11

Treatment postpartum – immediate and long term

T Firoz, J Sotunsa, OO Adetoro

SYNOPSIS

Hypertension may worsen transiently postpartum, especially between days 3 and 6 when blood pressure peaks. Hypertension and pre-eclampsia may even develop for the first time postpartum. Hypertension, proteinuria and the biochemical changes of pre-eclampsia begin to resolve by 6 weeks postpartum but may persist for longer, especially when those changes have been extreme. Care in the 6 weeks postpartum includes management of hypertension, ensuring resolution of biochemical changes, and screening for secondary causes of hypertension in women with resistant hypertension, impaired renal function, or abnormal urinalysis. Care providers should be aware of the mental health implications of the hypertensive disorders of pregnancy, such as anxiety, depression and post-traumatic stress disorder. The hypertensive disorders of pregnancy are also associated with a number of long-term complications and the postpartum period provides an ideal window of opportunity to address these risks, such as premature cardiovascular disease and chronic kidney disease. Women with a history of a hypertensive disorders of pregnancy should adopt a heart-healthy lifestyle and should be screened and treated for traditional cardiovascular risk factors according to locally accepted guidelines.

CARE IN THE FIRST 6 WEEKS AFTER BIRTH

Women and their maternity care providers may assume that, because delivery is the cure for pre-eclampsia, all aspects of the disease will improve postpartum. As such, it is important to manage expectations and prepare women for an alternative outcome.

Hypertension may antedate delivery in up to 50% of women with postpartum hypertension. Women with pre-existing hypertension who did not require antihypertensive medication antenatally may require such therapy after delivery[1]. Those at greatest risk of postpartum hypertension are those who delivered preterm and, for multiparous women, those with higher urate levels[2,3]. Postpartum deterioration of maternal end-organ function occurs in up to 25% of women with a hypertensive disorder of pregnancy; this deterioration usually occurs early in the puerperium, especially when women have had severe disease[4].

Hypertension that appears for the first time postpartum does so most commonly on days 3–6[5], when there is mobilisation of extracellular fluid and expansion of intravascular volume[2]. Postpartum hypertension may be isolated or associated with pre-eclampsia-related end-organ dysfunction. Two-thirds of women with postpartum pre-eclampsia have no antenatal hypertensive disorder of pregnancy and their postpartum

pre-eclampsia/eclampsia usually develops within days, but occasionally up to 3 weeks, after delivery[6].

Pre-eclampsia mimickers should be considered in women in whom pre-eclampsia worsens postpartum or in women who develop severe hypertension and HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome in the postpartum period (see Chapter 3, for further details). The differential diagnosis includes disorders such as thrombotic thrombocytopaenic purpura/haemolytic uraemic syndrome (TTP/HUS), systemic lupus erythematosus and exacerbation of pre-existing renal disease. They are important to recognise because they require individualised therapeutic interventions. Key issues to consider are the urinary sediment (which must be collected by urinary catheter because of lochia), the time course of the abnormalities relative to delivery, and manifestations that may point to disease processes other than pre-eclampsia, such as a skin rash of lupus.

Management of hypertension

At minimum, blood pressure should be measured during the time of peak postpartum blood pressure elevation (for all postnatal women), on days 3–6 after delivery so that the rise in blood pressure, which may be to severe levels, does not go undetected[5,7]. All severe hypertension should be treated, be it antenatally or postpartum[8].

There are no reliable data to guide whether antenatal antihypertensive therapy should be continued postpartum. The potential advantages of continuing antihypertensives postpartum would be to decrease the risk of non-severe or severe hypertension postpartum. However, postnatal antihypertensive therapy has not been shown to decrease the development of postnatal severe hypertension, shorten hospital stay, or result in any other beneficial or adverse effects in very small published, randomised controlled trials (3 trials, 313 women)[9]. Based on data outside pregnancy, blood pressure should be treated to <140/90 mmHg but possibly to <130/80 mmHg in women with *pre-gestational* diabetes mellitus[10]. Generally, antihypertensives are needed longer in women with pre-eclampsia (approximately 2 weeks) versus gestational hypertension (about 1 week)[11].

There is no clear best choice of antihypertensive agent[9]. Any antihypertensive agent used should be based on a clinician's familiarity with the drug. Antihypertensives used most commonly in pregnancy, as well as captopril and enalapril are 'usually acceptable' for breastfeeding[12,13]. The available studies have been small and evaluated maternal serum/plasma drug and/or active metabolite concentrations, the same levels in breast milk, and infant serum/plasma/urine levels; few case reports or series have described any clinical adverse effects in infants. However, any breastfed baby who is potentially exposed to drugs through breast milk should be observed for any behavioural (e.g., excessive crying) and/or physiological (e.g., diarrhoea) concerns. Caution may be exercised in preterm and low birth weight infants owing to immature drug clearance and/or increased susceptibility to drug effects. There is particular concern about the angiotensin converting enzyme (ACE) inhibitors, at least initially until the premature baby is stabilised, but the concerns expressed by neonatologists are largely theoretical[14].

Analgesia

Control of postpartum pain is discussed in Chapter 10.

Thromboprophylaxis

Guidelines vary in their recommendations about risk factors, the number of risk factors that should prompt thromboprophylaxis, and the duration of that thromboprophylaxis. Risk factors agreed upon by most guidelines include pre-eclampsia, advanced maternal age, obesity, prolonged antenatal bed rest, postpartum haemorrhage and emergency Caesarean delivery[15–17]. Pre-eclampsia is associated with an increased risk of venous thromboembolism (VTE) (adjusted odds ratio 2.9–3.1)[17]. The risk is further increased in women with pre-eclampsia and fetal growth restriction (adjusted odds ratio 5.8)[17]. The duration of thromboprophylaxis from delivery may vary from treatment until full mobilisation, to 4–6 weeks postpartum.

CARE BEYOND THE FIRST 6 WEEKS AFTER BIRTH

Work-up to rule out underlying disease

After gestational hypertension

Gestational hypertension usually resolves by 6 weeks postpartum[18]. If it persists, particularly beyond 6 months postpartum, the woman has 'pre-existing' or 'chronic' hypertension, either

essential or secondary to another aetiology. Further investigation is warranted at that time.

Hypertension that is difficult to control (such as with three agents) in particular should prompt evaluation for a secondary cause of hypertension.

After pre-eclampsia

The hypertension of severe pre-eclampsia may take up to 3–6 months to resolve[18]. As following gestational hypertension, hypertension that persists beyond 6 months after delivery indicates chronic hypertension and warrants consideration of secondary causes.

Screening for underlying causes of pre-eclampsia may better inform management of the woman's health after the current pregnancy, between pregnancies, and/or in subsequent pregnancies. These efforts are best undertaken at 3–6 months postpartum when pregnancy-related physiology can be relied upon to have resolved.

Screening for pre-existing hypertension and underlying renal disease should be undertaken if pre-eclampsia was: (1) of onset before 34 weeks or 'severe', or (2) was followed at 3–6 months postpartum by ongoing proteinuria, estimated glomerular filtration rate (eGFR) <60 mL/min, or abnormal urinary sediment. While it is essential to ensure resolution of target organ damage (e.g., proteinuria), routine measurement of microalbuminuria after pre-eclampsia resolution is not recommended without a specific renal indication. Appropriate specialist referral (e.g., internal medicine or nephrology) should be considered for women in whom blood pressure is difficult to control or a secondary cause (including renal disease) is suspected.

Special mention of thrombophilia screening is warranted. Thrombophilia confers, at most, a weakly increased risk of pre-eclampsia (and other placentally mediated pregnancy complications). Routine thrombophilia screening following pre-eclampsia is not recommended[20] because of this weak association and, also, because treatment with thromboprophylaxis has not been demonstrated to improve outcomes[21]; an individual patient data meta-analysis is being performed to examine whether there is a high-risk subgroup of women who may benefit from thromboprophylaxis and therefore, could be screened for thrombophilia[22]. Until such time, the one subgroup of women who may benefit from antiphospholipid antibody screening is pre-eclampsia with delivery at <34 weeks, as these women would meet criteria for the antiphospholipid antibody syndrome (APAS) and the diagnosis would influence future management outside pregnancy (e.g., choice of contraception) at minimum[23].

Future pregnancy planning

The recurrence risk of a hypertensive disorder of pregnancy depends in part on the disorder and its characteristics in the previous pregnancy and characteristics of the woman, particularly obesity. Recurrence is discussed in detail in Chapter 5. In brief, gestational hypertension is followed by a hypertensive disorder of pregnancy risk of about 25% in the subsequent pregnancy, and almost all is gestational hypertension (21%) rather than pre-eclampsia (4%). In contrast, pre-eclampsia is followed by a higher hypertensive disorder of pregnancy risk of 40%, with just over half as pre-eclampsia (22%) and the rest as gestational hypertension (15%); recurrence rates are higher (exceeding 50% in some reports) when pre-eclampsia was 'severe' or associated with HELLP syndrome specifically.

Implications for long-term paediatric health

The short-term implications for the fetus and newborn are discussed in Chapter 3. Discussed here is the fact that the hypertensive disorders of pregnancy may have long-term implications for the child beyond the complications of preterm delivery and/or fetal growth restriction. Although any potential impact on neurodevelopment is of keen interest to practitioners, there are other chronic diseases associated with the hypertensive disorders of pregnancy and/or preterm delivery of which the clinician should be aware.

Neurodevelopment

Pre-eclampsia superimposed on pre-existing hypertension (versus pre-existing hypertension alone) has no adverse effect on (or slightly better) intellectual development[24]. There is no literature available on the independent impact of antihypertensive therapy.

Gestational hypertension and pre-eclampsia may predict generally modest long-term effects on child development. Children of women with pre-eclampsia had better outcomes (i.e., *reduced*

internalising morbidity such as anxiety) at ages 5 and 8 years, but children of women with gestational hypertension were more likely to have poorer behaviour from 8 years onwards, with the largest difference seen at 14 years; no information was provided on the potential impact of antihypertensive therapy[25]. Both types of hypertensive disorders of pregnancy were associated with a small reduction in verbal ability of uncertain clinical significance[26]. The neurodevelopmental effects of pre-eclampsia persisted even when matched or adjusted for gestational age and growth restriction[27]. Although placental abruption is an additional risk factor for adverse neurodevelopmental outcomes, it has not been studied in conjunction with pre-eclampsia[28].

It should be noted that not all studies provide a consistent picture of the association between the hypertensive disorders of pregnancy and paediatric cognitive function. The mixed pattern of results likely arises from methodological differences, particularly varying study populations and study designs[27]. The lack of much information on antihypertensive therapy is a major drawback to this literature. There are a handful of small randomised controlled trials that have examined paediatric neurodevelopment. Babies of antihypertensive (mainly methyldopa)-treated mothers (versus normotensive controls) more often had delayed fine-motor function at 6 months of age, while those of placebo-treated hypertensive mothers more frequently had 'questionable' neurological assessment and delayed gross-motor function at 12 months[29]. In other small randomised controlled trials, antihypertensive therapy was not associated with negative effects on child development when assessed at 1 year, 18 months, or 7.5 years (methyldopa, 242 children)[30], 18 months (atenolol, 190 children)[31], or 7.5 years (nifedipine, 110 children)[32]. In contrast, in an observational controlled study, methyldopa (25 exposed children) (but not labetalol, 32 exposed children) was associated with lower intelligence quotient (IQ) scores, but in multivariable regression, IQ was associated with maternal IQ and duration of antihypertensive treatment[33].

Other long-term outcomes

Higher blood pressure A systematic review and meta-analysis found that children exposed to pre-eclampsia had higher systolic and diastolic blood pressure values during childhood and young adulthood when compared with controls[34,35]. The degree of elevated blood pressure is related to preterm birth and higher body mass index (BMI) of the children[34,35]. The blood pressure effects were present at age 21 years[36].

Stroke In the Helsinki birth cohort (6410 pregnancies), pre-eclampsia was associated with an increased risk of stroke in the adult offspring[37].

Pregnancy complications of their own In a population-based cohort study (24,119 women), hypertensive disorders of pregnancy and gestational diabetes mellitus (GDM) were increased in women who were themselves born preterm, especially before 32 weeks[38]. Although this was a study of preterm birth in general, the hypertensive disorders of pregnancy were found to be an important cause of iatrogenic preterm birth.

Implications for long-term maternal health

Pregnancy is considered a biological 'stress test' that can predict a woman's health in later life[39]. The hypertensive disorders of pregnancy, particularly pre-eclampsia, are associated with a number of future health risks. Identifying women at risk by virtue of the physiologic stress test of a pregnancy complicated by pre-eclampsia is a unique opportunity to address and prevent chronic illnesses.

Cardiovascular risk factors and disease

The American Heart Association has recognised pre-eclampsia and gestational hypertension as 'major' cardiovascular risk factors for women[40–42]. Pre-eclampsia has a pathophysiology remarkably similar to cardiovascular disease, in terms of metabolic abnormalities (such as hyperlipidaemia and insulin resistance), a heightened inflammatory response, a hypercoagulable state and endothelial dysfunction[43].

It is likely that some women are predisposed to pre-eclampsia because of an adverse pre-pregnancy cardiovascular risk profile, which lowers the threshold for a hypertensive response to placentally derived products[44]. The alternative hypothesis is that pre-eclampsia itself damages a woman's endothelium and produces permanent metabolic sequelae, leading to increased long-term cardiovascular risk[39,43].

A large prospective study examined the cardiovascular risk profiles of women who developed a hypertensive disorder of pregnancy and found that women with gestational hypertension and pre-eclampsia, compared with women who had a normotensive pregnancy, had higher BMI, lower levels of high density lipoprotein (HDL), and higher levels of triglycerides, low density lipoprotein (LDL) and total cholesterol[45].

A small case–control study conducted at 1 year postpartum showed asymptomatic left ventricular moderate–severe dysfunction/hypertrophy was significantly higher in women who had suffered from preterm pre-eclampsia (56%) compared with term pre-eclampsia (14%) or matched controls (8%; $p<0.001$)[46]. This suggests that pre-eclampsia is associated with persistent postpartum cardiovascular impairment.

Three large systematic reviews have consistently demonstrated that women with a history of pre-eclampsia have a higher risk of cardiovascular and cerebrovascular disease[47–49] (Table 11.1). The 2007 systematic review by Bellamy *et al.* included 25 studies, and approximately 3 million women of whom 25,000 had pre-eclampsia[47]. McDonald *et al.* in their 2008 review included 15 studies and a total of 118,990 women with a history of pre-eclampsia/eclampsia and 2,259,576 women with unaffected pregnancies[49]. A recent review by Brown *et al.* in 2013 included 50 papers but did not state the number of women included[48]. While there are methodological differences, the results have been generally similar amongst the reviews.

KEY POINT

Pre-eclampsia is associated with a number of long-term health complications including hypertension, heart disease, stroke, renal disease and diabetes

Hypertension

Bellamy *et al.* found that pre-eclampsia was associated with development of hypertension later in life, after a mean follow-up of 14 years with a relative risk of 3.7 (95% CI 2.70–5.05)[47]. For women with gestational hypertension, the risk of developing subsequent hypertension was similar to women with a risk of hypertension (RR 3.39, 95% CI 0.82–13.92) at a mean of 11 years postpartum[47]. Brown *et al.* had similar results with a relative risk of 3.13 (95% CI 2.51–3.89) for women with a history of pre-eclampsia/eclampsia[48].

Ischaemic heart disease

In the systematic review of Bellamy *et al.*, the relative risk of fatal or non-fatal ischaemic heart disease in women with pre-eclampsia was over twice that of women without pre-eclampsia (RR 2.16, 95% CI 1.86–5.20)[47]. The risk of ischaemic heart disease also occurred earlier at a mean of 11.7 years after the index pregnancy. In McDonald *et al.*'s review, women with a history of pre-eclampsia/eclampsia had an increased risk of subsequent cardiac disease, in both case–control studies (odds ratio 2.47, 95% CI 1.22–5.01) and cohort studies (RR 2.33, 95% CI 1.95–2.78)[49]. Brown *et al.* found that women who experienced pre-eclampsia were at more than two fold increased odds of cardiovascular disease (OR 2.28, 95% CI 1.87–2.77) with similar results between the cohort and control studies[48].

Bellamy *et al.* found that women with severe pre-eclampsia had a greater risk of developing later ischaemic heart disease (RR 2.86, 95% CI

Table 11.1 Risk of cardiovascular disease after pre-eclampsia (95% CI presented in parentheses)

	Bellamy[47] (2007)	*McDonald[49] (2008)*	*Brown[48] (2013)*
Hypertension	Pre-eclampsia: RR 3.7 (2.70–5.05) Gestational hypertension: RR 3.39 (0.82–13.92)	Not analysed	RR 3.13 (2.51–3.89)
Ischaemic heart disease	RR 2.16 (1.86–5.20)	OR 2.47 (1.22–5.01)* RR 2.33 (1.95–2.78)†	OR 2.28 (1.87–2.77)
Stroke	RR 1.81 (1.45–2.27)	OR 2.6 (1.5–4.3)* RR 2.03 (1.54–2.67)†	OR 1.77 (1.43–2.21)

* Case–control studies; †cohort studies

1.65–2.24) compared to women who had mild pre-elampsia (RR 1.92, 95% CI 1.65–2.24) particularly if pre-eclampsia occurred before 37 weeks (RR 7.71, 95% CI 4.40–13.52)[47]. This 'dose response' effect was not, however, demonstrated in the review by Brown. The review by Brown compared outcomes for pre-eclampsia both with and without preterm birth using three studies whilst the data from Bellamy came from only one study[48].

The risk of cardiovascular disease may be further increased in the presence of poor fetal outcomes. In a population-based retrospective cohort study of women with maternal placental syndrome (defined as pre-eclampsia, gestational hypertension, placental abruption, and/or placental infarction), the risk of premature cardiovascular disease was higher in the presence of poor fetal growth (adjusted hazard ratio (aHR) 3.1, 95% CI 2.2–4.5) or intrauterine fetal death (aHR 4.4, 95% CI 2.4–7.9)[50]. A Canadian population-based retrospective cohort study of 1985 women found that in middle-aged women (mean age 45 years) who underwent coronary revascularisation, prior maternal placental syndrome (such as pre-eclampsia) doubled the risk of death (aHR 1.61, 95% CI 1.00–2.58)[51].

Stroke

Bellamy's review found that the overall risk of fatal and non-fatal cerebrovascular disease (stroke or non-fatal stroke) after pre-eclampsia was 1.81 (95% CI 1.45–2.27) compared with women who had not developed pre-eclampsia. Subgroup analysis showed that the risk of fatal stroke (RR 2.98, 95% CI 1.11–7.96) was greater than that of non-fatal stroke (RR 1.76, 95% CI 1.40–2.2) after pre-eclampsia[47]. A diagnosis of pre-eclampsia before 37 weeks was associated with a further elevation in risk (RR 5.08, 95% CI 2.09–12.35) compared with pre-eclampsia after 37 weeks (RR 0.98, 95% CI 0.50–1.92). McDonald included only one eligible case–control study which reported an increased risk of 2.6 (95% CI 1.5–4.3) consistent with the pooled estimate in the six cohort studies (RR 2.03, 95% CI 1.54–2.67)[49].

Renal disease

Pre-eclampsia has been associated with an increased risk of end-stage kidney disease in large observational studies.

A large retrospective cohort study from Norway (20,918 women with pre-eclampsia) found that pre-eclampsia in the first pregnancy was associated with a relative risk of end-stage kidney disease of 4.7 (95% CI 3.6–6.1). This risk increased further to 6.7 (95% CI 4.3–10.6) among women who also had pre-eclampsia only in their second pregnancy, and increased again if women had pre-eclampsia in both their first and second pregnancies or in three pregnancies (RR 15.5, 95% CI 7.8–30.8)[52].

In a population-based study from Taiwan (8653 women with gestational hypertension, 17,998 women with pre-eclampsia), having had either gestational hypertension or pre-eclampsia was associated with a greater risk of chronic kidney disease (aHR 9.4, 95% CI 7.1–12.4) and end-stage renal disease (aHR 12.4, 95% CI 8.5–18.0), even after controlling for several factors including coronary artery disease, congestive heart failure, hyperlipidaemia and abruption[53]. The greatest risk of end-stage renal disease was associated with having had pre-eclampsia or eclampsia (aHR 14.0, 95% CI 9.4–20.7) compared with gestational hypertension (aHR 9.0, 95% CI 5.2–15.7)[53].

Other chronic diseases

Diabetes In a population-based study (50,598 women with a hypertensive disorder of pregnancy), women with a prior hypertensive disorder of pregnancy had a two-fold increased risk of developing diabetes when followed up to 16.5 years after pregnancy, even in the absence of a prior history of gestational diabetes[54]. A history of a hypertensive disorder of pregnancy and gestational diabetes together increased the risk associated with GDM alone[54].

Elevated thyroid stimulating hormone (TSH) In a nested case–control study of women with pre-eclampsia from two large cohort studies (Calcium for Pre-eclampsia Prevention trial[55] and the Nord-Trondelag Health Study[56]), women with prior pre-eclampsia had higher thyroid stimulating hormone (TSH) levels compared with controls who had no history of a hypertensive disorder of pregnancy[57]. Of note, women with prior pre-eclampsia were less likely to have thyroid peroxidase antibodies, suggesting that their hypothyroidism was occurring in the absence of an autoimmune process. The association between

pre-eclampsia and elevated TSH was especially strong (adjusted OR 5.8, 95% CI 1.3–25.5) if pre-eclampsia had occurred in both the first and the second pregnancies[57].

Central nervous system white-matter lesions Several studies have shown that women whose pregnancies were complicated by pre-eclampsia or eclampsia are more likely than controls to have white matter lesions; although these may reflect a predisposition to vascular disease, the significance of these lesions is currently unknown[58,59].

Mental health Pre-eclampsia can be very stressful for women and their partners[60], especially relative to expectations of a routine, normal pregnancy and no prior significant illness[60]. Women may have to deal with postpartum recovery from hypertension, end-organ complications, and frequently, Caesarean delivery. In addition, women may have to deal with perinatal loss or illness, such as care in the neonatal intensive care unit (NICU).

A systematic review showed that while the evidence is not entirely consistent, in general, there is an association with prior pre-eclampsia or HELLP syndrome and more anxiety, depression and post-traumatic stress disorder (6 studies, 5636 women)[61]. Women who experienced severe maternal morbidity were shown to be at particular risk of post-traumatic stress disorder (1824 women)[62]. Women with severe pre-eclampisa who must deal with a perinatal death or NICU admission are at particular risk of poor health-related (especially mental health-related) quality of life[63]. These effects of pre-eclampsia on mental health may persist beyond the short term; women with preterm birth owing to severe, early-onset pre-eclampsia (compared with women with preterm birth for other reasons) more often experienced post-traumatic stress symptoms an average of 7 years postpartum[64].

Postpartum care of women with pre-eclampsia should include evaluation and referral for postpartum psychological care. It is important for women to receive relevant information about not only their medical condition, but their psychological condition as well. It is also necessary to examine coping strategies after pre-eclampsia and offer adequate supportive interventions when they are needed[60].

Investigations and interventions to improve long-term health

Pregnancy and the immediate postpartum period may be one of the few times in a woman's life when she accesses the health care system regularly. Therefore, the postpartum period provides a unique window of opportunity for early identification and reduction of primary cardiovascular risk.

Education/awareness

Among women A small study using focus groups found that women with prior pre-eclampsia were unaware of the link between pre-eclampsia and future cardiovascular disease, but were eager to learn about the link and motivated to achieve a healthy lifestyle[65]. Another study found that women generally had a low level of cardiovascular risk factor knowledge[66].

Although some guidelines, such as those from NICE (UK), recommend that future cardiovascular risk should be communicated to the woman before discharge from maternal services, some argue that it may be too early for most women[67,68]. Women may be recovering from serious morbidity whilst balancing the demands of the neonate; this may limit the efficacy of the communication. Women's reactions to learning about the link between pre-eclampsia and future cardiovascular disease included both positive feelings (i.e., motivation, empowerment) and negative ones (i.e., being scared, angry, guilty, or isolated)[65]. Therefore, it is important that women are followed on an ongoing basis and receive information about cardiovascular health over time.

Recently, an educational intervention to promote cardiovascular knowledge and awareness was tested amongst women with a history of pre-eclampsia. The intervention, delivered by telephone given that postpartum women have many demands on their time, had several components: diet, exercise, medication compliance, screening for risk factors and symptoms of myocardial infarction. It was found to be a practical and effective method of contacting postpartum women following pre-eclampsia and increasing perception of cardiovascular risk[66].

Among health care providers There is also a lack of awareness amongst health care providers and gaps in identification and routine follow-up.

Though the American Heart Association recommends that health professionals disclose the future risk of cardiovascular disease to women with a history of pre-eclampsia, a study revealed that only a third of health professionals provide that counselling[69]. A review of the existing literature on engaging obstetricians and gynaecologists in cardiovascular risk reduction found that while they agreed that their role extended beyond reproductive care, there was variation in practice and they were unlikely to manage hypertension or elevated cholesterol. Obstetricians and gynaecologists identified knowledge and skill deficits, concerns about liability, and barriers to prevention presented by their practice structure. Some providers also emphasised difficulties completing referrals to primary care providers[70]. A Canadian survey of maternity care providers found that only 54% of participants were familiar with the long-term cardiovascular risks of pre-eclampsia[71]. A small retrospective review from The Netherlands examined cardiovascular risk factor management and found that only 50% of women with pre-eclampsia had their blood pressure measured by 3 months postpartum. Blood glucose and lipids were infrequently checked even though some of the women had cardiovascular risk factors prior to the index pregnancy[72]. Appendix 11.1 contains training materials for health care providers including multiple choice questions and a case study. Knowledge translation tools for health care providers are included in Appendix 11.2.

Cardiovascular risk factor screening

At present, there are no guidelines advising when to screen women with a prior hypertensive disorder of pregnancy or pre-eclampsia for cardiovascular risk factors. (Cardiovascular risk factor screening in women with pre-existing or chronic hypertension has been published by all national societies.) The very earliest would be at 3–6 months postpartum when the metabolic changes of pregnancy (such as dyslipidaemia) have resolved.

Traditional cardiovascular markers appear to be more abnormal in women who have suffered from pre-eclampsia, as early as 1 year postpartum[73]. A small study from the Maternal Health Clinic, a postpartum cardiovascular risk reduction clinic in Kingston, Canada, sought to determine whether women with a history of pre-eclampsia (N = 99) compared with those without pre-eclampsia (N = 118) had 10-year, 30-year and lifetime cardiovascular risk estimates that were high enough at 1 year postpartum to identify them as warranting further counselling and follow-up regarding lifestyle modification and/or pharmacotherapy[74]. Using traditional cardiovascular risk markers (i.e., sex, age, smoking, serum total cholesterol, serum LDL cholesterol, serum HDL cholesterol, fasting plasma glucose, systolic blood pressure, diastolic blood pressure and antihypertensive use), the study found that women who had suffered from pre-eclampsia (versus those who had not) more often had elevated 10-year cardiovascular risk (i.e., 18.2% vs. 1.7%, respectively; OR 13.1, 95% CI 3.4–85.5), 30-year cardiovascular risk (i.e., 31.3% vs. 5.1%, respectively, OR 8.4, 95% CI 3.5–23.2), and lifetime cardiovascular risk (i.e., 41.4% vs. 17.8%, respectively; OR 3.3, 95% CI 1.8–6.1)[74]. A follow-up study showed that the Maternal Health Clinic could identify a population of postpartum patients with increased 10- and 30-year cardiovascular risk[75].

KEY POINT

Following pre-eclampsia, it would seem prudent to screen women for traditional cardiovascular risk markers according to national guidelines which should also dictate intervention for abnormal results

It remains unclear whether traditional risk factors, such as those used in the Maternal Health Clinic, are sufficient for cardiovascular risk screening. First, global risk assessment tools like the Framingham Risk Score may not accurately estimate cardiovascular risk in young women, especially in the short term; a study of 2333 women using the Framingham Offspring cohort showed that the 10-year model estimates negligible risks for young women, whereas the 30-year model suggests a risk that is 10 times higher[76]. Second, cardiovascular risk factors used in prediction models like the Framingham or Reynolds Risk Score may not fully explain the risk of cardiovascular disease after pre-eclampsia; in a literature based study that included 16 studies, a major part of the observed OR of cardiovascular disease after pre-eclampsia remained after adjustment for these traditional cardiovascular risk factors[77].

In summary, it remains unclear both *when* cardiovascular risk screening should take place

following pre-eclampsia, and at *what threshold* treatment should begin. There are public health implications and costs to consider. Although it may be appropriate to intervene at earlier stages in this population, we should await supportive research findings. In the meantime, it would seem prudent to screen women who have had pre-eclampsia for traditional cardiovascular risk markers according to national guidelines which should also dictate intervention for abnormal results.

A simple approach that has been proposed in this population of women is the identification of any of the components of metabolic syndrome as the syndrome does not predict clinical outcomes better than its individual components[78]. These components include:

- Blood pressure
- Weight and height are measured to calculate the BMI
- Lipid panel
- Glucose intolerance screening.

All women with gestational diabetes should undergo postpartum glucose tolerance testing. In addition, some recommend that postpartum testing for glucose intolerance should be ordered for all women with one of the other components of metabolic syndrome, such as obesity[78]. Abnormalities in any of the above components should be treated as per current national guidelines or prompt referral to an internal medicine specialist.

Lifestyle change

What is appropriate and evidence-based for all is adoption of a heart-healthy diet and lifestyle to decrease cardiovascular risk (Table 11.2)[40]. Of course, neither is an easy intervention and there are barriers to change that are specific to postpartum women.

Women may be motivated by the knowledge that weight *gain* between pregnancies predicts pre-eclampsia and other pregnancy complications (e.g., gestational diabetes and Caesarean delivery)[80,81], and weight *loss* between pregnancies may improve future pregnancy outcome in addition to long-term cardiovascular risk. However, there are many competing demands on a new mother's time.

Major perceived barriers to lifestyle change identified in a qualitative (American) study of 20 postpartum women were lack of time, cost of healthy foods and family responsibilities[65]. Another (Dutch) study of 36 women identified additional barriers of poor postpartum physical and psychological recovery, and lack of postpartum medical and psychological support from health care providers[82]. Perceived facilitators have included knowledge of the link between pre-eclampsia and cardiovascular disease, a desire to stay healthy, and creating a healthy home for their children[65]. This link to child health may be a key motivator of change.

Currently, postpartum lifestyle interventions tailored specifically for women following a hypertensive disorder of pregnancy are lacking, although those demonstrated to be effective outside

Table 11.2 Dietary and lifestyle modifications recommended for all women[40] (with permission from Society of Obstetricians and Gynaecologists of Canada)

Intervention	*Details*
Heart-healthy diet	Maintain a healthy balanced diet (high in fruits, vegetables, low-fat dairy products, reduced in saturated fat and cholesterol) in addition to dietary and soluble fibre, whole grains and protein from plant sources[79]
Regular physical activity	Undertake 150 minutes/week of moderate to vigorous-intensity aerobic physical activity (such as walking, jogging, cycling or swimming)
Alcohol consumption	Reduce alcohol consumption to <2 drinks/day and <9/week
Weight reduction	Attain and maintain ideal body weight (i.e., BMI 18.5–24.9 kg/m^2)
Reduce waist circumference	Attain and maintain a waist circumference of <88 cm
Salt intake	Reduce intake to <1500 mg/d
Smoking cessation	Quit smoking in addition to ensuring a smoke-free environment

BMI, body mass index

pregnancy have been tested in unselected postpartum populations[83]. Among postpartum women in general (21 studies, 6288 women), most weight loss interventions (6 of 8) were effective, as were most smoking cessation interventions (4 of 5). Also effective were individualised tailoring of counselling, group counselling sessions, and use of diaries or other correspondence material. Of note, the Maternal Health Clinic (Kingston, ON) has designed 'The Postpartum Mother's Health Record', a card that allows women to set goals and track weight loss[84]. The timing of data collection coincides with the infant's scheduled visits and immunisations, linking maternal and child health going forward – a practical and potentially more feasible approach for the new mother. Appendix 11.2 highlights knowledge translation tools for women including mobile apps, programmes and research studies.

Focus groups with women with prior pre-eclampsia indicated potential interest in a web-based programme focused on lifestyle strategies to decrease cardiovascular risk[65]. This approach was tested in a small feasibility study (20 women) of a web-based, tailored health education intervention related to diet and exercise, in conjunction with counselling by a psychologist (Dutch ProActive study, Postpartum Rotterdam Appraisal of Cardiovascular Health and Tailored Intervention)[85]. The intervention was initiated at 6 months postpartum and continued for 3 months. In all 60% of women participated and anthropometric measurements at 13 months postpartum improved significantly, although metabolic parameters did not[85].

Bariatric surgery for women with morbid obesity

Women who are morbidly obese and have failed lifestyle interventions to achieve weight loss are candidates for bariatric surgery without considering potential effects on future pregnancy, which are mixed. There are no randomised controlled trials for women planning pregnancy, but in a retrospective cohort study of insurance claims data (585 women)[86] and two controlled registry studies (identifying 1085 women with prior bariatric surgery)[87,88], women who had undergone bariatric surgery (vs. those who had not) experienced lower rates of all hypertensive disorders of pregnancy (including pre-eclampsia)[86], gestational diabetes and large-for-gestational infants[87], as well as fewer emergency Caesarean deliveries[88] following adjustment for confounders. However, these benefits have not been consistently demonstrated, with one registry study demonstrating *higher* rates of hypertension and gestational diabetes following bariatric surgery[88]. In addition, potential benefits appear to come at the price of more gastrointestinal problems[88,89], lower birth weight[88], more small-for-gestational age (SGA) infants[87], earlier delivery[87] and, possibly, higher perinatal mortality[87,88] and admission to NICU[88]. Therefore, at present, there are insufficient data to support recommendations to undergo bariatric surgery to favourably affect future pregnancy outcomes.

BEST PRACTICE POINTS

(Please see Appendix 11.3 for the evaluation of the strength of the recommendations and the quality of the evidence on which they are based.)

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.
2. Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising *de novo* or worsening from the antenatal period).
3. Antihypertensive therapy may be continued postpartum, particularly in women with antenatal pre-eclampsia and those who delivered preterm.
4. Severe postpartum hypertension must be treated with antihypertensive therapy, to keep systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.
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.

6. Antihypertensive agents acceptable for use in breastfeeding include nifedipine XL, labetalol, methyldopa, captopril and enalapril.
7. There should be confirmation that end-organ dysfunction of pre-eclampsia has resolved.
8. Non-steroidal anti-inflammatory druds (NSAIDs) 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.
9. Postpartum thromboprophylaxis should be considered in women with pre-eclampsia who have other risk factors for thromboembolism.

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.
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).
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.
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.
5. Women who are normotensive but who have had a hypertensive disorder of pregnancy, may benefit from assessment of traditional cardiovascular risk markers.
6. All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

The priorities for postpartum care of women with hypertensive disorders of pregnancy in under-resourced settings are outlined in Table 11.3. A sample policy brief that focuses on postnatal care is contained in Appendix 11.4.

In LMICs, routine postnatal care has the potential to improve both maternal and neonatal outcomes. In LMICs, almost 40% of women experience complications after delivery and an estimated 15% develop potentially life-threatening problems[90]. More than half of maternal deaths occur postpartum and the vast majority (i.e., 80%) of those occur in the first week postpartum[91]. Such visits are most likely to detect early complications that may be addressed by referral for specialist care.

Also, postnatal care has the potential to identify neonatal sepsis and asphyxia/hypothermia, the leading causes of neonatal death in LMICs. Finally, postnatal care helps to promote healthy maternal behaviours, such as exclusive breastfeeding and proper care of babies with low birth weight.

> "By the 6th week the child is due for pentavalent. That is . . . the diphtheria, tetanus and all . . . at that 6 week [mark]. That is the time (when) the lady is also due for the 6 week postnatal review. But many a time the postnatal review is not done . . . because of lack of manpower at the PHC. You have a lot of children and . . . so sometimes to attend to mother, and educate and counsel takes time."
>
> Stakeholder, Local Government in Ogun, Nigeria

Postnatal care is reported at much lower rates than for other maternal and infant health services[92]. In a review of Demographic and Health Survey (DHS) data from 1990 to 2009 in 38 countries in four regions (i.e., sub-Saharan Africa; North Africa/West Asia/Europe; South/Southeast Asia; and Latin America and the Caribbean), approximately half of the countries with data (i.e., 8 of 18) provided at least one demonstrated postnatal visit to more than half (64–92%) of postpartum women within 41 days after giving birth[93]. Even within those countries, postnatal visits varied from 64% to

Table 11.3 Priorities for postpartum care in under-resourced settings

	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	A health care visit within 24 hours after the birth	A health care visit within 24 hours after the birth and then again at least three more times – on day 3, in the second week, and again at 6 weeks
	BP measurement shortly after birth and at 6 hours	BP measurement shortly after birth and at 6 hours
	Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit	Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit
Facility		
Secondary-level facility (detect, manage and refer if necessary) Tertiary-level (referral) facility (detect and manage definitively)	Delivery in facility of all women with a HDP	Delivery in facility of all women with a HDP
	Management of women with HDPs, including postpartum pre-eclampsia (see Table 4.4, Chapter 4)	Management of women with HDPs, including postpartum pre-eclampsia (see Table 4.4, Chapter 4)
		Counselling about BP monitoring as well as heart-healthy diet and lifestyle following a HDP

BP, blood pressure; HDP, hypertensive disorder of pregnancy

92% of relevant women. Although there was a strong relationship between receiving postnatal care and both more antenatal visits and having skilled birth attendance, the major determinant of postnatal care was delivery in facility. (A recent systematic review found that inequities in the use of postnatal services is also based on socioeconomic status, education, ethnicity and geographical location[94].) Following delivery in facility, at least two-thirds of women reported postnatal care in all countries except Uganda and Zimbabwe where less than half of the women reported postnatal checkups. Women who delivered in a health facility (compared with those who did not) were more likely to report postnatal visits, to have the first visit within 2 days after birth, and to receive postnatal care from a doctor, nurse, or midwife. Among women who did not deliver at a health facility, postnatal care was reported for less than 50% with the exception of a few countries in South/Southeast Asia (i.e., Cambodia and the Philippines), sub-Saharan Africa (i.e., Ghana and Madagascar), and Latin America and the Caribbean (i.e., Bolivia, the Domincan Republic and Peru).

In recognition of the postnatal period as ". . . a critical phase in the lives of mothers and newborn babies", the 2013 WHO guidelines on postnatal care[95] recommend the following:

- A health care visit within 24 hours after the birth and then again at least three more times – on day 3, in the second week, and again at 6 weeks;
- Blood pressure measurement shortly after birth and at 6 hours, although there is no guidance around blood pressure measurement during the rest of the postpartum period;
- Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit.

It is important to recognise that in a LMIC, postpartum care may be provided in the community rather than in facility, and by varying cadres of health care workers. For example, lay health workers may undertake promotion of postpartum care, while nurses and midwives may initiate treatment of pre-eclampsia[96]. All of these workers need to be trained accordingly.

Global initiatives that address the link between a woman's reproductive health and long-term health are lacking. To prevent non-communicable diseases in the offspring, the International Federation of Gynaecology and Obstetrics (FIGO) recently announced that it is partnering with other agencies and organisations that focus on enforcing interventions, such as good nutrition and minimisation of harmful environmental exposures during pregnancy[97]. While this initiative

acknowledges the role of non-communicable diseases within the reproductive, maternal, neonatal and child health continuum, it does not address the long-term chronic illnesses that may develop as a result of a complicated pregnancy.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 11.5)

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[99], AOM (Association of Ontario Midwives), NICE (National Institutes of Clinical Excellence)[67], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[100], QLD (Queensland, Australia)[101,102], SOGC (Society of Obstetricians and Gynaecologists of Canada)[103,104], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[105,106], WHO (World Health Organization)[107].

Most international guidelines highlighted that pre-eclampsia may develop *de novo* or worsen in the postpartum period (AOM, ACOG, NICE, SOGC, QLD).

The majority of guidelines stated that blood pressure may increase postpartum and recommended continuing antihypertensive therapy that women had been taking antepartum (NICE, ACOG, SOGC). Importantly, no guideline recommended that antenatal antihypertensive therapy be stopped. Although the treatment of severe hypertension followed similar recommendations to those antenatally, treatment targets for non-severe hypertension were generally lower and varied amongst guidelines (NICE, SOGC, ACOG); most commonly, clinicians are recommended to aim for a blood pressure <150/100 mmHg for women with gestational hypertension or pre-eclampsia (NICE, ACOG).

Most of the guidelines specifically mentioned the association between the hypertensive disorders of pregnancy (particularly pre-eclampsia) and future cardiovascular health, and suggested lifestyle counselling as the logical response (AOM, ACOG, NICE, SOGC, QLD, SOMANZ).

SUMMARY

Care in the immediate postpartum period should focus on the management of hypertension using treatment options that are acceptable during breastfeeding. Consideration should be given to postpartum thromboprophylaxis in women with a hypertensive disorder of pregnancy if other risk factors are present. NSAIDs should be avoided if hypertension is difficult to control or there is either a coagulopathy or renal dysfunction. All women with pre-eclampsia should be followed closely after delivery to ensure resolution of end-organ damage. Women should be screened for underlying disease that may have predisposed to pre-eclampsia and pre-eclampsia mimickers should also be ruled out. Finally, the postpartum period offers a unique window of opportunity to address short- and long-term risks of hypertensive disorders of pregnancy. Women should be counselled about the ideal inter-pregnancy interval as well as risks in future pregnancies. Women should be evaluated for risk factors for premature cardiovascular disease as well as other complications such as chronic kidney disease. Currently, the focus should be on the adoption of a heart-healthy lifestyle and screening for traditional cardiovascular risk factors.

PRIORITIES FOR FUTURE RESEARCH

Given the global rise in non-communicable diseases and the risk stratification that pregnancy appears to provide, there is an urgent need to identify how a woman's pregnancy history can be added to currently available cardiovascular disease risk scoring systems to identify and manage women at increased risk for cardiovascular disease.

REFERENCES

1. Firoz T, Melnik T. Postpartum evaluation and long term implications. Best Pract Res Clin Obstet Gynaecol 2011;25(4):549–561

2. Ferrazzani S, De Carolis S, Pomini F, Testa AC, Mastromarino C, Caruso A. The duration of hypertension in the puerperium of preeclamptic women: relationship with renal impairment and week of delivery. Am J Obstet Gynecol 1994;171(2):506–512

3. Tan LK, de Swiet M. The management of postpartum hypertension. BJOG 2002;109(7):733–736

4. Deruelle P, Coudoux E, Ego A, Houfflin-Debarge V, Codaccioni X, Subtil D. Risk factors for post-partum complications occurring after preeclampsia and HELLP syndrome. A study in 453 consecutive pregnancies. Eur J Obstet Gynecol Reprod Biol 2006; 125(1):59–65

5. Bayliss H, Beevers D, Churchill D. A study of puerperal blood pressure in hypertensive and

normotensive pregnancies. Hypertens Pregnancy 2002;21(Suppl 1)

6. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. Obstet Gynecol 2011 Nov;118(5):1102–1107

7. Davison JM, Dunlop W. Changes in renal hemodynamics and tubular function induced by normal human pregnancy. Semin Nephrol 1984;4(3): 198–207

8. Martin JN,Jr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol 2005 Feb;105(2): 246–254

9. Magee L, von Dadelszen P. Prevention and treatment of postpartum hypertension. Cochrane Database Syst Rev 2013 Apr 30;4:CD004351

10. Daskalopoulou SS, Khan NA, Quinn RR, Ruzicka M, McKay DW, Hackam DG, et al. The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. Can J Cardiol 2012 May;28(3): 270–287

11. Denolle T, Weber J, Calvez C, Daniel J, Cheve M, Marechaud M, et al. Home blood pressure measured telemetrically in hypertensive pregnant women. Am J Hypertens 2001;14(11):43A

12. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 2001 Sep;108(3):776–789

13. National Institutes of Health. Drugs and Lactation Database (LactMed). 2015; Available at: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. Accessed March 16, 2015

14. Shannon ME, Malecha SE, Cha AJ. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) and lactation: an update. J Hum Lact 2000 May;16(2):152–155

15. Mathews DD, Agarwal V, Shuttleworth TP. A randomized controlled trial of complete bed rest versus ambulation in the management of proteinuric hypertension during pregnancy. Br J Obstet Gynaecol 1982 Feb;89(2):128–131

16. Jacobsen AF, Skjeldestad FE, Sandset PM. Ante- and postnatal risk factors of venous thrombosis: a hospital-based case-control study. J Thromb Haemost 2008 Jun;6(6):905–912

17. Royal College of Obstetricians & Gynaecologists. Green-top Guideline 37a: Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. 2015; Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/. Accessed Jul/19, 2015

18. Karumanchi S, August P, Podymow T. Renal complications in normal pregnancy. In: Jurgen F, Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology, 4th edn. New York: Elsevier; 2010

19. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, et al. The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol 2015 5; 31(5):549–568

20. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 111: Inherited thrombophilias in pregnancy. Obstet Gynecol 2010 Apr;115(4): 877–887

21. Rodger MA, Hague WM, Kingdom J, Kahn SR, Karovitch A, Sermer M, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet 2014 Nov 8;384(9955): 1673–1683

22. Rodger MA, Langlois NJ, de Vries JI, Rey E, Gris JC, Martinelli I, et al. Low-molecular-weight heparin for prevention of placenta-mediated pregnancy complications: protocol for a systematic review and individual patient data meta-analysis (AFFIRM). Syst Rev 2014 Jun 26;3:69-4053-3-69

23. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006 Feb;4(2):295–306

24. Ounsted M, Cockburn J, Moar VA, Redman CW. Maternal hypertension with superimposed pre-eclampsia: effects on child development at 71/2 years. Br J Obstet Gynaecol 1983 Jul;90(7):644–649

25. Robinson M, Mattes E, Oddy WH, de Klerk NH, Li J, McLean NJ, et al. Hypertensive diseases of pregnancy and the development of behavioral problems in childhood and adolescence: the Western Australian Pregnancy Cohort Study. J Pediatr 2009 Feb;154(2): 218–224

26. Whitehouse AJ, Robinson M, Newnham JP, Pennell CE. Do hypertensive diseases of pregnancy disrupt

neurocognitive development in offspring? Paediatr Perinat Epidemiol 2012 Mar;26(2):101–108

27. Tuovinen S, Eriksson JG, Eero K, Räikkönen K. Maternal hypertensive pregnancy disorders and cognitive functioning of the offspring: a systematic review. Am Soc Hypertens 2014;8(11):8328470

28. Ananth CV, Friedman AM. Ischemic placental disease and risks of perinatal mortality and morbidity and neurodevelopmental outcomes. Semin Perinatol 2014; 38(3):151–158

29. Mutch LM, Moar VA, Ounsted MK, Redman CW. Hypertension during pregnancy, with and without specific hypotensive treatment. II. The growth and development of the infant in the first year of life. Early Hum Dev 1977 Oct;1(1):59–67

30. Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1982 Mar 20;1(8273):647–649

31. Reynolds B, Butters L, Evans J, Adams T, Rubin PC. First year of life after the use of atenolol in pregnancy associated hypertension. Arch Dis Child 1984;59(11): 1061–1063

32. Bortolus R, Ricci E, Chatenoud L, Parazzini F. Nifedipine administered in pregnancy: effect on the development of children at 18 months. BJOG 2000; 107(6):792–794

33. Chan WS, Koren G, Barrera M, Rezvani M, Knittel-Keren D, Nulman I. Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database. Hypertens Pregnancy 2010;29(3):271–283

34. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, et al. Cardiovascular Risk Factors in Children and Young Adults Born to Preeclamptic Pregnancies: A Systematic Review. Pediatrics 2012;129(6):e1552-e1561

35. Lazdam M, de lH, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. Hypertension 2012;60(5):1338–1345

36. Mamun AA, Kinarivala MK, O'Callaghan M, Williams G, Najman J, Callaway L. Does hypertensive disorder of pregnancy predict offspring blood pressure at 21 years? Evidence from a birth cohort study. J Hum Hypertens 2012;26(5):288–294

37. Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke 2009;40(4):1176–1180

38. Boivin A, Luo ZC, Audibert F, Mâsse B, Lefebvre F, Tessier R, et al. Pregnancy complications among women born preterm. Can Med Assoc J 2012;184(16): 1777–1784

39. Williams D. Pregnancy: a stress test for life. Curr Opin Obstet Gynecol 2003 Dec;15(6):465–471

40. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, et al. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004 Feb 10; 109(5):672–693

41. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007 Mar 20;115(11): 1481–1501

42. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011 Mar 22;57(12):1404–1423

43. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? Ther Adv Cardiovasc Dis 2008 Aug;2(4): 249–259

44. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007 Nov 10; 335(7627):978

45. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol 2009 Nov;114(5):961–970

46. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension 2011 Oct;58(4):709–715

47. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007 Nov 10;335(7627):974

48. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol 2013;28(1):1–19

49. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J 2008 Nov;156(5):918–930

50. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005 Nov 19; 366(9499): 1797–1803

51. Ray JG, Booth GL, Alter DA, Vermeulen MJ. Prognosis after maternal placental events and revascularization: PAMPER study. Am J Obstet Gynecol 2015; 214(1):106.e1-e14

52. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. N Engl J Med 2008 Aug 21;359(8): 800–809

53. Wang IK, Muo CH, Chang YC, Liang CC, Chang CT, Lin SY, et al. Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. CMAJ 2013 Feb 19; 185(3):207–213

54. Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, et al. Preeclampsia as a risk factor for diabetes: a population-based cohort study. PLoS Med 2013; 10(4):e1001425

55. Levine RJ, Esterlitz JR, Raymond EG, DerSimonian R, Hauth JC, Ben Curet L, et al. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. Control Clin Trials 1996 Oct;17(5): 442–469

56. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, et al. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003;13(1):19–32

57. Levine RJ, Vatten LJ, Horowitz GL, Qian C, Romundstad PR, Yu KF, et al. Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study. BMJ 2009 Nov 17;339:b4336

58. Aukes AM, De Groot JC, Wiegman MJ, Aarnoudse JG, Sanwikarja GS, Zeeman GG. Long-term cerebral imaging after pre-eclampsia. BJOG 2012 Aug;119(9): 1117–1122

59. Wiegman MJ, Zeeman GG, Aukes AM, Bolte AC, Faas MM, Aarnoudse JG, et al. Regional distribution of cerebral white matter lesions years after preeclampsia and eclampsia. Obstet Gynecol 2014 Apr;123(4): 790–795

60. Mautner E, Stern C, Deutsch M, Nagele E, Greimel E, Lang U, et al. The impact of resilience on psychological outcomes in women after preeclampsia: an observational cohort study. Health Qual Life Outcomes 2013;11:194

61. Delahaije DH, Dirksen CD, Peeters LL, Smits LJ. Anxiety and depression following preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. A systematic review. Acta Obstet Gynecol Scand 2013;92(7):746–761

62. Furuta M, Sandall J, Cooper D, Bick D. The relationship between severe maternal morbidity and psychological health symptoms at 6–8 weeks postpartum: a prospective cohort study in one English maternity unit. BMC Pregnancy Childbirth 2014;14(1):133

63. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Steegers EA, et al. Poor health-related quality of life after severe preeclampsia. Birth 2011 Sep;38(3): 246–255

64. Gaugler-Senden IP, Duivenvoorden HJ, Filius A, De Groot CJ, Steegers EA, Passchier J. Maternal psychosocial outcome after early onset preeclampsia and preterm birth. J Matern Fetal Neonatal Med 2012 Mar;25(3):272–276

65. Seely EW, Rich-Edwards J, Lui J, Nicklas JM, Saxena A, Tsigas E, et al. Risk of future cardiovascular disease in women with prior preeclampsia: a focus group study. BMC Pregnancy Childbirth 2013;13(1):240

66. Spratling PM, Pryor ER, Moneyham LD, Hodges AL, White-Williams CL, Martin JN,Jr. Effect of an educational intervention on cardiovascular disease risk perception among women with preeclampsia. J Obstet Gynecol Neonatal Nurs 2014 Mar-Apr;43(2): 179–189

67. 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

68. Brown MC, Bell R, Collins C, Waring G, Robson SC, Waugh J, et al. Women's perception of future risk following pregnancies complicated by preeclampsia. Hypertens Pregnancy 2013;32(1):60–73

69. Young B, Hacker MR, Rana S. Physicians' knowledge of future vascular disease in women with preeclampsia. Hypertens Pregnancy 2012;31(1):50–58

70. Ehrenthal DB, Catov JM. Importance of engaging obstetrician/gynecologists in cardiovascular disease prevention. Curr Opin Cardiol 2013 Sep;28(5): 547–553

71. MacDonald SE, Walker M, Ramshaw H, Godwin M, Chen XK, Smith G. Hypertensive disorders of pregnancy and long-term risk of hypertension: what do Ontario prenatal care providers know, and what do they communicate? J Obstet Gynaecol Can 2007 Sep; 29(9):705–710

72. Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE, et al. Cardiovascular risk factor assessment after pre-eclampsia in primary care. BMC Fam Pract 2009 Dec 8;10:77-2296-10-77

73. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009 Jan;200(1): 58.e1-58.e8

74. Smith GN, Pudwell J, Walker M, Wen SW. Ten-year, thirty-year, and lifetime cardiovascular disease risk estimates following a pregnancy complicated by preeclampsia. J Obstet Gynaecol Can 2012 Sep;34(9): 830–835

75. Cusimano MC, Pudwell J, Roddy M, Cho CK, Smith GN. The maternal health clinic: an initiative for cardiovascular risk identification in women with pregnancy-related complications. Am J Obstet Gynecol 2014 May;210(5):438.e1-438.e9

76. Pencina MJ, D'Agostino RB S, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009 Jun 23;119(24):3078–3084

77. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013 Jul;120(8): 924–931

78. Carson MP. Society for maternal and fetal medicine workshop on pregnancy as a window to future health: Clinical utility of classifying women with metabolic syndrome. Semin Perinatol 2015 Jun;39(4):284–289

79. Health Canada. Eating well with Canada's food guide. 2011; Available at: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/food-guide-aliment/view_eatwell_vue_bienmang-eng.pdf. Accessed Jan/05, 2016

80. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 2006 Sep 30;368(9542): 1164–1170

81. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, et al. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynecol 2013 Nov;122(5):999–1009

82. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Oenema A, et al. Motivators and barriers to a healthy postpartum lifestyle in women at increased cardiovascular and metabolic risk: a focus-group study. Hypertens Pregnancy 2012;31(1):147–155

83. Hoedjes M, Berks D, Vogel I, Franx A, Visser W, Duvekot JJ, et al. Effect of postpartum lifestyle interventions on weight loss, smoking cessation, and prevention of smoking relapse: a systematic review. Obstet Gynecol Surv 2010 Oct;65(10):631–652

84. The MotHERS Program. The MotHERS Program: Mothers' Health Education, Research and Screening. 2015; Available at: http://www.themothersprogram.ca. Accessed Aug/10, 2015

85. Berks D, Hoedjes M, Franx A, Habbema D, Raat H, Duvekot H, et al. T14.2 Postpartum lifestyle intervention after complicated pregnancy proves feasible. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2010;1:S25

86. Bennett WL, Gilson MM, Jamshidi R, Burke AE, Segal JB, Steele KE, et al. Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data. BMJ 2010 Apr 13; 340:c1662

87. Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med 2015 Feb 26;372(9):814–824

88. Berlac JF, Skovlund CW, Lidegaard O. Obstetrical and neonatal outcomes in women following gastric bypass: a Danish national cohort study. Acta Obstet Gynecol Scand 2014 May;93(5):447–453

89. Armstrong C. ACOG Guidelines on Pregnancy After Bariatric Surgery. 2010;81(7)

90. Rahman MM, Haque SE, Zahan MS. Factors affecting the utilisation of postpartum care among young mothers in Bangladesh. Health Soc Care Community 2011;19(2):138–147

91. Li XF, Fortney JA, Kotelchuck M, Glover LH. The postpartum period: the key to maternal mortality. Int J Gynaecol Obstet 1996 Jul;54(1):1–10

92. Fort AL. Coverage of post-partum and post-natal care in Egypt in 2005–2008 and Bangladesh in 2004–2007: levels, trends and unmet need. Reprod Health Matters 2012;20(39):81–92

93. Wang W, Alva S, Wang S, Fort A. Levels and Trends in the use of Maternal Health Services in Developing Countries. DHS Comparative Reports 2011;26

94. Langlois E, Miszkurka M, Zunzunegui M, Ghaffar G, Ziegler D, Karp I. Inequities in postnatal care in low- and middle-income countries: a systematic review and meta-analysis. Bull World Health Organ 2015;93(4)

95. World Health Organization. WHO Recommendations on postnatal care of the mother and newborn. 2013; Available at: http://www.who.int/maternal_child_adolescent/documents/postnatal-care-recommendations. Accessed Aug/10, 2015

96. World Health Organization. WHO Recommendations – OPTIMIZEMNH. 2012; Available at: http://www.optimizemnh.org/. Accessed Aug/10, 2015

97. Roura L, Arulkumaran S. Facing the noncommunicable disease (NCD) global epidemic – The battle of prevention starts in utero – The FIGO challenge. Best Pract Res Clin Obstet Gynaecol 2015;29(1):514

98. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PLoS One 2014;9(12):e113715

99. 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

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

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

102. Queensland Maternity and Neonatal Clinical, Guidelines Program. Supplement: hypertensive disorders of pregnancy. 2013;MN10.15.V4-R15

103. 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

104. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, SOGC Hypertension Guideline Committee. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can 2014 Jul;36(7):575–576

105. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy 2014. Aust N Z J Obstet Gynaecol 2015;55:11–16

106. Lowe SA, Brown MA, Dekker GA, Gatt S, McLintock CK, McMahon LP, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. Aust N Z J Obstet Gynaecol 2009 Jun;49(3):242–246

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