'urgency', a hypertensive 'emergency' is associated with end-organ complications, such as eclampsia, pulmonary oedema and renal failure. Whether headache and visual symptoms should be considered

end-organ complications of a hypertensive 'emergency' is not known. They are non-specific and common, being documented in about 30% of women who are hospitalised with pre-eclampsia[17].

There is a general appreciation that the goal of antihypertensive therapy for severe hypertension is not normalisation of blood pressure, but rather, lowering of blood pressure to a non-severe level of hypertension that decreases the risk of stroke[18]. Also, there is recognition that lowering of blood pressure, even to levels that remain outside the hypertensive range has the potential to precipitate fetal distress and fetal heart rate monitoring (FHR) monitoring is advised[8,18].

Based on extrapolation of the approach outside pregnancy, hypertensive emergencies should be treated with short-acting antihypertensive agents and an arterial line when possible aimed at lowering mean arterial blood pressure by no more than 25% over minutes to hours; this is equivalent to taking a blood pressure of 220/130 mmHg to 165/98 over 1–2 hours, and then further lowering blood pressure below 160/100 mmHg over the next 2 hours.

Outside pregnancy, American[19], British[20] and European guidelines[21] all recommend that antihypertensive therapy be initiated with two oral agents when blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target. The American (JNC VII) guidelines stress that initial therapy of severe hypertension should be with two oral agents. This recommendation is based on the multifactorial nature of the blood pressure elevation and the limited (but variable) average blood pressure reduction of 9.1 mmHg systolic and 5.5 mmHg diastolic achieved after treatment with any one agent, given compensatory mechanisms in response to any single agent of a given class[22]. However, these recommendations are based on treatment in the setting of chronic hypertension, outside pregnancy, and following long-term therapy[19]. In pregnancy, initiating antihypertensive therapy with one agent may be more appropriate given the intravascular volume depletion associated with both severe hypertension and pre-eclampsia, and the potential for fetal compromise if blood pressure is acutely lowered too much.

KEY POINTS

- Women with severe hypertension in pregnancy (or postpartum) should be treated with antihypertensive therapy
- The antihypertensive agents used most commonly are oral nifedipine (capsules or tablets) or IV labetalol or hydralazine (see Table 8.1 and Appendix 8.1, Figures S8.1 and S8.2)

Choice of antihypertensive agent

Table 8.2 presents the antihypertensive agents used most commonly for hypertensive urgencies in pregnancy, as well as alternatives that have a different pharmacology. Only hydralazine is on the WHO Model List of Essential Medicines (2015) for treatment of severe hypertension, although nifedipine capsules (10 mg) are listed as a tocolytic[23].

The treatment approach recommended here is cautious, in an attempt to lower blood pressure progressively, over hours and to minimise the risk of maternal hypotension and/or fetal distress. First, although nifedipine capsules have been recommended in doses of 20 mg by the American College of Obstetricians and Gynecologists if a 10 mg dose fails[18], this dosing approach is not recommended here because few of the relevant trials have administered nifedipine in this way[24,25]. Second, none of the agents recommended here are to be repeated prior to 30 min unless there is a hypertensive emergency, although some societies recommend more frequent administration (i.e., every 10 min for labetalol and every 20 min for either hydralazine or nifedipine)[18].

Recommendations about antihypertensive therapy for severe hypertension in pregnancy come from 47 trials (4322 women) that have compared one short-acting antihypertensive with another[26–28]. Just over half of these trials (i.e., 28/47) involved comparisons between parenteral hydralazine (usually 5 mg), parenteral labetalol (usually 20 mg) and calcium channel blockers (usually oral nifedipine 10 mg capsules). Each of these three agents is a reasonable choice for treatment of severe hypertension (in doses listed in Table 8.2). Some antihypertensive agents may be more or less appropriate for some women based on associated medical conditions (such as asthma) or therapies (such as current treatment with full doses of labetalol as an outpatient). Hydralazine may be associated with more adverse effects for the mother and labetalol with neonatal bradycardia, as discussed below.

Most published trials have compared parenteral hydralazine (usually 5 mg IV) with either calcium channel blockers (N = 11 trials, 699 women, usually nifedipine 10 mg capsules orally)[26,27,29] or parenteral labetalol (N = 8 trials, 384 women, usually 20 mg IV)[26,27], with repeat doses administered every 15–20 minutes to achieve blood pressure control in at least 80% of women; in nine other trials, hydralazine was compared with drugs used regionally or infrequently: mini-dose diazoxide (1 trial, 124 women)[30], ketanserin (4 trials, 210 women)[26], urapidil (3 trials, 101 women)[27,31] and prostacyclin (1 trial, 47 women)[26].

Compared with calcium channel blockers (usually nifedipine), hydralazine may be a *less* effective antihypertensive and also associated with more maternal side-effects (11 trials of which 9 studied oral nifedipine 10 mg, one nifedipine 5 mg, and one parenteral isradipine[26,27,32]. There is no published review of all relevant trials, so one summary statistic is not available.

Compared with labetalol, hydralazine may be a *more* effective antihypertensive but also associated with more maternal hypotension and maternal side-effects (8 trials, 384 women)[26,27]. Most of the published hydralazine trials were included in a 2003 meta-analysis that compared hydralazine with any other short-acting antihypertensive agent; hydralazine was found to be associated with more adverse effects, including maternal hypotension, Caesarean delivery and adverse FHR effects[26]. It should be noted that in two hydralazine versus labetalol trials, parenteral labetalol was associated with more neonatal bradycardia (which required intervention in one of six affected babies in one trial[26,33,34].

Compared with labetalol, oral nifedipine (N = 7 trials, 363 women)[28,35–39] appears to be similarly effective for blood pressure control (RR 0.42, 95% CI 0.18–0.96), as does parenteral nicardipine (60 women)[40], although there is only one such trial.

In the trials discussed above, labetalol was administered parenterally; however, it has been given orally for hypertensive urgencies. In a dose of 200 mg, oral labetalol has been used with good effect as part of a regional pre-eclampsia protocol[41]. In a clinical trial of preterm severe hypertension, 100 mg of oral labetalol every 6 hours achieved the stated blood pressure goal (of about 140/90 mmHg) in 47% of women[42]. We believe that these data are insufficient to support the NICE 2010 recommendation to use oral labetalol as initial therapy for severe hypertension in pregnancy[43]; however, if severe hypertension is detected in the office setting, an oral dose of labetalol or another antihypertensive may be useful to administer while the woman is being transported to hospital for further evaluation and treatment[44]. Other than oral nifedipine (discussed above), methyldopa may be suitable although probably starting with a 750 mg dose rather than the 250 mg used in the one relevant randomised controlled trial[42]; IV methyldopa is manufactured for women who are unable to take the medication by mouth. Prazosin may be associated with an increase in stillbirth and is not recommended[45].

The nifedipine preparations that are appropriate for treatment of severe hypertension are the capsule and the PA tablet[29,46]. The PA tablets have been withdrawn from some markets. Most authors of randomised trials did not specify whether nifedipine capsules were bitten (prior to swallowing), which may have a greater effect on blood pressure. The 10 mg tablet may be associated with less maternal hypotension than the 10 mg capsule when bitten/punctured (2 trials, 87 women)[29,46]. Theoretically, the 5 mg (instead of the 10 mg) capsule may reduce the risk of a precipitous fall in blood pressure, although there are only two published reports comparing nifedipine 5 mg with hydralazine 5 mg IV (250 women)[34,47].

Nifedipine or other calcium channel blockers can be used together with $MgSO_4$. The risk of neuromuscular blockade with contemporaneous use of nifedipine and $MgSO_4$ is <1%, based on a single-centre, controlled study and a complete data synthesis from the literature[48,49]. Blockade is reversed with 10 g of IV calcium gluconate.

$MgSO_4$ is not an antihypertensive agent[50]. However, transient decreases in blood pressure may be seen. Observational literature describes no decrease[51] or a transient decrease in blood pressure[52–55] 30 minutes after 2–5 g of IV $MgSO_4$ (with or without ongoing infusion), usually in patients with pre-eclampsia. In randomised controlled trials of $MgSO_4$ for fetal neuroprotection, an excess of hypotension was seen (i.e., 9.7% with $MgSO_4$ versus 6.5% with placebo, RR 1.51, 95% CI 1.09–2.09)[56]. When $MgSO_4$ was compared directly with parental nimodipine, $MgSO_4$ was less effective in lowering blood pressure (2 trials, 1683 women)[27] or parenteral labetalol (1 trial, 177 women)[57]. Therefore, although a sustained

Table 8.2 Agents used most commonly for treatment of a blood pressure ≥160/110 mmHg

			*Pharmacokinetics**			
Agent	*Mechanism of action*	*Dosage*	*Onset*	*Peak*	*Duration*	*Comments*
Most commonly recommended						
Labetalol	†Peripheral alpha-1 and (non-selective) beta-1 and 2 receptor antagonist	Intermittent dosing Start with 20 mg IV over 2 min Repeat with 40 mg then 80 mg IV (each over 2 min) q 30 min Continuous infusion 1–2 mg/min (max dosage 300 mg)	5 min	30 min	4 h	Best avoided in women with asthma or heart failure Neonatology should be informed if the woman is in labour, as parenteral labetalol may cause neonatal bradycardia Parenteral therapy should be followed by ongoing oral therapy to maintain BP
Nifedipine	Calcium channel blocker (vasodilator)	Capsule 5–10 mg to swallow without biting Repeat every 30 min	5–10 min	30 min	6 h	There are three types of nifedipine preparations with which all staff must be familiar: capsules, intermediate-release tablets (PA, SR or retard tablet) and slow-release tablets (XL, MR or LA) Nifedipine may be given at the same time as $MgSO_4$
		PA, SR or retard tablet 10 mg to swallow Repeat every 30 min (max dosage 30 mg)	30 min	240 min	6 h	
Hydralazine	Direct-acting vasodilator	Intermittent dosing 5 mg IV Repeat 5–10 mg IV every 30 min (may be given IM but unusual) Continuous infusion 0.5–10 mg/h IV (max dosage 45 mg)	5 min	30 min	3–8 h	May increase the risk of maternal hypotension

Labetalol	†Peripheral alpha-1 and (non-selective) beta-1 and -2 receptor antagonist	200 mg orally Repeat in 4 h (max dosage 2400 mg/day in 4 divided doses‡)	20–120 min	1–4 h	8–12 h	Duration is dose-dependent
Methyldopa	Centrally acting alpha-2 receptor agonist	750 mg orally Repeat in 6 h (max dosage 2000 mg/day in 4 divided doses‡)	Not known	4–6 h	24–48 h	Less effective than oral nifedipine
Clonidine¶	Centrally acting alpha-2 receptor agonist	0.1–0.2 mg orally Repeat in 1 h (max dosage 0.8 mg‡)	30–60 min	2–4 h	6–10 h	Clonidine therapy is not recommended during breastfeeding§
Captopril¶ *only postpartum*	Angiotensin-converting enzyme inhibitor	6.25–12.5 mg orally Repeat in 1 h (max dosage 75 mg)	30 min	60–90 min	≥8 h	Captopril must NOT be administered before delivery, but it is acceptable for use during breastfeeding§ Duration is dose-dependent
Nitroglycerin infusion	Direct vasodilators that has its affects veins more than arterioles	5 μg/min, increased every 5 min (max rate 100 μg/min)	2–5 min	5 min	5–10 min	Main side-effects are headache (due to direct vasodilation) and tachycardia (from reflect sympathetic activation) Methaemoglobinaemia has been reported after 24 h of treatment

BP, blood pressure; IM, intramuscular; IV, intravenous; $MgSO_4$, magnesium sulphate

* General reference www.drugs.com

† Beta-blockade is 3–7 times more than alpha-blockade, especially at lower doses

‡ Dosing of this drug may continue after the severe hypertension has resolved, as it is used for chronic treatment of non-severe hypertension

¶ Captopril (25 mg) and clonidine (0.1 mg) are being compared in a postpartum randomised controlled trial (NCT01761916) based on the effectiveness of these medications for severe hypertension treatment outside pregnancy

§ http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

lowering of blood pressure cannot be anticipated following a loading dose of $MgSO_4$, the potential for a transient lowering of blood pressure 30 minutes after administration should be considered when antihypertensives are co-administered.

Nitrogylcerin (by infusion) compared favourably with oral nifedipine in one small trial (32 women)[58] and no adverse clinical effects were demonstrated in other small studies[58.60].

Mini-dose diazoxide (i.e., 15 mg IV every 3 minutes) was associated with less persistent severe hypertension compared with parenteral hydralazine (5 mg) in another small trial (124 women)[30].

For refractory hypertension in an intensive care setting, consideration can be given to using sodium nitroprusside or higher dose diazoxide. The theoretical concerns about nitroprusside are well known: light-sensitivity, the need for careful monitoring and the potential to cause fetal cyanide toxicity. A published review of case reports (22 women, 24 fetuses) documented stillbirths among five of 18 women (27.8%) treated antenatally with nitroprusside, although the authors could not attribute these deaths to fetal cyanide toxicity[61]. High dose diazoxide (i.e., 75 mg IV every 30 min) was associated in one trial (90 women) with an excess of maternal hypotension (17.8%) compared with IV labetalol (0%)[62].

Observational literature illustrates that hypotension may result with any short-acting antihypertensive agent administered to women with pre-eclampsia, because they are intravascularly volume depleted. Therefore, it is prudent to continuously monitor FHR until blood pressure has stabilised.

Postpartum, hydralazine, labetalol, nifedipine and methyldopa are appropriate for use during breastfeeding, although only two trials have compared hydralazine with either labetalol[63] or nifedipine[64] for treatment of severe hypertension. Nitroglycerine and diazoxide have not been studied in breastfeeding, although treatment with one of these agents would be expected to be very brief. Nitroprusside is not advised in breastfeeding because of the potential for toxic metabolites (thiocyanate and cyanide) to cross into breast milk[65]. Captopril could also be administered orally for severe hypertension based on its effectiveness for this indication outside pregnancy[66] and its acceptability during breastfeeding[65]. Although neonatologists may express concerns about this in babies born preterm or of low birth weight, no reports of adverse effects were identified. Oral clonidine which is effective for severe hypertension outside pregnancy is not advocated for use in breastfeeding because of high serum levels in breastfed infants[65].

No relevant economic analyses were identified.

Antihypertensive treatment of non-severe hypertension (blood pressure of 140–159/90–109 mmHg)

Management of a pregnant woman with a blood pressure of 140–159/90–109 mmHg is much debated. Any antihypertensive therapy will, compared with placebo or no therapy, decrease the risk of transient, severe hypertension (RR 0.49, 95% CI 0.40–0.60; 20 trials, 2558 women; NNT 10, 95% CI 8–13) without a clear difference in other maternal or perinatal outcomes, such as stroke, perinatal death, or preterm delivery (29 trials, 3350 women)[67]. The results of a small pilot randomised controlled trial (132 women)[68] and a meta-regression of randomised controlled trials (42 trials, 3892 women[69,70]) raised concerns that antihypertensive therapy may be harmful. The meta-regression of randomised controlled trials found a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of SGA infants or lower birth weight. On the other hand, a small trial of 125 women with mild essential or gestational hypertension found that 'very tight' (goal blood pressure <130/80 mmHg) versus 'tight' control (goal blood pressure 130–139/80–89 mmHg) was associated with fewer antenatal hospitalisations and a later gestational age at delivery[71].

The results of a large definitive trial, CHIPS (Control of Hypertension In Pregnancy Study), has provided evidence that non-severe hypertension in pregnancy should be treated with antihypertensive therapy[72]. 'Tight' blood pressure control (target diastolic 85 mmHg) (versus 'less tight' control, target diastolic 100 mmHg) achieved a lower blood pressure by 5.8/4.6 mmHg ($p < 0.001$). 'Tight' (versus 'less tight') control resulted in similar rates of adverse perinatal outcome: the primary outcome of perinatal death or high level neonatal care for >48 hours (30.7% versus 31.4%; aOR 0.98, 95% CI 0.74–1.30) and birth weight <10th percentile for gestational age and gender (19.7% versus 16.1%; aOR 1.28, 95% CI 0.93–1.79). However, 'tight' (versus 'less tight') control resulted in fewer adverse

maternal outcomes: a significant decrease in severe maternal hypertension (27.5% versus 40.6%; aOR 0.56, 95% CI 0.42–0.75) but similar rates of serious maternal complications (2.0% versus 3.7%; aOR 0.57, 95% CI 0.26–1.27).

Although there is ongoing debate about whether blood pressure should be lowered below a diastolic blood pressure of 80 mmHg in the setting of proteinuria (compared with non-proteinuric) patients, a goal of <130/80 mmHg is specified only for patients with diabetes mellitus in order to decrease the risk of long-term cardiovascular disease and diabetic nephropathy[73].

As blood pressure is lowest at about 20 weeks', women may be able to discontinue antihypertensives in early pregnancy. Medication should be restarted as blood pressure rises again later in pregnancy.

There is no evidence that blood pressure should be managed differently in women with pre-eclampsia compared with those with pre-existing or isolated gestational hypertension. It should be noted that 47.3% of women developed pre-eclampsia in the CHIPS trial, and the diastolic blood pressure goal to which women were randomised continued to be applied until delivery[72].

Guidance on treatment of secondary causes of hypertension is available from general hypertension sources[73].

When a decision is made to lower blood pressure, antihypertensive therapy is warranted. Relaxation techniques (such as guided imagery) were not successful in lowering blood pressure in one trial (69 women)[74].

Therapy is usually initiated with one antihypertensive agent, although this will not be sufficient if blood pressure is more than 20/10 above the target[19]. It is important to be familiar with a number of antihypertensive options. Outside pregnancy, only 30–50% of patients respond to a particular antihypertensive drug. Also, women may have another medical problem that is a contraindication to a specific medication (such as severe asthma and beta-blockers) or a characteristic that makes one type of agent more likely to be effective (such as Black race and calcium channel blockers).

Choice of antihypertensive agent

Table 8.3 presents the most commonly used antihypertensive agents for non-severe pregnancy hypertension.

There is little to guide the choice of antihypertensive agent, including effects on FHR and pattern, maternal and perinatal outcomes, and long-term paediatric neurodevelopment. Methyldopa, labetalol and nifedipine are the most commonly recommended antihypertensives in international practice guidelines, although oral labetalol is not widely available in LMICs[75]. Only methyldopa is on the WHO Model List of Essential Medicines (2015) for non-severe pregnancy hypertension[23], and it appears to be a reasonable antihypertensive choice; in the CHIPS trial, women treated with methyldopa (versus labetalol) may have had better outcomes, although this comparison was non-randomised and subject to the possibility of residual confounding[76]. Angiotensin converting enzyme inhibitors and receptor blockers should not be used later in pregnancy, and prazosin and atenolol may be best avoided, as discussed below.

KEY POINTS

- Antihypertensive therapy for non-severe pregnancy hypertension does not affect outcomes for the baby, but does decrease severe hypertension and therefore, risk, for the mother
- 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
- ACE inhibitors and ARBs should NOT be used in pregnancy

Whether pre-eclampsia haemodynamics (either high cardiac output or peripheral vascular resistance) should be used to guide therapy is unclear; although haemodynamics may interact with the pharmacodynamics of antihypertensives to influence development of fetal growth restriction or pre-eclampsia[77], it is unknown if individualised therapy would improve outcomes and be cost-effective.

FHR and pattern

Oral antihypertensives do not appear to change FHR or pattern, but the quality of the data is poor[78]. A prudent approach would be to regard changes in FHR or pattern to evolution of the

Table 8.3 Agents used most commonly for a blood pressure of 140–159/90–109 mmHg

Agent	*Mechanism of action*	*Dosage*	*Comments*
Methyldopa	Centrally acting alpha-2 receptor agonist → decreased sympathetic outflow → decreased peripheral vascular resistance	250–500 mg PO BID-QID (max dosage 2000 mg/day)	There is no evidence to support a loading dose of methyldopa Psychological side-effects (e.g., drowsiness or depression) may occur but women do not change drugs more frequently than with other medication Within first 6 weeks of therapy, <10% may develop hepatitis or cholestasis that can be detected by laboratory testing; abnormalities should reverse with discontinuation, but liver failure is rare After 6 months of therapy, 10–20% develop a positive direct Coombs test, but it does not interfere with typing or cross matching and associated haemolytic anaemia is rare
Labetalol	*Peripheral alpha-1 and (non-selective) beta-1 and 2 receptor antagonist → decreased peripheral vascular resistance with no reflex increase in heart rate	100–400 mg PO BID-QID (max 2400 mg/day)	Some experts recommend a starting dose of 100 mg PO TID because the half-life of labetalol is shorter in pregnancy May be associated with postural hypotension, especially at higher doses
Nifedipine	Calcium channel blocker → vascular smooth muscle relaxation → decrease peripheral vascular resistance	PA, SR or retard tablets 10–20 mg PO BID-TID (max 180 mg/day) XL, MR or LA preparation 20–60 mg PO OD-BID (max 120 mg/day)	Peripheral oedema as a side-effect may be more common at doses of 120 mg/day or more

BID, twice/day; PO, per os; QID, four times/day; TID, three times/day)
* Beta-blockade is 3–7 times more than alpha-blockade, especially at lower doses

underlying hypertensive disorder of pregnancy, and not to the antihypertensive agent that the woman is taking.

Maternal and perinatal outcomes

In randomised controlled trials, usually of women without comorbidities, a wide variety of antihypertensive agents (started after the first trimester of pregnancy) have been compared with placebo or no therapy and shown to decrease the risk of severe hypertension (as discussed above): methyldopa, labetalol, other pure beta-blockers (acebutolol, mepindolol, metoprolol, pindolol and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine and verapamil), hydralazine, prazosin and ketanserin (29 trials, 3350 women)[67].

In comparative trials of one antihypertensive agent versus another, meta-analysis has revealed no clear differences in maternal and perinatal outcomes (22 trials, 1723 women)[67], and small trials published subsequently have been consistent with these conclusions (2 trials, 163 women)[79,80]. Most trials have compared beta-blockers with methyldopa. Although alternative drugs may be more effective at reducing the risk of severe hypertension than methyldopa (RR 0.54, 95% CI 0.30–0.95; 11 trials, 638 women), and beta-blockers and calcium channel blockers considered together may decrease the risk of proteinuria (as a surrogate for pre-eclampsia) (RR 0.73, 95% CI 0.54–0.99; 11 trials, 997 women), the significance of these findings is unclear. The effects on both severe hypertension and proteinuria are not seen in individual drug comparisons.

Thiazide diuretics can be considered for use in hypertensive women, but they are used mainly in specific circumstances identified before pregnancy, such as medullary sponge kidney for which a decrease in renal calcium excretion is advantageous.

Despite concerns that they may inhibit the normal plasma volume expansion of pregnancy, thiazides used after the first trimester in randomised controlled trials for pre-eclampsia prevention did not (negatively or positively) affect maternal or perinatal outcomes, including pre-eclampsia (5 trials, 1836 women)[81].

ACE inhibitors and angiotensin receptor blockers (ARBs) should not be used in pregnancy as they are fetotoxic. The hypertensive disorders of pregnancy guidelines in the UK have identified advising women about these risks as a key priority for implementation[43]. If used prior to pregnancy for renoprotection among women with diabetes mellitus and pre-pregnancy microalbuminuria, there is no reasonable alternative available in pregnancy. However, most renoprotection is afforded by good control of blood pressure. Some ACE inhibitors are acceptable during breastfeeding and, as such, can be restarted after delivery[65].

There are a number of drugs that may be best not to use in pregnancy. It is not clear why atenolol (in contrast to other beta-blockers, even cardioselective) may be associated with adverse effects on fetal growth[81–86], an effect that has not been consistently observed[87]. Until further data are available on the risks of atenolol in pregnancy, other agents may be preferable to use. More stillbirths were reported in the prazosin arm of one trial of early severe pre-eclampsia (150 women)[45]. Oral hydralazine is not recommended because of maternal side-effects when used alone[88].

For women with pre-existing hypertension, antihypertensive choice for pregnancy is best made pre-pregnancy. However, 50% of pregnancies are unplanned. Relative to the baseline risk of major malformations (1–5%), most antihypertensives are not teratogenic but the quality of the evidence is only fair and controversies remain. As blood pressure falls in early pregnancy (reaching its nadir at 20 weeks), many women may be able to discontinue their antihypertensive therapy and maintain normotension, thereby avoiding first trimester exposure of the fetus to antihypertensive agents. If this is not possible, it should be noted that methyldopa, labetalol and nifedipine are used commonly in early pregnancy. Although clinical practice guidelines from the UK state that thiazides are teratogenic, no specific reference was provided[43]. There is even controversy over whether ACE inhibitors increase the risk of major malformations following first trimester exposure. A high-impact study that found ACE inhibitors were teratogenic[89], but the study was criticised because of potential residual confounding of the drug–outcome relationship. A subsequent prospective cohort study did not find ACE inhibitors (or ARBs) to be teratogenic following first trimester exposure, but they were associated with an increase in miscarriage[90]. A meta-analysis of controlled cohort studies found that any antihypertensive therapy (and not just treatment with ACE inhibitors or ARBs) was associated with heightened teratogenic risk, although the quality of the evidence was not high (five cohort studies involving 786 infants exposed to ACE inhibitors or ARBs, 1723 exposed to other antihypertensives, and 1,091,472 unexposed)[91]. Whether to replace ACE inhibitors, ARBs, atenolol, or less commonly used antihypertensives before or in early pregnancy, and if so with what, is uncertain. Conception may take up to 12 months, but women over 30 years suffer more subfertility.

Long-term paediatric neurodevelopment

There is very little published research on the potential long-term developmental effects of antihypertensive therapy and the hypertensive disorders of pregnancy for which they are prescribed. Unfortunately, different studies have focused on either the hypertensive disorders of pregnancy or the antihypertensive treatment, each type of study focusing on different confounders. Most studies are observational cohort studies and cannot address effectively both known and unknown confounders of the relationship between outcomes and either the hypertensive disorder of pregnancy or its antihypertensive therapy. Also, few existing studies have been published over a 35-year period, making it difficult to synthesise them owing to major changes in methods of treatment for hypertensive disorders of pregnancy, paediatric follow-up and neurodevelopmental testing methods.

What can be said is that follow-up data from placebo-controlled randomised controlled trials have not revealed clear adverse effects on health or neurodevelopment of nifedipine at 1 year of age (110 children)[92], atenolol at 18 months of age (190 children)[93], or methyldopa at 7.5 years (242 children)[94]. Data from a controlled observational study were reassuring for labetalol (N = 32

pregnancies), but compared with women exposed to medications without known neurodevelopmental effects (N = 42), women who took methyldopa in pregnancy (N = 25) had children with lower scores on measures of Full-Scale IQ (105.2 ± 12.5 vs. 111.9 ± 11.4, $p = 0.04$) and Performance IQ (98.8 ± 16.2 vs. 110.2 ± 12.9, $p = 0.002$); although the mean scores were within the normal range, the duration of treatment with methyldopa was an independent predictor of children's Performance IQ[95].

What is important to note is that the hypertensive disorders of pregnacy do appear to be associated with some effects on neurodevelopment, independent of any antihypertensive therapy. We were unable to identify literature on the impact on child development of pre-existing hypertension itself (compared with normotensive pregnancy). However, the children of women with gestational hypertension or pre-eclampsia appear to have a relatively modest, inconsistent increase in neurodevelopmental problems, such as inattention and externalising behaviours (e.g., aggressiveness), fine or gross motor function, or verbal ability[96–99]. These studies are presented in detail elsewhere[8].

The reader should also be aware of a growing literature describing adverse effects of pre-eclampsia on offspring health, particularly cardiovascular[100], reproductive[101] and even cognitive at advanced age[102].

No relevant analyses were found about the cost-effectiveness of antihypertensive therapy (or not) for non-severe hypertension in pregnancy, although an economic analysis of the CHIPS trial (see above) is anticipated for publication in 2016[103]. No economic analyses were identified for comparisons of different antihypertensive agents.

Magnesium sulphate therapy for eclampsia prevention and treatment, and fetal neuroprotection

Magnesium sulphate ($MgSO_4$) is listed on the WHO Model List of Essential Medicines (2015) for treatment of eclampsia and severe pre-eclampsia[23]. Benzodiazepines are listed as anticonvulsants, but not specifically for eclampsia.

For eclampsia treatment

$MgSO_4$ is effective for eclampsia treatment, more than halving the risk of recurrent seizures compared with phenytoin (7 trials, 972 women)[104], diazepam (7 trials, 1396 women)[105], or a lytic cocktail (usually chlorpromazine, promethazine and pethidine) (3 trials, 397 women)[106]. Also, $MgSO_4$ was associated with a reduction in some other adverse maternal outcomes, such as death (compared with diazepam or a lytic cocktail) or pneumonia and ventilatory support (compared with phenytoin or a lytic cocktail). Of note, the protocol for women in the $MgSO_4$ arm of the largest of these trials, the Collaborative Eclampsia Trial, did not include administration of benzodiazepines for seizure termination. The initial intravenous treatment protocol was $MgSO_4$ 4 g IV (or 5 g in South Africa) over 5 minutes, followed by an infusion of 1 g/h; a recurrent seizure was treated with another 2–4 g IV over 5 minutes. Serum magnesium levels were not measured, but women were followed clinically for adverse magnesium-related effects. Algorithms have been published to improve eclampsia care.

We were unable to identify a cost-effectiveness analysis of $MgSO_4$ for eclampsia treatment.

For pre-eclampsia (eclampsia prevention)

$MgSO_4$ is more effective than placebo/no therapy for eclampsia prevention among women with pre-eclampsia, more than halving the occurrence of seizures (RR 0.41, 95% CI 0.29–0.58; 6 trials, 11,444 women)[107]. In the Magpie Trial, the largest of the prevention trials, pre-eclampsia was defined as hypertension and ≥1+ proteinuria[108]. The initial treatment protocol was $MgSO_4$ 4 g IV over 10–15 minutes, followed by an infusion of 1 g/h. The number needed to treat (NNT) (95% CI) to prevent one seizure among women with severe pre-eclampsia was 50 (34–100) and for non-severe pre-eclampsia 100 (100–500). (Severe pre-eclampsia was defined as severe hypertension (systolic blood pressure ≥170 mmHg or diastolic ≥110 mmHg, measured twice) and proteinuria ≥3+ by dipstick, or more moderate hypertension (systolic blood pressure ≥150 mmHg or diastolic ≥100 mmHg, measured twice) and proteinuria (≥2+), as well as TWO or more symptoms/signs of 'imminent eclampsia' (unspecified).) $MgSO_4$ also decreased the risk of abruption (RR 0.64, 95% CI 0.50–0.83; NNT of 100 (50–1000)) but increased the risk of Caesarean delivery (50% vs. 47%; RR 1.05, 95% CI 1.01–1.10). $MgSO_4$ was more frequently associated with side-effects (24% vs. 5%; RR 5.26, 95% CI 4.59–6.03).

$MgSO_4$ is more effective than other agents for eclampsia prevention among women with pre-eclampsia (9 trials, 6301 women). $MgSO_4$ compared with phenytoin reduced eclampsia (RR 0.08, 95% CI 0.01–0.60) but increased Caesarean delivery (RR 1.21, 95% CI 1.05–1.41; 4 trials, 2343 women)[107]. $MgSO_4$ compared with nimodipine reduced eclampsia, but there were more maternal respiratory problems (1.3% vs. 0.4%; RR 3.61, 95% CI 1.01–12.91) and the need for additional antihypertensive therapy (54% vs. 46%; RR 1.19, 95% CI 1.08–1.31; 1 trial, 1650 women)[109]. Other trials comparing $MgSO_4$ with other agents (diazepam in 2 trials, 2241 women; methyldopa in 1 trial, 31 women; and nitrates in 1 trial, 36 women) were too small for conclusions to be drawn[107].

Although $MgSO_4$ is effective for eclampsia prevention in women with pre-eclampsia, the challenge remains how to use $MgSO_4$ cost-effectively for this purpose. $MgSO_4$ for eclampsia prevention is costly[110]. In high income countries, the number of women who need to receive $MgSO_4$ to prevent one case of eclampsia is 324 (95% CI 122–∞), compared with 43 (95% CI 30–68) in low-income countries[110]. The incremental cost of preventing each case of eclampsia in 2001 US$ was $21,202 in high-income and $456 in low-income countries, driven by the costs of maternal surveillance in high-income settings and by the drug cost in low-income ones. If only women with severe pre-eclampsia were to be treated with $MgSO_4$, the incremental cost would be US$12,942 in high- and $263 in low-income countries.

The high costs of $MgSO_4$ for eclampsia prevention has generated controversy about whether women with non-severe pre-eclampsia should receive $MgSO_4$, particularly as $MgSO_4$ is associated with more Caesarean deliveries and maternal adverse effects[110]. Potential solutions to this challenge include restricting treatment to 'severe' pre-eclampsia and lowering the $MgSO_4$ dose and/or duration of therapy.

Restricting therapy to 'severe' pre-eclampsia only

There are a number of concerns about this approach. First, in a comprehensive review of eclampsia (21,149 women with eclampsia from 26 countries contributing to at least one variable of interest), a significant proportion lacked evidence of 'severe pre-eclampsia' based on severe hypertension (32% of 3443 women), headache (66% of 2163 women), visual disturbances (27% of 2163 women), or epigastric pain (25% of 2053 women); 25% (of 3443 women) were actually normotensive and 25% (of 1092 women) asymptomatic[111]. Second, in a large American centre that changed its policy from universal prophylaxis of all women with gestational hypertension to a selective approach for only women with severe gestational hypertension, there was more eclampsia and, in those women, more general anaesthesia and adverse neonatal outcomes, although absolute rates of these complications were very low[112]. Finally, whether we could successfully target at least 80% of women with severe pre-eclampsia if we tried is questionable; only 62% of women who were hospitalised with pre-eclampsia and also suffered an adverse maternal outcome were treated with $MgSO_4$ in an international prospective cohort study[17]. Also, if we chose this approach, cost-savings would be offset by the need to administer $MgSO_4$ for fetal neuroprotection when women with non-severe pre-eclampsia deliver at <32 weeks (see below)[113].

Lowering the dose or duration of $MgSO_4$ therapy

Interest in $MgSO_4$ dose reduction has been fuelled by fear of serious maternal side-effects and the perception that women must have serum magnesium levels, as illustrated by the following quote:

> "We know that the gold standard is magnesium sulphate, but you know the problem associated with that, monitoring level and so on and so forth. But then the diazepam that can be used without much monitoring."
>
> Society of Obstetricians and Gynaecologists of Nigeria, Nigeria

However, in a comprehensive review of 143 publications (including 21 randomised controlled trials, total of 23,916 women), appropriate administration of $MgSO_4$ was not associated with an increase in maternal death or cardiorespiratory arrest, and estimates from non-randomised studies largely supported those from randomised controlled trials[114]. In a review specifically of 24 studies (9556 women) conducted in LMICs, serious side-effects

were infrequent (i.e., one maternal death associated with a serum magnesium level of 24 mEq/L; 1.3% respiratory arrest; cardiac arrest not reported) and when concerns arose (e.g., absent patellar reflex, 1.6%), a delay in repeat administration (3.6%) was generally sufficient to mitigate the effect; calcium gluconate was administered to <0.2% of treated women[115].

Dose reduction is of particular interest in LMICs, where women tend to have lower body weight and the cost of $MgSO_4$ itself drives the cost of treatment; 22/25 published studies of $MgSO_4$ administration in LMICs used a modified dosing regimen that decreased overall dose and was associated with a median eclampsia rate of 3.0%, even when studies of eclampsia treatment were included[116]. However, an important consideration is that global obesity rates are rising and women with a BMI >30 kg/m^2 may need *higher* than standard doses of $MgSO_4$[117].

Modified regimens for eclampsia *treatment* have been studied in six trials (899 women). Two trials (481 women) compared a $MgSO_4$ loading dose with loading dose plus maintenance therapy for 24 hours; there were no clear between-group differences in recurrent seizures or other outcomes but the 95% CIs were wide[118,119]. Four trials (359 women) compared low dose $MgSO_4$ with standard dosing over 24 hours; the studies were small but at least one found that lower doses were associated with a higher risk of recurrent seizures[120–123]. One trial (98 women) evaluated a postpartum course of $MgSO_4$ shortened to two intramuscular doses given 4 hours apart; there was no difference in outcomes[124].

Modified regimens for eclampsia *prevention* among women with pre-eclampsia have been evaluated in six trials (685 women)[125–127]; an additional trial (60 women) that compared 1 g/h versus 2 g/h maintenance dosing antenatally (and found no difference in outcomes) was not considered to have studied a reduced dosing regimen[128]. One trial (17 women) compared an IV with an IM maintenance regimen for 24 hours; no reliable conclusions could be drawn[129]. Five trials (668 women) evaluated shortened maintenance regimens of postpartum $MgSO_4$, compared with continuing the $MgSO_4$ for 24 hours after the birth; eclampsia was not more common in the abbreviated treatment groups but the trials were too small for reliable conclusions to be drawn[125,130–132]. Given a rate of 0.75% of eclampsia in the $MgSO_4$ arm of women in eclampsia prevention trials, a sample size of 3285/group would be required to rule out a doubling of the eclampsia rate (from 0.75% to 1.5%) with a modified $MgSO_4$ therapy regimen (assuming an alpha of 0.05 and power of 80%). Therefore, there are insufficient data to evaluate the effectiveness of a modified (reduced dose) regimen of $MgSO_4$ for eclampsia prevention.

All $MgSO_4$ data presented thus far relate to administration in facilities. In-community administration of $MgSO_4$ for eclampsia decreased recurrence in one randomised controlled trial (265 women)[133], and administration for pre-eclampsia is being studied in a cluster randomised controlled trial in four LMICs[134] (pre-empt.cfri.ca).

KEY POINTS

$MgSO_4$ for eclampsia treatment and prevention

- *IV only*: 4 g $MgSO_4$ IV (over 5 min), then maintenance dose of 1 g/h
- *IV & IM*: 4 g $MgSO_4$ IV (over 5 min) + 5 g IM into each buttock (total 10 g IM), then 5 g IM every 4 h
- Administer an additional 2–4 g IV (over 5 min) if there is a seizure while on $MgSO_4$
- There are insufficient data to evaluate the effectiveness of a modified (reduced dose) regimen of $MgSO_4$ for eclampsia prevention

Fetal neuroprotection

- 4 g $MgSO_4$ IV (with/without 1 g/h until delivery or 24 h maximum) for women with imminent delivery at <34 weeks who do not otherwise quality for eclampsia prevention or treatment

For fetal neuroprotection

At <32 weeks, $MgSO_4$ decreased the risk of cerebral palsy (RR 0.68, 95% CI 0.52–0.91) or 'death or cerebral palsy' (RR 0.86, 95% CI 0.74–1.00) (3 trials, 3981 infants). As such, $MgSO_4$ is recommended for fetal neuroprotection in the setting of imminent preterm birth (i.e., within the next 24 hours) at gestational ages up to 31^{+6} weeks[56].

Women with pre-existing or gestational hypertension who are at risk of imminent preterm birth at up to 33^{+6} weeks would be candidates to

receive $MgSO_4$ for fetal neuroprotection. $MgSO_4$ for fetal neuroprotection (compared with no treatment) is cost-effective. $MgSO_4$ leads to better outcomes for the baby (56.684 vs. 56.678 quality-adjusted life years) and costs less (US$1739 vs. US$1917) when administered to women at high risk of preterm birth before 31^{+6} weeks owing to preterm labour or preterm premature rupture of membranes[135,136].

Therapies for HELLP syndrome

Platelet count may decrease rapidly in HELLP, mandating frequent serial measurement of platelet count within hours. After delivery, most women have a further decrease in their platelet count and/or rise in their liver enzymes until day 2 postpartum. By day 4 after delivery, some improvement in laboratory parameters should be apparent such that by day 6 (or within 3 days of the platelet nadir), the platelet count should be at least 100×10^9/L[137].

Transfusion

Blood and blood components (including coagulation factors) are listed on the WHO Model List of Essential Medicines (2015)[23]. WHO recognises that, ". . . self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements." The reality is very different in LMICs, as illustrated by the following quote:

> "Blood problem is the main problem, blood is not available in government hospitals, sometimes drug addicts or hepatitis patient blood is transfused"
>
> Male decision-maker, Pakistan, CLIP Feasibility Study 2012

Platelet transfusion (with/without other blood products) is indicated based on platelet count, mode of delivery, presence of active bleeding, and coagulopathy, as shown in Table 8.4. There is general agreement that perioperative, prophylactic transfusion of platelets is not necessary above a count of 50×10^9/L[138] in the absence of clinical bleeding or platelet dysfunction[139]. At platelet counts <10–20×10^9/L, prophylactic pre-delivery transfusion of platelets may be considered as the risk of profound haemorrhage is increased even with non-operative delivery[140]. Platelets must be

KEY POINTS

- The laboratory abnormalities of pre-eclampsia that describe HELLP syndrome may worsen for up to 5 days after delivery
- Platelet count is not a sensitive indicator of coagulopathy in pre-eclampsia
- Corticosteroids should be administered only if more rapid resolution of laboratory abnormalities will change management

Table 8.4 Recommendations about transfusion of platelets related to mode of delivery (and packed red blood cells, cryoprecipitate and fresh frozen plasma if necessary) in HELLP[8] (from SOGC 2014 guidelines, with permission)

	Mode of delivery	
Platelet count	*Caesarean delivery*	*Vaginal delivery*
<20×10^9/L	✔	✔
20–49×10^9/L	✔	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy
≥50×10^9/L	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy
Regardless of the platelet count	X No platelets should be transfused if there is a strong suspicion of HIT or TTP-HUS	

HIT, heparin-induced thrombocytopaenia; TTP-HUS, thrombotic thrombocytopaenic purpura – haemolytic uraemic syndrome

thawed prior to administration, and a standard unit of apheresis platelets can be expected to raise the platelet count by at least 5×10^9/L, with a peak at 10–60 minutes post-transfusion. Four units of platelets can contain as much as 2 mL of RBCs to which women who are anti-D(Rho)-negative may become sensitised. Therefore, women who are anti-D negative and receive a platelet transfusion should receive a 300 μg dose of anti-D immune globulin, a dose sufficient to prevent sensitisation following transfusion of up to 30 units of platelets[140].

Although a platelet count $<150 \times 10^9$/L is associated with a heightened risk of abnormal coagulation, platelet count is not a sensitive indicator of coagulopathy. Coagulation should be assessed independently of platelet count in pre-eclampsia prior to neuraxial analgesia/anaesthesia or surgery[141].

Corticosteroids

Dexamethasone is listed on the WHO Model List of Essential Medicines (2015) for maternal administration to benefit the neonate[23], based on evidence that the drug accelerates fetal pulmonary maturation when indicated at <34 weeks[142].

When given specifically for HELLP syndrome, corticosteroids (particularly dexamethasone) more rapidly improve platelet count and other haematological and biochemical indices of the HELLP syndrome (ALT, AST, LDH), especially when the treatment is initiated before delivery (11 trials, 550 women)[143]; however, no significant impact was seen on major maternal (death or severe morbidity) or perinatal (death or severe morbidity) outcomes, and transfusion requirements and rates of regional anaesthesia were not reported. In a small retrospective study of 37 women, regional anaesthesia was more often achieved (in 42% of women vs. 0%) when steroids were given to women with platelet counts $<90 \times 10^9$/L[144]. When dexamethasone for HELLP was incorporated into the local treatment protocol (along with $MgSO_4$ and antihypertensive therapy), one centre noted a reduction in severe maternal morbidity and a low rate of disease progression[145]. However, these data are not sufficient to guide practice. The COHELLP trial (NCT00711841) will determine whether postpartum dexamethasone decreases the key clinical outcome – severe maternal morbidity[146].

Other

HELLP syndrome must be differentiated from other 'imitators', as discussed in Chapter 3. Women with progressive HELLP syndrome, particularly postpartum, have been described in observational studies to improve with plasma therapies that are effective for thrombotic thrombocytopaenic purpura (TTP), a HELLP mimicker[147]. No randomised controlled trials were identified.

Thromboprophylaxis

Unfractionated heparin (sodium) is listed on the WHO Model List of Essential Medicines (2015)[23].

Thromboprophylaxis (with unfractionated or low molecular weight heparin) should be considered when thromboembolic risk is at least 1%. This risk level is reached antenatally, when pre-eclampsia is associated with two or more other risk markers, and postnatally, when either pre-eclampsia is associated with at least one other risk marker (e.g., obesity or maternal age >35 years) or women with any hypertensive disorder of pregnancy were on antenatal bedrest for at least 7 days (regardless of mode of delivery)[148,149]. Whether emergency Caesarean delivery warrants thromboprophylaxis in all women is not consistent between guidelines. It must be noted that guidelines are based largely on observational data. Although the influential Royal College of Obstetricians and Gynaecologists Guidelines[149] have been associated with a decline in thromboembolism-related maternal deaths in the UK, there are insufficient data from randomised controlled trials on which to base guideline recommendations[150].

Novel therapies for pre-eclampsia

Novel therapies for pre-eclampsia target various aspects of pre-eclampsia pathogenesis and are in development[151]. Most of these therapies ultimately target increased nitric oxide (NO) production and vasodilatation. There is insufficient information to evaluate their effects, and their use in clinical practice is not yet recommended.

Agents under active investigation and that show promise include pravastatin, L-arginine, S-nitrosoglutathione (GSNO), sildenafil, esomeprazole[152] and antithrombin.

Pravastatin is being evaluated in a randomised controlled trial for prevention of severe

complications in women with early 'severe' pre-eclampsia[153] (STaMP, EudraCT Number: 2009-012968-13). The rationale is that statins reduce antiangiogenic factors and increase NO production (Figure 8.1). With an ageing obstetric population, these medications will be used more frequently for cardiovascular disease prevention; although questioned as being teratogenic, particularly with regards to central nervous system and limb anomalies, a recent large retrospective cohort study failed to find that statins are teratogenic[154].

In multiple small randomised controlled trials, women with gestational hypertension or pre-eclampsia were administered L-arginine, a NO precursor, as it is an amino acid required for the body's production of NO. L-arginine is available as a powder, tablet, or intravenous infusion. L-arginine increased the time to delivery (mean difference 11.5 days, 95% CI 5.2–17.9; 2 trials, 135 women) and reduced blood pressure, diastolic (mean difference 4.9 mmHg, 95% CI 4.2–5.5; 4 trials, 204 women) more than systolic (mean difference 3.2 mmHg, 95% CI -1.5–7.9; 4 trials, 204 women) (7 trials in total, 916 women)[155].

S-nitrosoglutathione (GSNO) is a NO donor that causes vascular relaxation. When given to women with severe pre-eclampsia, GSNO improved blood pressure, platelet count and uterine artery Doppler resistance. This, in addition to the fact that it does not appear to induce tolerance, makes it an interesting drug for future study[151].

Sildenafil is a phosphodiesterase type-5 inihbitor that increases concentrations of cGMP, resulting in relaxation of vascular smooth muscle (Figure 8.1). It has been marketed extensively for treatment of erectile dysfunction in men. Sildenafil is currently being studied in four randomised controlled trials

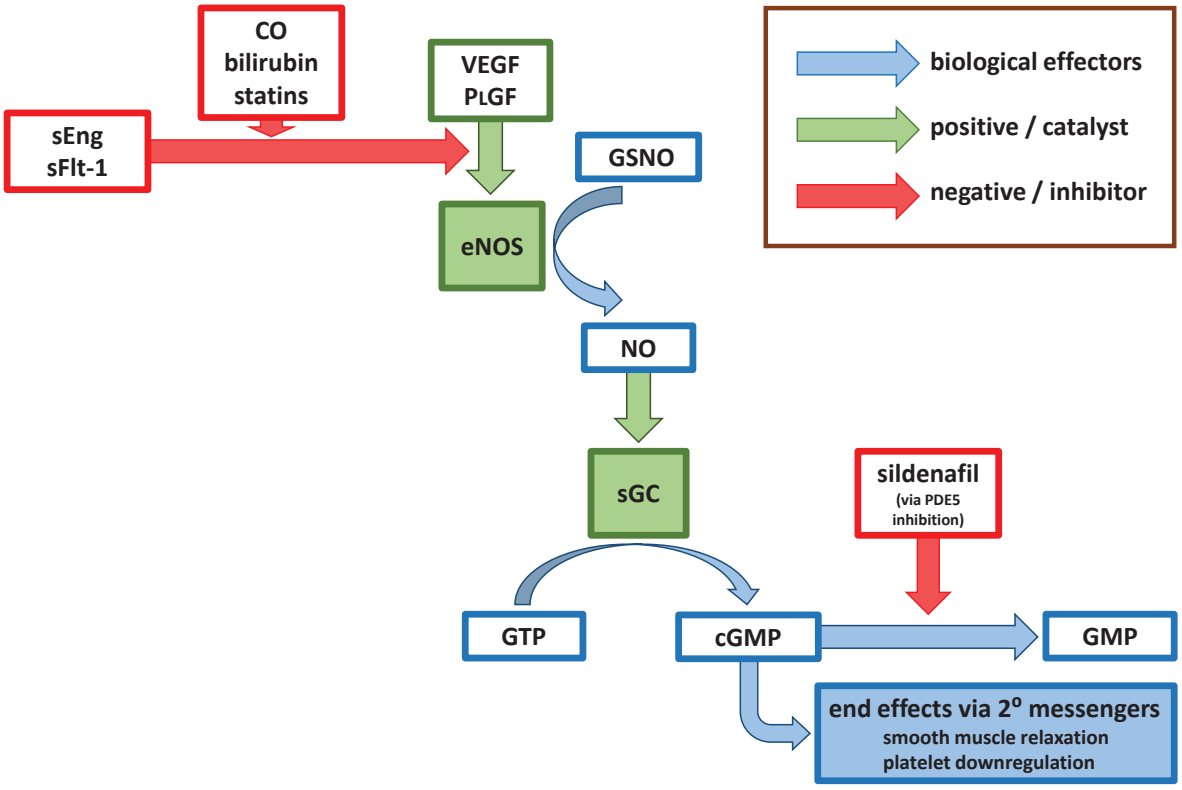

Figure 8.1 Overview of the mechanisms of action of various novel therapies for pre-eclampsia (modified from Everett *et al. J Matern Fetal Neonatal Med* 2012;25(1):50–52). 2°, secondary; cGMP, cyclic guanosine monophosphate; CO, carbon monoxide; GMP, guanosine monophosphate; GSNO, S-nitrosoglutathione; GTP, guanosine triphosphate; PDE5, phosphodiesterase-5; PlGF, placental growth factor; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase; sGC, soluble guanylyl cyclase; VEGF, vascular endothelial growth factor

for treatment of severe, early-onset IUGR[156]. The randomised controlled trial of sildenafil for pre-eclampsia did not improve maternal or perinatal outcomes, but the pre-eclampsia was of late-onset, the type less likely to have the abnormal placentation that sildenafil aims to target (see Chapter 3).

Esomeprazole is a proton pump inhibitor used to treat gastric reflux. Preclinical laboratory studies have demonstrated that esomeprazole decreases sFlt-1, soluble endoglin, and measures of oxidative stress[157].

Recombinant antithrombin (ATryn®) is being studied for the treatment of preterm pre-eclampsia at $<31^{+0}$ weeks[158].

Remote literature describes potentially beneficial effects of abdominal decompression, by application of intermittent negative pressure over the abdomen for 30 minutes, once to three times daily (3 trials, 367 women)[159]. Each trial was potentially biased, and only one enrolled women with pre-eclampsia or pre-existing hypertension. However, abdominal decompression was associated with beneficial effects: a reduction in pre-eclampsia or worsening pre-eclampsia (RR 0.36, 95% CI 0.18–0.72; 1 trial, 80 women), low birth weight babies (RR 0.50, 95% CI 0.40–0.63; 2 trials, 304 women), and perinatal mortality (RR 0.39, 95% CI 0.22–0.71; 3 trials, 367 women).

Sleep-disordered breathing has been linked with gestational hypertension. Treatment of that sleep-disordered breathing did not improve blood pressure, but the one relevant trial (24 women) treated women for only one night, so it is impossible to draw conclusions[160].

Also, immediate postpartum curettage, usually under ultrasound guidance, was associated with lower blood pressure, higher platelet count and higher urine output, but differences in harder clinical outcomes (such as hospitalisation or need for transfusion) were not demonstrated (3 trials, 497 women)[161–163]. Uterine perforation was not documented to have occurred.

Agents that have shown disappointing results in studies to date include Digibind and recombinant activated protein C.

Digibind (anti-digoxin antibody) was studied in a randomised controlled trial (NCT00158743) of postpartum women with severe pre-eclampsia. The rationale was that binding of endogenous digitalis-like factors would lead to vasodilatation. Deterioration in creatinine clearance was blunted in the Digibind group, but there was no difference in hard clinical outcomes, including blood pressure[164].

Activated protein C (APC) is a serine protease that was studied as a disease-modifying treatment for critically ill subjects. Despite its anti-inflammatory, antithrombotic and fibrinolytic properties, APC did not improve mortality in sepsis and it was withdrawn from the market. In a controlled series of nine women with antenatal, severe pre-eclampsia, APC increased urine output (consistent with initiation of disease resolution), but did not improve other clinical outcomes[165].

Evidence-based care in under-resourced settings

The hypertensive disorders of pregnancy rate among the four top causes of maternal mortality and morbidity worldwide, but more than 99% of hypertensive disorder of pregnancy-related maternal deaths occur in under-resourced settings, particularly sub-Saharan Africa and South Asia[166]. There, efforts to improve outcomes by promoting evidence-based care in facility have taken many approaches, including practice audit and development of practice guidance and tools[15]. Care in the community, including task-shifting to community health workers is complementing this approach. These approaches are discussed in detail below, but it should be noted that their application in well-resourced settings could improve care there as well.

Audit of practice and outcomes

Introducing quality of care indicators for pre-eclampsia/eclampsia appears to be acceptable to hospital-based practitioners (South Thailand)[167]. Practice audit according to those indicators can identify case management problems; however, the quality of the analysis, clarity of recommendations for improvement, and follow-up to confirm implementation of solutions are related to their effectiveness (Benin, West Africa)[168]. When done properly, criteria-based audit at university teaching hospitals has improved pregnancy outcomes, including maternal mortality (Tanzania)[169].

Whether high-quality practice audit works equally well at all levels of the health care system has been questioned. After a multifaceted intervention, adherence with practice indicators

increased, but variably, being substantially lower at district (for approximately 70% of indicators) than at referral hospitals (>90%) (South Thailand)[167]. Similar results were seen in a cluster randomised controlled trial (Senagal and Mali); the intervention of maternal death reviews combined with best practice implementation for emergency obstetric care, was supported by regular visits by trained facilitators. Hospital-based maternal mortality was decreased (OR 0.85, 95% CI 0.73–0.98), but only at first-level referral hospitals and not at regional referral hospitals[170].

Various audit data collection sheets have been published, although they have been designed to comply with either local guidelines[171] or national guidelines[43]. As such, they may be less applicable at other sites or in other countries, especially as many criteria are not based on high-quality evidence but rather, on what is achievable in that particular setting.

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. Formal programmes have been developed, such as the Essential Steps in Managing Obstetric Emergencies (ESMOE) – Emergency Obstetric Simulation Training (EOST) and then adapted for use in countries such as South Africa. This programme's drills for eclampsia and pre-eclampsia (N = 2) have been provided in Appendix 8.2.

Standardising care in facility

The lack of easy to use protocols and monitoring charts in the management of pre-eclampsia/eclampsia are felt to contribute to substandard care of women in resource-poor settings, particularly when care is provided by those with less experience. Even when the necessary drugs and supplies are available for high-quality pre-eclampsia/eclampsia management, there is a lack of provider knowledge and experience (Afghanistan)[172].

Although developing guidance is hampered by the lack of high-quality evidence in some areas of care, a variety of tools have been studied to improve evidence-based hypertensive disorder of pregnancy care, including monitoring and treatment guides and emergency medical kits, building on the popularity of the 'eclampsia box' in the Collaborative Eclampsia Trial. A tool that provided a visual record of monitoring and treatment, as well as treatment guidance of women with severe pre-eclampsia/eclampsia, was viewed as potentially useful in clinical care by the majority of skilled birth attendants surveyed and an implementation study has been planned (sub-Saharan Africa)[173]. Single-use obstetric emergency medical kits made available for in-hospital care were used frequently for care of women with pre-eclampsia/eclampsia (in 52/192 cases of kit use), and there was an associated (non-significant) 30% decrease in all-cause maternal mortality (Kenya)[174]. Lack of IV pumps for administration of $MgSO_4$ maintenance therapy was addressed by a single trial (300 women); women allocated to IV $MgSO_4$ using a mechanical, flow-controlled pump (Springfusor®) experienced less pain and fewer other side-effects than women allocated to IV and IM $MgSO_4$ loading with IM maintenance[175]. More than 90% of women in both groups completed their full course of therapy.

The NICE guidelines published detailed algorithms for care in well-resourced settings. These were based on the 2010 NICE guidelines, UK, but the algorithms could be adapted for local use[43].

Initiating treatment in the community

At the primary health centre level, fewer than half of centres initiated treatment for pre-eclampsia (40.0%) or eclampsia (28.0%) prior to transfer to facility (rural Nigeria)[176]. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome.

The nine manuals of the Perinatal Education Programme (PEP) in South Africa have been produced and distributed by the Perinatal Education Trust, a non-profit organisation that aims to improve outcomes for pregnant women and their babies, especially in poor, rural communities (pepcourse.co.za). PEP is self-help training for health professionals who are responsible for their own education. The course is cheap and does not require a teacher. Material is presented in a series of

manuals that learners can either download for free or purchase from suppliers of medical books. Learners usually study in groups of 5–10 to foster co-operative learning. The group studies the chapters independently, usually meeting every 2–3 weeks to allow for discussion of the units or demonstration of specific skills. Since the inception of PEP in 1988, approximately 50,000 manuals have been distributed and an estimated 80,000 health care providers have used PEP course work. Course evaluation takes the form of self-assessed multiple choice tests before and after each chapter, and a final multiple-choice examination by the Perinatal Education Trust for each manual. By 2014, over 20,000 PEP certificates had been awarded to more than 10,000 participants in South Africa.

The Community-Level Interventions for Pre-eclampsia (CLIP) Trial is a cluster randomised controlled trial that is evaluating a community-based package of triage, treatment and transport for women identified with hypertensive pregnancy (2013–2017) in four LMICs (India, Nigeria, Mozambique and Pakistan)[134] (pre-empt.cfri.ca). Community health workers are being instructed to administer oral methyldopa for severe hypertension and $MgSO_4$ IM for eclampsia prevention and treatment (Appendix 8.1).

BEST PRACTICE POINTS

(Please see Appendix 8.3 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

Fluid

1. Plasma volume expansion is not recommended for women with pre-eclampsia.
2. IV fluid intake should be minimised to 80 mL/h in women with pre-eclampsia to avoid pulmonary oedema.
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.
4. For treatment of persistent oliguria, neither dopamine nor furosemide is recommended.

Antihypertensive therapy for severe hypertension

1. Blood pressure should be lowered to <160 mmHg systolic and <110 mmHg diastolic.
2. Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting (capsules), parenteral hydralazine, or parenteral labetalol.
3. Alternative antihypertensive medications include oral methyldopa, oral labetalol, oral clonidine, oral captopril (only postpartum), or a nitroglycerin infusion (for doses, see Table 8.2).
4. Refractory hypertension may be treated with sodium nitroprusside.
5. Nifedipine and $MgSO_4$ can be used contemporaneously.
6. $MgSO_4$ is not recommended solely as an antihypertensive agent.
7. Continuous FHR monitoring is advised until blood pressure is stable.

Antihypertensive therapy for non-severe hypertension

1. Antihypertensive drug therapy should aim for a diastolic blood pressure of 85 mmHg.
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.

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).
4. ACE inhibitors and ARBs should not be used during pregnancy.
5. Atenolol and prazosin are not recommended prior to delivery.
6. Captopril, enalapril, or quinapril may be used postpartum, even during breastfeeding.
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.
8. Gestational hypertension and pre-eclampsia may each be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalising behaviours.

$MgSO_4$

1. $MgSO_4$ is recommended for first-line treatment of eclampsia.
2. $MgSO_4$ is recommended for eclampsia prevention in women with *severe* pre-eclampsia.
3. $MgSO_4$ may be considered for eclampsia prevention in women with *non-severe* pre-eclampsia based on cost considerations.
4. $MgSO_4$ should be used in standard dosing, usually 4 g IV loading dose followed by 1 g/h.
5. Routine monitoring of serum magnesium levels is not recommended.
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.
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.

Therapies for HELLP syndrome

Recommendations

1. Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units.
2. For a platelet count $<20 \times 10^9$/L, platelet transfusion is recommended, regardless of mode of delivery.
3. For a platelet count $20–49 \times 10^9$/L platelet transfusion is recommended prior to Caesarean delivery.
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).
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.
6. We do not recommend corticosteroids for treatment of HELLP until they have been proven to decrease maternal morbidity.
7. We recommend against plasma exchange or plasmapheresis for HELLP, particularly within the first 4 days postpartum.

Other therapies for treatment of pre-eclampsia

1. Women with pre-eclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity.
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 postnataly among women any hypertensive disorder of pregnancy who were on antenatal bed rest for at least 7 days.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Table 8.5 outlines priorities for care in the community (to prevent eclampsia and hypertension-related stroke prior to referral to facility[177]) and in facilities (to prevent and treat severe acute maternal morbidity and decrease maternal and perinatal mortality, particularly for the periviable fetus)[178–180].

All of the interventions relevant specifically to the hypertensive disorders of pregnancy and recognised by the WHO as essential medicines are included here: antihypertensive therapy for severe or non-severe hypertension, $MgSO_4$ for eclampsia prevention or treatment, blood products, and

Table 8.5 Priorities for management of women with a hypertensive disorder of pregnancy (HDP) by level of health care system at which care is delivered

	Antepartum & postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Antihypertensives for severe hypertension	Antihypertensives for severe or non-severe hypertension
	$MgSO_4$ administered before referral in order to prevent or treat eclampsia	$MgSO_4$ administered before referral in order to prevent or treat eclampsia
	Clear communication with referral unit regarding transport and medication	Clear communication with referral unit regarding transport and medication (including individualisation of antenatal corticosteroid therapy)
Facility		
Secondary-level facility (detect, manage and refer if necessary)	In women with a HDP, appropriate use of antihypertensive therapy, $MgSO_4$	In women with a HDP, appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted), and corticosteroids
	Appropriate triage of women for referral to tertiary-level care (including those eligible for expectant care* and those at high risk of or with severe maternal morbidity)	Appropriate triage of women for referral to tertiary-level care (including those eligible for expectant care and those with or at high risk of severe maternal morbidity)
	Availability of pRBCs	Availability of pRBCs, platelets, and clotting factors
Tertiary-level (referral) facility (detect and manage definitively)	Appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted) and corticosteroids in women with a HDP	Appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted), and corticosteroids in women with a HDP
	Appropriate triage and care of women eligible for expectant care* and those at high risk of or with severe maternal morbidity	Appropriate triage and care of women eligible for expectant care and those at high risk of or with severe maternal morbidity
	Availability of pRBCs, platelets, and clotting factors	Availability of pRBCs, platelets, and clotting factors
	Management of the periviable neonate	Management of the periviable fetus and neonate
		Advanced management options including the establishment of Obstetric Critical Care Units in close proximity to labour wards to provide advanced monitoring (e.g., intra-arterial BP measurement) and treatment (e.g., ventilatory support) of complicated cases

pRBCs, packed red blood cells; BP, blood pressure

* For a discussion about timing of delivery, see Chapter 9

antenatal corticosteroids for acceleration of fetal pulmonary maturity. Sample policy statements for antihypertensive therapy and $MgSO_4$ are provided for local adaptation (Appendix 8.4).

An initial focus should be on the early administration of antihypertensive agents and $MgSO_4$ in the community prior to transfer to facility, or in secondary-level facilities prior to transfer to tertiary-level facility. Reluctance to care for these women prior to their arrival at tertiary-level facilities is illustrated by the following quote:

> "Many doctors also don't like to treat eclampsia. If the lady has eclampsia, or imminent eclampsia or severe pre-eclampsia because of the risk with the morbidity and the mortality to both the baby and the mother they try to shift the patient to the higher centres"
>
> Obstetrician, CLIP Feasibility Study, Bagalkot, India

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 8.5)

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[181], AOM (Association of Ontario Midwives), NICE (National Institute for Health and Clinical Excellence)[43], NVOG (National Obstetrics and Gynaecology Society, The Netherlands)[182,] PRECOG II (Pre-eclampsia Community Guideline) and PRECOG II (Pre-eclampsia Community Guideline II), QLD (Queensland, Australia)[183,184], SOGC (Society of Obstetricians and Gynaecologists of Canada)[22], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[185], WHO (World Health Organization)[10].

Fluid management

Multiple guidelines recommend against plasma volume expansion (SOGC, NICE, SOMANZ). Fluid restriction in pre-eclampsia is recommended by two guidelines (SOGC, NICE), one of which recommends administration of no more than 80 mL/h of IV fluids (NICE).

Antihypertensive therapy

Seven guidelines discuss antihypertensive therapy (SOGC, WHO, NICE, ACOG, NVOG, SOMANZ, QLD).

For severe hypertension

There is uniform agreement in all seven guidelines that severe hypertension should be treated, although most guidelines do not rate the recommendation highly because of the lack of randomised controlled trials of antihypertensive versus placebo/no therapy (as discussed above under 'Antihypertensive therapy for severe hypertension'). Most guidelines recommend a blood pressure goal of <160/110 mmHg (SOGC, ACOG, QLD), but a goal of <150/80–100 mmHg is recommended in the UK (NICE), <160/100 mmHg in Australasia (SOMANZ), and ACOG makes a specific recommendation for women with chronic hypertension for whom blood pressure should be <160/105 mmHg. Recommended drugs of first choice are IV labetalol (SOGC, NICE, NVOG, SOMANZ), oral nifedipine (SOGC, NICE, NVOG, SOMANZ), and IV hydralazine (SOGC, NICE, SOMANZ); two CPGs leave the choice to the clinician (WHO, QLD). Two guidelines highlight that $MgSO_4$ should not be used as an antihypertensive (SOGC, SOMANZ).

For non-severe hypertension

Guidance for treatment of non-severe hypertension is reported by five guidelines and is highly variable, in part based on associated comorbidities and/or the type of hypertensive disease of pregnancy. All guidelines were published prior to release of the CHIPS Trial results (see 'Antihypertensive therapy for non-severe hypertension', above) which have clarified optimal management and will be incorporated into future updates. For women with end-organ dysfunction that can be exacerbated by elevated blood pressure, treatment to <140/90 mmHg is recommended (SOGC, NICE). For women without target-organ damage, treatment targets are: (1) for any hypertensive disorder of pregnancy, <150/80–100 mmHg (NICE), 130–159/80–105 mmHg (SOGC), 140–160/90–100 mmHg (SOMANZ), or <160/110 mmHg (NVOG); (2) for women with chronic hypertension, 120–159/80–104 mmHg (ACOG); and (3) for women with gestational hypertension or non-severe pre-eclampsia <160/110 mmHg (ACOG). Oral methyldopa (SOGC, NICE, ACOG, NVOG, SOMANZ), oral labetalol (SOGC, NICE, ACOG, NVOG, SOMANZ), and nifedipine (SOGC,

NICE, ACOG, NVOG, SOMANZ) are most commonly recommended.

ACE inhibitors and ARBs should not be used in pregnancy. For women with antihypertensive-treated chronic hypertension who are planning pregnancy, counselling should be undertaken (SOGC, NICE, NVOG, QLD). Alternatives to ACE inhibitors and ARBs should be discussed, and women should be instructed to stop ACE inhibitors and ARBs if inadvertently taken in early pregnancy (SOGC, NICE, ACOG, NVOG).

$MgSO_4$

There is general agreement that $MgSO_4$ is indicated for treatment of eclampsia (SOGC, WHO, NICE, ACOG, NVOG, QLD) and severe pre-eclampsia (SOGC, WHO, NICE, ACOG, NVOG), although ACOG recommends only intrapartum and postpartum treatment. There is less certainty about recommending $MgSO_4$ for non-severe pre-eclampsia (SOGC, ACOG, NVOG), although no guideline recommended *against* it. One guideline recommended that units define their own protocols for eclampsia prophylaxis (SOMANZ). $MgSO_4$ is otherwise indicated for fetal neuroprotection if women are delivering imminently at <34 weeks (SOGC, SOMANZ).

Therapies for HELLP

Corticosteroids are not recommended to improve clinical outcomes in HELLP syndrome (SOGC, WHO, NICE, ACOG, SOMANZ), but one guidelines suggests considering this therapy if an improvement in platelet count would be useful (ACOG).

One guideline discusses platelet thresholds for platelet transfusion (SOGC).

PRIORITIES FOR FUTURE RESEARCH

Significant progress has been and is being made to reduce the impact of pre-eclampsia in LMICs, but it remains a priority focus as we continue to struggle to achieve the 75% reduction in maternal mortality – the goal set in Millennium Development Goal 5 with a target date of 2015)[166].

Global priorities for hypertensive disorder of pregnancy management include: whether nifedipine is superior to parenteral agents for treatment of severe pregnancy hypertension; how to improve the cost-effectiveness of $MgSO_4$ for eclampsia prevention with regards to an abbreviated treatment course or reduced dose; and whether dexamethasone reduces severe maternal morbidity in HELLP syndrome without increasing maternal risk.

In general, hypertensive disorder of pregnancy management research has focused on institutional-level interventions. However, maternal lives lost from pre-eclampsia and eclampsia result from delays in triage, transport and treatment, such that if we limit ourselves to studying inpatient, facility-level interventions, many women will die or be irreversibly affected by pre-eclampsia complications prior to arriving at the inpatient facility. The future lies in getting diagnosis and care into the community, and improving transport to facility for definitive treatment.

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