

# Hypertensive Disorders *in* Pregnancy



GUIDELINE SUMMARY

New York State Department of Health

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# Hypertensive Disorders in Pregnancy (HDP)

## Guideline Summary

### 1. Background

#### *Introduction*

Hypertensive disorders in pregnancy (HDP) are associated with severe maternal obstetric complications and are a leading contributor to maternal mortality.<sup>1</sup> Furthermore, HDP lead to preterm delivery, fetal intrauterine growth restriction, low birth weight and perinatal death.<sup>2</sup> Although the exact incidence is unknown, it has been estimated that 5-10% of US pregnancies are complicated by HDP.<sup>3</sup> Data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project and National Hospital Discharge Survey have shown marked increases in the incidence of gestational hypertension and preeclampsia in the past two decades, and more women entering pregnancy with chronic (preexisting) hypertension.<sup>4,5</sup> Women with chronic (preexisting) hypertension have been shown to have a markedly increased risk of severe adverse outcomes, such as maternal cerebrovascular accidents and placental abruption, compared to normotensive women.<sup>6</sup> The prevalence of HDP is believed to be increasing due to obesity trends and childbearing in older aged women.<sup>7</sup> Due to the frequent occurrence and potential sequelae of hypertensive disorders in pregnancy, prompt identification and appropriate management are essential.

#### *Purpose*

This guidance document is intended for healthcare providers who care for pregnant women in a variety of clinical settings. The aim is to promote quality services and enhance communication among the myriad of providers who provide health care to pregnant women, including obstetricians, family practice physicians, emergency department physicians, midwives, anesthesiologists, nurses and others.

This document summarizes existing guidelines for the diagnosis, evaluation and management of hypertensive disorders in pregnancy. This document is not intended to replace clinical judgment in the care of women with hypertensive disorders in pregnancy. It should be noted that diagnostic and management strategies that are not recommended specifically for their impact on outcomes of hypertensive disorders in pregnancy may have other general benefits in pregnancy.

Initiatives to standardize care have been shown to improve clinical outcomes.<sup>8</sup> For hypertension in pregnancy, the introduction and dissemination of evidence-based clinical guidelines have been associated with improved maternal and perinatal outcomes.<sup>9,10</sup> Effective health care delivery for complex conditions such as HDP depends on a well-functioning, coordinated care team of health care providers. Collaboration and communication among care team members is essential for successful management and reducing error.<sup>11</sup>

## Process

In 2010, the New York State Department of Health implemented a new Maternal Mortality Review (MMR) Initiative. The new process is completed in conjunction with Island Peer Review Organization (IPRO) and an expert committee that includes representation from American Congress of Obstetricians and Gynecologists (ACOG) and many other professional organizations and experts. The updated initiative is intended to ensure a comprehensive review of factors leading to maternal deaths in New York State, based on sufficient information to develop strategies and measures to decrease the risk of these deaths. The first meeting of the expert committee included a review of preliminary 2006-2008 data on 70 maternal deaths, showing leading causes of death to be: hypertension (20%), hemorrhage (19%) and embolism (17%). Chronic illness, obesity and prenatal risk factors were identified as important circumstances in the cases reviewed. This resulted in the identification of several priorities including management of hypertension, obesity and embolism/DVT for development of clinical guidelines. Management of hypertension during pregnancy was selected as the first topic for development. A multidisciplinary subcommittee of the Expert Review Committee and the Department worked with IPRO and the subcommittee to develop guidelines on the diagnosis, evaluation, and management of Hypertensive Disorders in Pregnancy.

The updated maternal mortality review initiative is consistent with the department's priorities of improving birth outcomes and decreasing maternal mortality in accordance with Title V Maternal and Child Health Services Block Grant and the department's prevention agenda. Maternal and infant mortality and morbidity are key indicators of the health of a society. These measures are a reflection of the current health status of a large segment of the population and a predictor of the health of the next generation.

Effective and error-free health care delivery for complex conditions such as HDP depends on a well-functioning, coordinated care team that fosters collaboration and communication among care team members.<sup>12</sup>

The process for the development of this guidance document included a review of ACOG and American Academy of Pediatrics (AAP) guidelines, practice bulletins and committee opinions; the Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; the 2000 Report of the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy; Hypertension in Diverse Populations: a New York State Medicaid Clinical Guidance Document; Institute of Medicine (IOM) guidelines; Cochrane reviews and selected literature. International guidelines reviewed included those of the Royal College of Obstetricians and Gynaecologists National Institute for Health and Clinical Excellence (NICE), Society of Obstetricians and Gynaecologists of Canada (SOGC), and Society of Obstetric Medicine of Australia and New Zealand (SOMANZ), with consideration of evidence grading included in the documents.

A bibliography of documents included in the guideline comparison is attached in Appendix A.

Subsequent to guideline review and comparison, findings were discussed by the MMR Hypertension Subcommittee and consensus statements for areas without clear evidence were defined. The summary document and MMR Hypertension Subcommittee recommendations were submitted to the Expert Review Committee and subsequently to the NYSDOH for approval and finalization of recommendations. Final recommendations are *italicized* for each section in the document.

## 2. Definitions and stratification of hypertension in pregnancy

Hypertensive Disorders in Pregnancy (HDP) are comprised of a spectrum of disorders typically classified into categories that include chronic (preexisting) hypertension, gestational hypertension, preeclampsia (including chronic (preexisting) hypertension with superimposed preeclampsia) and eclampsia. Hypertension and preeclampsia are stratified according to severity. Clear definitions and severity stratification are essential, because they form the basis of management recommendations and promote accurate, effective communication among health care providers. While there is general consensus across guidelines for most major definitions, including those of the NHBPEP Working Group, there are some noteworthy differences in definitions and criteria for severity stratification.

### a. Hypertension

*Hypertension in pregnancy is defined as a systolic blood pressure  $\geq 140$  OR diastolic blood pressure  $\geq 90$  mmHg or both. Both systolic and diastolic blood pressure elevations are important in the identification of HDP. Hypertensive blood pressure readings should be confirmed using appropriate measurement technique as described below, and should be remeasured after 10-15 minutes of rest.*

There is broad agreement across guidelines that hypertension in pregnancy is defined as a diastolic blood pressure  $\geq 90$  mmHg or a systolic blood pressure  $\geq 140$  mmHg or both. The inclusion of systolic blood pressure elevation in the definition of hypertension in pregnancy reflects evidence that both diastolic and systolic elevated readings have been associated with adverse outcomes such as perinatal morbidity.<sup>13</sup> Therefore, systolic blood pressure readings are considered as important as diastolic readings in the identification of HDP.

Although the NHBPEP report and ACOG practice bulletin for preeclampsia caution that a relative rise in systolic blood pressure of 30 mmHg or diastolic relative rise of 15 mmHg warrants close observation, there is no systematic evidence that this relative rise in blood pressure is predictive of pregnancy outcomes. Therefore, defining hypertension in pregnancy by a relative rise is no longer endorsed in published guidelines. In addition, relative blood pressure rise as a criterion for defining hypertension has a high false positive rate, especially because of the variability of blood pressure across trimesters of pregnancy. Blood pressure in healthy pregnancies decreases during the first trimester, reaching its lowest point by mid-pregnancy, and typically returns to pre-pregnancy levels during the third trimester. In women who develop preeclampsia, the pattern differs, with blood pressure stable for the first half of pregnancy and then continuously rising until delivery.<sup>14</sup> The ACOG practice bulletin regarding chronic hypertension notes that previously undiagnosed chronic (preexisting) hypertension may be masked by the normal decrease in blood pressure in women presenting for care after 12 weeks gestation.<sup>15</sup>

Elevated blood pressure readings should be confirmed, and should be remeasured after 15 minutes of rest. The ACOG committee opinion Emergent Therapy for Acute Onset, Severe Hypertension with Preeclampsia or Eclampsia indicates that acute onset, severe hypertension that persists for 15 minutes or more is considered a hypertensive emergency,<sup>16</sup> and SOGC guidelines cite expert consensus that severe hypertension should be confirmed with remeasurement in 15 minutes.<sup>17</sup>

The ACOG practice bulletin Chronic Hypertension in Pregnancy recommends documentation of blood pressure levels that meet criteria for hypertension on more than one occasion, at least 4 to 6 hours apart. SOGC guidelines also recommend basing the identification of hypertension on an average of two readings more than 4 hours apart for non-severe hypertension, noting high rates of normal readings on subsequent measurements, which is consistent with NYSDOH recommendations for diverse populations.<sup>18</sup> When confirming elevated blood pressure readings, blood pressure should be measured in both arms and appropriate measurement technique as described below should be ensured. There is greater variation in systolic than diastolic blood pressure.

In the setting of pregnancy, SOMANZ guidelines cite reports that isolated office hypertension, or “white coat hypertension,” confers some risk of adverse outcomes, and therefore women with isolated office hypertension warrant monitoring. Ascribing a hypertensive blood pressure reading to “white coat hypertension” in pregnant women is discouraged. Women with isolated hypertensive blood pressure readings should be further evaluated with determination of risk for HDP, including consideration of conditions that confer risk, such as obesity and lupus, as well as assessment of proteinuria.

### *b. Severe hypertension*

*Severe hypertension in pregnancy is defined as systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 110$  mmHg, or both. The SOGC expert consensus suggests that a single reading at this level be confirmed within 15 minutes. Severe hypertension in pregnancy is considered to be a hypertensive emergency that requires urgent intervention. The ACOG Committee Opinion “Emergent Therapy for Acute Onset, Severe Hypertension with Preeclampsia or Eclampsia” recommends that severe hypertension that persists for 15 minutes or more in the setting of preeclampsia or eclampsia is a hypertensive emergency that requires immediate intervention.<sup>19</sup>*

Although definitive evidence is lacking for a threshold blood pressure to define severe hypertension, there is consensus across most guidelines that severe hypertension is defined as a systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 110$  mmHg, or both. Women with confirmed blood pressure readings consistent with severe hypertension require immediate intervention. The ACOG Committee Opinion “Emergent Therapy for Acute Onset, Severe Hypertension with Preeclampsia or Eclampsia” recommends that severe hypertension that persists for 15 minutes or more in the setting of preeclampsia or eclampsia is a hypertensive emergency that requires immediate intervention. The immediate goal of management of severe hypertension in pregnant women is predominantly related to maternal safety, such as the prevention of stroke, rather than the prevention of the long term sequelae of hypertension. There is evidence that cerebral autoregulation is altered in severe preeclampsia and eclampsia, and therefore acute intervention thresholds based on cerebral autoregulation studied in other populations may not be applicable.<sup>20</sup> There have been reports of stroke associated with elevated systolic blood pressure without elevated diastolic blood pressure in women with severe preeclampsia.<sup>21</sup> The prevailing definition of severe hypertension is based on fair evidence that there is an increased risk of stroke in pregnancy with systolic blood pressure readings  $\geq 160$  mmHg, although there is no definitive evidence for any discrete threshold.



### 3. Blood pressure measurement technique

*Appropriate blood pressure measurement technique is essential for identifying and monitoring HDP. Blood pressure is highly variable within subjects; appropriate care must be taken to standardize practice in order to minimize various factors that affect clinic blood pressure measurement, especially choice of cuff size, degree of stimulation, posture, and talking.*

*Caffeine and tobacco should be avoided for at least 30 minutes prior to measurement. Ideally, prior to blood pressure measurement, the patient should be undisturbed and at rest for at least 5 minutes, in a quiet room if possible. Neither the patient nor the trained observer should talk during the measurement itself. Blood pressure should be measured with the patient sitting in a chair with feet flat on the floor and back supported. If upright sitting posture is not possible, blood pressure should be measured in the left, lateral recumbent position, and it should be recognized that blood pressure will be reduced by a few mmHg if taken in the free arm. The blood pressure cuff should be appropriate in size such that the inflatable bladder covers 75%-100% of the circumference of the upper arm.*

*Blood pressure should be measured in both arms at the initial visit ideally, with the higher value taken as the blood pressure of record and that arm noted in the record as the basis for all subsequent determinations.*

*Diastolic readings should reflect Korotkoff phase V readings (disappearance of tones), if blood pressure is measured with a manual device. Semi-automated oscillometric devices should be checked periodically for accuracy. Office BP remains the gold standard for detection of HDP despite the increasing use of non-office BP values (self-determined home blood pressure and 24-hour ambulatory) in non-pregnant individuals with hypertension. Observational studies have shown that self-determined home blood pressure and 24-hour ambulatory blood pressure monitoring may be useful in the identification and surveillance of HDP. Ambulatory blood pressure monitors are fully automatic and are capable of recording blood pressure for 24 hours or longer while patients conduct their normal daily activities.*

There are several general recommendations for blood pressure measurement technique in pregnant women that are consistent with recommendations for the general population as outlined by the JNC and NYSDOH Medicaid documents. There is consensus across HDP guidelines that blood pressure should be measured with women seated and upright, when possible. If upright posture is not possible, blood pressure should be measured in the left lateral recumbent position, though it should be recognized that modestly lower blood pressure readings can result in this position, because the right arm is usually elevated above heart level. Standard technique requires that the patient rest undisturbed, not talking, for 5 to 10 minutes with feet on the floor and back supported. Caffeine and tobacco should be avoided for at least 30 minutes prior to blood pressure measurement. It is critical that a blood pressure cuff size appropriate to patient size be used to ensure accurate readings. Blood pressure should be measured with a cuff with a cuff bladder that encircles 75-100% of the upper arm, with the cuff midpoint and the arm at the level of the heart. Diastolic readings should reflect Korotkoff phase V readings (disappearance of tones), if blood pressure is measured with a manual device.

Although automated oscillometric blood pressure readings can reduce operator error, and are now most commonly used, automated and aneroid devices require periodic validation against mercury

devices. Clinicians should be aware that not all automated blood pressure measuring devices have been validated in pregnancy and in women with HDP, and it has been reported that automated blood pressure readings can vary and underestimate blood pressure in preeclampsia.

Home blood pressure monitoring and 24-hour ambulatory blood pressure monitoring are cited in guidelines as modalities that may be useful in the identification of isolated office hypertension and home monitoring of HDP. Reviews of evidence reported in the SOGC guidelines and a Cochrane review have indicated that there is insufficient evidence for clarifying the role of these modalities in the identification and management of HDP and their impact on pregnancy outcomes.<sup>22</sup> Ambulatory blood pressure monitoring has been more commonly used for surveillance of women with HDP. Home blood pressure monitoring is easier to implement than 24-hour ambulatory blood pressure monitoring, but it has not been validated against adverse outcomes. Negative 24-hour ambulatory blood pressure monitoring results only modestly decrease the risk of adverse outcomes; SOGC guidelines note that the role of monitoring women with HDP with this modality is limited.

## 4. Classification of Hypertensive Disorders in Pregnancy (HDP)

### a. Recommendation for classification

*Hypertensive Disorders in Pregnancy (HDP) are comprised of a spectrum of disorders typically classified into categories and stratified according to severity: chronic (preexisting) hypertension, gestational hypertension, preeclampsia (including chronic (preexisting) hypertension with superimposed preeclampsia) and eclampsia. Hypertension and preeclampsia are stratified according to severity. These classifications promote accurate, effective communication among health care providers and form the basis of management recommendations.*

### b. Chronic (preexisting) hypertension

*Chronic (preexisting) hypertension is defined as hypertension (systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg or both) that is present before 20 weeks of gestation or prior to pregnancy. Elevated readings should be documented on more than one occasion.*

Chronic (preexisting) hypertension is defined as hypertension (systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg or both) that is present before 20 weeks of gestation or predating pregnancy. The ACOG practice bulletin for chronic hypertension in pregnancy cites criteria including the use of antihypertensive medications before pregnancy and hypertension persisting beyond 12 weeks postpartum in the classification of chronic (preexisting) hypertension. The criterion of persistence beyond 12 weeks postpartum allows women presenting late in pregnancy to have their hypertension retrospectively categorized, which is important for appropriate ongoing care. For management considerations, SOGC guidelines define a subgroup of women with chronic (preexisting) hypertension and comorbid conditions that represent major cardiovascular risk, such as preexisting diabetes, renal disease, vascular disease or other conditions that impact antihypertensive therapy outside of pregnancy. JNC guidelines also differentiate pregnant women with chronic

(preexisting) hypertension who have evidence of target organ damage in management considerations, though not specifically defined as a subgroup. ACOG notes that the incidence of adverse pregnancy outcomes appears to be related to the duration of chronic (preexisting) hypertension, which is likely a proxy for end-organ damage.

### *c. Gestational Hypertension*

*Gestational hypertension is defined as new hypertension (systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg or both) presenting at or after 20 weeks gestation without proteinuria or other features of preeclampsia; this terminology replaces the term "Pregnancy Induced Hypertension."*

Gestational hypertension is defined as new hypertension presenting after 20 weeks gestation without proteinuria or other features of preeclampsia; this terminology replaces the term Pregnancy Induced Hypertension (PIH) that was widely used in older guidelines and literature.

### *d. Preeclampsia and chronic (preexisting) hypertension with superimposed preeclampsia*

*Preeclampsia is defined as hypertension plus significant proteinuria, specifically gestational hypertension plus new onset proteinuria, or chronic (preexisting) hypertension with new or worsening proteinuria. When preeclampsia develops in women with chronic (preexisting) hypertension, the classification of disease is chronic (preexisting) hypertension with superimposed preeclampsia. Preeclampsia can also occur without proteinuria, with hepatic, hematopoietic, or other manifestations. Edema is no longer considered a specific diagnostic criterion for preeclampsia. Pregnant women with hypertension plus other adverse conditions but no proteinuria should have further evaluation for preeclampsia.*

Early identification and management is essential for preeclampsia, which is characterized by a complex group of multi-organ processes and variable presentation. Traditionally, preeclampsia has been defined as hypertension plus significant proteinuria. Women with gestational hypertension plus new onset of 300 mg or more of urinary protein in a 24 hour period are classified as having preeclampsia. Women with chronic (preexisting) hypertension with new or worsening proteinuria are classified as having chronic (preexisting) hypertension with superimposed preeclampsia. This definition, which is cited in ACOG and JNC documents based on the NHBPEP Working Group definition, is typically used in research protocols, and therefore reflects the characteristics of pregnant women who comprise the study population in most published studies of preeclampsia. In addition, this traditional definition of preeclampsia is based on the most common maternal manifestations of preeclampsia: hypertension and proteinuria. Up to 30% or more of women with chronic (preexisting) hypertension or gestational hypertension also develop preeclampsia. Women with mild chronic (preexisting) hypertension have a 20% risk of developing superimposed preeclampsia, and those with severe chronic (preexisting) hypertension have a 50% risk of superimposed preeclampsia. Women with chronic (preexisting) hypertension and end-organ disease, severe hypertension or secondary hypertension are at greatest risk for superimposed preeclampsia.<sup>23</sup>

The development of new proteinuria or sudden increase over baseline proteinuria should trigger an assessment for superimposed preeclampsia in women with chronic (preexisting) hypertension.

JNC guidelines define worsening proteinuria in women with chronic (preexisting) hypertension as a sudden, 2-3 fold increase in proteinuria.

Preeclampsia can also occur without proteinuria, and manifest as hypertension plus other adverse conditions, reflecting the multi-organ processes that characterize this disorder. SOGC and SOMANZ guidelines define preeclampsia as hypertension with proteinuria or other adverse conditions, since there is evidence that end-organ complications can occur without proteinuria. It has been reported that up to 20% of women with eclampsia have hypertension without proteinuria in the week preceding the onset of eclampsia.<sup>24</sup> The definition for preeclampsia in the ACOG preeclampsia practice bulletin and NHBPEP Working Group report specify proteinuria as a required element. The NHBPEP Working Group report notes that preeclampsia should be suspected even without proteinuria in the presence of other adverse conditions. The ACOG practice bulletin for chronic hypertension in pregnancy indicates that women with chronic (preexisting) hypertension who develop abnormal laboratory values or clinical symptoms such as headache, right upper quadrant pain or an increase in blood pressure warrant consideration of superimposed preeclampsia. For women presenting with hypertension with adverse conditions but without proteinuria, a diagnosis of preeclampsia should be entertained to ensure identification of women at risk; however, the diagnosis would be uncertain and would require further investigation and consideration of other possible conditions that the signs and symptoms may represent. In cases identified as suspected preeclampsia in the absence of proteinuria, medical subspecialty or maternal-fetal medicine consultation should be considered.

There are various adverse conditions identified across SOGC, SOMANZ, JNC and ACOG guidelines as criteria that should raise suspicion for preeclampsia in the absence of proteinuria. Several of the identified conditions also comprise criteria for severe preeclampsia in these guidelines. Adverse conditions included in the consideration of preeclampsia center on maternal end-organ dysfunction, maternal symptomatology, abnormal maternal laboratory testing and evidence of fetal morbidity.

Adverse conditions that are reflective of maternal end-organ dysfunction include eclampsia, pulmonary edema, stroke, placental abruption and severe hypertension. For women with chronic (preexisting) hypertension, SOGC guideline-cited adverse conditions include resistant hypertension, defined as hypertension requiring three medications for blood pressure control after 20 weeks gestation.

Maternal symptoms that guidelines identify as adverse conditions that raise suspicion for preeclampsia are generally not specific for preeclampsia. These symptom-based adverse conditions include symptoms that may reflect occipital cortical or other cerebral ischemia or edema (severe headache, visual disturbance), hepatic capsular irritation (epigastric or right upper quadrant pain) or pulmonary edema (dyspnea). Other maternal symptoms cited as adverse conditions that could raise suspicion for preeclampsia include severe nausea and vomiting and chest pain. SOGC guidelines specifically note that adverse conditions differ in significance, and that maternal symptoms such as headache do not have the same weight as signs of maternal end-organ dysfunction such as the manifestation of eclampsia.

Abnormal maternal laboratory testing reflecting end-organ dysfunction includes elevated liver enzymes and thrombocytopenia, which are cited by SOGC, JNC, ACOG and SOMANZ guidelines as possible manifestations of preeclampsia. SOGC guidelines also cite elevated serum creatinine and serum

albumin less than 2.0 g/dl, which SOGC guidelines indicate has been associated with an increased risk of pulmonary edema and other complications. SOGC guidelines note that hyperuricemia has been associated with perinatal complications, but there is no evidence that it is predictive of adverse maternal outcomes, and it has therefore not been included as laboratory evidence of adverse conditions.

Signs of fetal morbidity are included as adverse conditions in both SOGC and SOMANZ guidelines and include oligohydramnios, intrauterine growth restriction, abnormal Doppler umbilical artery velocimetry and intrauterine fetal death. As diagnostic criteria have evolved over the past decade, edema is no longer cited as a required criterion for preeclampsia in guidelines, since there is evidence that edema is neither a sensitive nor specific indicator for preeclampsia.<sup>25</sup> The absence of edema does not exclude a diagnosis of preeclampsia.

#### *e. Significant proteinuria in pregnancy*

*In the context of identification of preeclampsia, significant proteinuria is present when 24 hour urine protein is equal to or exceeds 300 mg of protein. The spot urine protein: creatinine ratio has also been used to define significant proteinuria in the identification of preeclampsia. The ACOG practice bulletin "Chronic Hypertension in Pregnancy" notes that a protein : creatinine ratio in the range of 0.15 to 0.3 g protein/g creatinine has been used to identify women who should be further evaluated.<sup>26</sup> The SOGC and the National Collaborating Centre for Women's and Children's Health, National Institute for Health and Clinical Excellence (NICE) identify significant proteinuria as a protein: creatinine ratio of  $\geq 30$  mg protein/mmol creatinine.<sup>27</sup>*

Significant proteinuria is defined across guidelines as greater than or equal to 300 mg of protein in a 24 hour urine collection. The ACOG practice bulletin Chronic Hypertension in Pregnancy identifies a spot urine protein: creatinine ratio in the range of 0.15 to 0.3 g protein/g creatinine as an indicator that has been used to identify pregnant women who warrant further evaluation, but notes that there has not been consensus on the best cutoff value. Other guidelines (SOGC and NICE) identify a spot urine protein: creatinine ratio of  $\geq 30$  mg protein/mmol creatinine as significant proteinuria in the context of identifying preeclampsia among pregnant women. Morris et al., in a systematic review and meta-analysis of diagnostic accuracy of spot urinary protein and albumin to creatinine ratios in suspected preeclampsia found that the optimum threshold (maximal sensitivity and specificity) for significant proteinuria in the identification of preeclampsia was a protein: creatinine ratio in the range of 0.30 and 0.35.<sup>28</sup>

"Proteinuria", a term that is commonly used in medical practice, is not fully interchangeable with "albuminuria." Total urinary protein includes globulins and other substances and is therefore higher in amount than urinary albumin excretion. It is the abnormal filtration of albumin that defines the presence of any glomerulopathy. Accordingly, standards have been established by the National Kidney Foundation KDOQI guidelines such that albuminuria in women is defined as urinary albumin excretion  $>300$  mg/day or  $>355$  mg/g creatinine.<sup>29</sup> SOGC guidelines note that more evidence is needed regarding the clinical use of urinary albumin: creatinine ratio (ACR) in identifying preeclampsia among women at risk. Morris et al. in their systematic review, concluded that there was insufficient evidence for the clinical use of ACR in diagnosis of suspected preeclampsia; meta-analysis was not possible due to differing thresholds and characteristics across studies.<sup>30</sup>

## *f. Severe preeclampsia*

*ACOG parameters should be used to define severe preeclampsia; ACOG criteria for severe preeclampsia include the presence of any one of the following: severe hypertension (systolic blood pressure  $\geq$  160 mmHg or diastolic blood pressure  $\geq$  110 mmHg, or both), cerebral or visual disturbance, epigastric or right upper quadrant pain, oliguria, pulmonary edema, cyanosis, impaired liver function, thrombocytopenia or intrauterine growth restriction (IUGR).*

It is important to identify severe preeclampsia, since crucial management decisions such as seizure prophylaxis depend on severity stratification. ACOG parameters should be used to define severe preeclampsia; these parameters overlap adverse conditions noted in guidelines for the identification of preeclampsia in the absence of proteinuria. ACOG criteria for severe preeclampsia include maternal symptoms (cerebral or visual disturbance, epigastric or right upper quadrant pain), evidence of maternal end-organ complications (severe hypertension, oliguria, pulmonary edema or cyanosis), abnormal maternal laboratory tests (impaired liver function, thrombocytopenia) and fetal morbidity (intrauterine growth restriction).

There is no strong evidence for a defined cutoff point for the prognostic value of degrees of proteinuria, and quantification has not proven useful for prognostic determinations; however, there is evidence that the risk for adverse outcome increases as proteinuria increases.<sup>31</sup> Several guidelines include the degree of proteinuria in the definition of severe preeclampsia, including the ACOG preeclampsia practice bulletin that cites proteinuria of 5 grams or more in a 24 hour urine sample and SOGC guidelines, which include “heavy” proteinuria of 3-5 grams/day despite an acknowledgement of the lack of clear evidence.

Although ACOG does not include the early onset of preeclampsia in its definition of severe preeclampsia, SOGC guidelines include the onset of preeclampsia prior to 34 weeks gestation as a marker of severe preeclampsia. Recent evidence has suggested that early and late preeclampsia should be differentiated, since onset prior to 34 weeks gestation is associated with more severe disease, perhaps due to etiological differences between early and late onset preeclampsia.<sup>32</sup> Early onset preeclampsia is postulated to be mediated by placental factors with resultant adverse outcomes, with late onset more likely associated with maternal factors such as obesity and perhaps with outcomes that are less severe.<sup>33</sup> Although there is no definitive evidence to support this approach, health care providers may want to consider hospitalizing women presenting with suspected preeclampsia at less than 34 weeks gestation for monitoring.

## *g. Eclampsia*

*Eclampsia is defined as new onset grand mal seizures in women with preeclampsia. Some women presenting with eclampsia do not have diagnosed preeclampsia, and some women may present with eclampsia in the post-partum period.*

Eclampsia and HELLP syndrome are two severe conditions that can manifest in women with preeclampsia, and each triggers distinct management considerations. Eclampsia is defined as new onset grand mal seizures in women with preeclampsia. Eclampsia may manifest in women with

preeclampsia post partum, but ACOG guidelines note that other causes may be more likely if seizures occur beyond 48-72 hours postpartum.

#### *h. HELLP syndrome*

*HELLP syndrome is a serious systemic disorder associated with preeclampsia and manifested by hemolysis, elevated liver enzymes and a low platelet count.*

HELLP syndrome manifests with hemolysis, elevated liver enzymes and a low platelet count. HELLP syndrome can manifest with or without proteinuria. HELLP syndrome has been noted to occur in approximately 20% of women with severe preeclampsia, as noted in the ACOG preeclampsia practice bulletin.

### **5. Assessment of HDP**

*Assessment of HDP includes assessment of the risk for preeclampsia, the severity of preeclampsia, and the presence of additional relevant findings, including identifiable causes of hypertension or kidney disease.*

#### *a. Assessment of risk for preeclampsia*

*Various conditions predispose to preeclampsia, including chronic (preexisting) hypertension, previous preeclampsia, autoimmune disease/antiphospholipid antibodies, chronic kidney disease, and preexisting diabetes mellitus. Women with these conditions are considered to be at high risk for HDP. Other factors that increase the risk for HDP include, but are not limited to, multifetal pregnancy, elevated pre-pregnancy Body Mass Index (BMI), maternal age  $\geq 40$ , nulliparity, vascular and connective tissue disease, family history of preeclampsia, thrombophilia and interpregnancy interval of greater than 10 years. Black race has also been associated with increased risk for preeclampsia. Consideration should be given to risk factors for preeclampsia when developing surveillance and monitoring strategies, including visit frequency.*

There has been substantial study in the past decade regarding the identification of risk factors for preeclampsia, since early identification of women at risk is essential for prevention and for reducing the risk of some preeclampsia-associated complications.<sup>34,35</sup> Risk factors cited in guidelines reflect etiological theories, including abnormal trophoblastic invasion, inflammatory and immune response and genetics. In addition to recommendations for prophylaxis, the nature of maternal testing for the presence of preeclampsia, such as proteinuria, is also guided by the degree of risk.

There are several risk factors for preeclampsia that are commonly cited across guidelines to identify women at risk; these include factors that confer high risk and factors that confer moderate risk. There is consensus that chronic (preexisting) hypertension, previous preeclampsia, autoimmune disease/antiphospholipid antibodies, chronic kidney disease, and preexisting diabetes mellitus all confer high risk for preeclampsia, increasing the relative risk of developing preeclampsia two to four fold.<sup>36</sup>

Moderate risk factors for preeclampsia for which there is consensus across guidelines include vascular disease, thrombophilia, first pregnancy, older age (most often defined as  $\geq$  age 40 years, ACOG

defined as  $\geq 35$  years), multifetal pregnancy and obesity (defined variably across guidelines). Family history of preeclampsia is also commonly cited, reflecting a theory of genetic predisposition, as is interpregnancy interval of greater than 10 years.

Some of the guidelines also include race/ethnicity (Black race in ACOG and SOGC guidelines), low socioeconomic status, increased triglycerides pre-pregnancy, family history of early onset of cardiovascular disease, cocaine or methamphetamine use, interpregnancy interval less than 2 years, assisted reproductive technology, excessive weight gain and infections such as urinary tract infection or periodontal infection. If multiple moderate risk factors are present, they should be considered in planning for maternal monitoring and proteinuria testing.

SOGC and NICE guidelines cite fair evidence that women with onset of gestational hypertension prior to 34 weeks gestation are more likely to develop preeclampsia than women with later onset hypertension, and that these women have an increased risk of complications such as IUGR. This evidence is consistent with the distinction between early and late presenting disease that has been recently considered.

There are several investigational laboratory markers for risk of preeclampsia, such as leptin, placental growth factor and plasminogen activator inhibitor, which have not been shown individually to have sufficient predictive value to be clinically useful.

#### *b. Assessment for presence/absence of preeclampsia*

*All women diagnosed with hypertension in pregnancy should be assessed for the presence or absence of preeclampsia. Women with high risk for preeclampsia should have more definitive evaluation of proteinuria than women at low risk, and high-risk women should be evaluated for preeclampsia through other clinical and laboratory evaluations.*

All women diagnosed with hypertension in pregnancy should be assessed for the presence or absence of preeclampsia. Many women with HDP will develop preeclampsia, and the JNC report notes that up to 25% of women with chronic (preexisting) hypertension will develop preeclampsia. Women with severe hypertension should be carefully monitored for the development of preeclampsia. Women with high risk for preeclampsia should have more definitive evaluation of proteinuria than women at low risk, and high-risk women should also be evaluated for preeclampsia through other clinical and laboratory evaluations as discussed below.

#### *c. Assessment of proteinuria*

*Proteinuria testing is a priority area for the identification and management of HDP. All women should have standard dipstick screening for proteinuria at each prenatal visit. Women diagnosed with hypertension in pregnancy and other women at high risk for preeclampsia should have more definitive evaluation of proteinuria than women at low risk, with either 24-hour urine collection for protein or spot urinary protein: creatinine ratio to quantify the amount of proteinuria.*

Though it is widely accepted that all pregnant women should be assessed for proteinuria, the current evidence for recommending specific measurement methods and thresholds to identify women at risk



for complications is of poor quality. For low-risk women with low suspicion of preeclampsia, standard dipstick screening is logistically easy and inexpensive. Automated reagent-strip reading devices can enhance the performance of dipstick screening, and several studies have noted superior sensitivity and specificity of automated reagent-strip reading devices relative to visual strip readings.<sup>37</sup> If a screening standard dipstick reading is 1+ or more, further testing for proteinuria should be undertaken, since a standard dipstick reading of 1+ is correlated with 0.3 g or more in a 24 hour urine but requires confirmation.<sup>38</sup> Further testing for a positive screening result should be conducted and could include a spot urinary protein: creatinine ratio or 24-hour urine collection to quantify the amount of proteinuria.

All women diagnosed with hypertension in pregnancy should be assessed for the presence or absence of preeclampsia, including definitive assessment for proteinuria. Women with risk factors for preeclampsia should also undergo definitive testing for proteinuria, since the usefulness of dipstick screening in women with hypertension or other increased risk for preeclampsia is unclear from current evidence.<sup>39</sup> There is good evidence to recommend more definitive testing with either a spot urinary protein: creatinine ratio or 24-hour urine collection if there is a suspicion of preeclampsia, although there is no definitive evidence for which method is best to identify women at risk for complications. The ACOG practice bulletin Chronic Hypertension in Pregnancy identifies the 24-hour urine collection as the preferred method for quantifying proteinuria. While a 24-hour urine collection for protein is often the gold standard to which other tests are compared, samples are often incomplete and logistically difficult to collect. SOGC guidelines note that the National Kidney Foundation favors spot urine samples over 24-hour urine collections for quantifying proteinuria due to these logistical issues. If a 24-hour urine collection is the testing method chosen, a recognized method of evaluating completeness of the sample should be used. To verify appropriate collection, ACOG recommends that measurement of creatinine is included to ensure excretion is in the range of 10-15 mg/kg. SOGC guidelines note that the use of urinary albumin: creatinine ratio (ACR) to identify significant proteinuria in assessing for preeclampsia has been reported, but that more information is needed regarding the clinical use of ACR in this context. Morris et al. also concluded in a systematic review that there was insufficient evidence available regarding the diagnostic use of ACR in suspected preeclampsia; meta-analysis of ACR was not possible in this review due to differing thresholds and characteristics across studies.<sup>40</sup>

Significant proteinuria for the identification of preeclampsia is defined across guidelines as greater than or equal to 300 mg of protein in a 24 hour urine collection. The ACOG practice bulletin regarding chronic hypertension notes that although protein: creatinine ratios of .15 to .3 have been used to identify women who should be evaluated with a 24 hour urine for proteinuria, there is no consensus for the best cutoff value.

Standards have been established by the National Kidney Foundation KDOQI guidelines such that albuminuria in women is defined as urinary albumin excretion >300 mg/day or >355 mg/g creatinine. Microalbuminuria, 30-300 mg albumin/day or ACR of 30-300 mg albumin/g creatinine (American Diabetes Association cutoff), is also a known marker of incipient renal disease.<sup>41</sup> Evidence for the use of albumin: creatinine ratio in identifying preeclampsia has been limited, and different thresholds have been used across studies.<sup>42</sup> SOGC guidelines cite insufficient evidence for a specific recommendation regarding the clinical use of urinary ACR in the identification of preeclampsia.

#### *d. Other assessments of women at risk for preeclampsia*

*Baseline renal function assessment, including serum creatinine, blood urea nitrogen and 24-hour urinary protein or spot urine for protein: creatinine ratio, is recommended for all pregnant women with chronic (preexisting) hypertension. Most guidelines recommend additional laboratory testing for women at risk for preeclampsia, including but not limited to complete blood count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), bilirubin and serum uric acid. Uterine Doppler velocimetry is not recommended in the assessment of women at low risk for preeclampsia.*

In addition to specific testing for proteinuria, SOGC and SOMANZ guidelines recommend that women with risk factors should receive a stratified clinical and lab evaluation work-up beyond routine baseline antenatal lab tests; this recommendation is based on fair evidence. Such testing for women at risk would include complete blood count and differential, blood film, platelet count, coagulation studies, serum creatinine, glucose, liver enzymes, and serum albumin. SOGC guidelines include uric acid in testing for women at risk due to a reported association of elevated uric acid and perinatal complications. The ACOG practice bulletin Chronic Hypertension in Pregnancy notes that serum uric acid may be helpful in diagnosing superimposed preeclampsia.

The ACOG practice bulletin Chronic Hypertension in Pregnancy recommends evaluation for end-organ damage in women with chronic (preexisting) hypertension, based on consensus and expert opinion, since women with end-organ damage are at increased risk for adverse outcomes. Evaluation depends on severity, but could include assessment of renal function, electrocardiography and ophthalmologic evaluation. ACOG recommends baseline renal assessment for all pregnant women with chronic (preexisting) hypertension, including serum creatinine, blood urea nitrogen, creatinine clearance and 24-hour urinary protein or spot urine for protein: creatinine ratio.

ACOG and SOGC guidelines recommend consideration of an evaluation of secondary causes in women with chronic (preexisting) hypertension, with only a basic workup for secondary causes if suspicion is low. The ACOG practice bulletin for chronic hypertension notes that while many women with chronic (preexisting) hypertension have previously been under care for their hypertension, young women who are first diagnosed with severe hypertension early in pregnancy are candidates for evaluation of secondary causes of hypertension, since they are among those more likely to have secondary hypertension. ACOG notes that consultation with maternal-fetal medicine or a medical subspecialist should be sought when secondary causes of hypertension are being evaluated. Renal artery stenosis should be considered, as it would be the most likely secondary cause of hypertension, and testing could include renal artery velocimetry or magnetic resonance angiography, which is noted in the ACOG practice bulletin.

Both ACOG and SOGC note that though pheochromocytoma is rare, it is associated with high morbidity and mortality in pregnancy, and recommend catecholamine testing if there is a concern.<sup>43</sup> SOGC guidelines also recommend considering additional baseline testing for women with conditions that may make later lab investigation difficult to interpret. Such testing could include liver function testing for obese women, who may have associated non-alcoholic steatohepatitis.

Uterine artery Doppler velocimetry has not proved to be useful for screening women who are at low risk for preeclampsia. Initial screening of women with chronic (preexisting) hypertension with uterine artery Doppler velocimetry would not alter decision making regarding prophylactic aspirin therapy, which would be recommended regardless of findings. However, SOGC guidelines note that uterine artery Doppler velocimetry may be useful among hypertensive women to support a placental origin for hypertension, proteinuria and/or adverse conditions.

#### *e. Fetal testing for women at risk for preeclampsia*

*ACOG-AAP perinatal guidelines recommend initiating fetal tests of well being for women with major risk factors for preeclampsia, including antiphospholipid syndrome, systemic lupus erythematosus, chronic kidney disease, preexisting insulin dependent diabetes mellitus, and multiple gestation. There is no clear evidence for the timing, nature and frequency of fetal testing for these women.*

Maternal and fetal assessment for prognosis or surveillance of women with HDP is described below in section 7, Ambulatory Care of HDP.

## **6. Risk reduction for preeclampsia and other complications of HDP**

### *a. Aspirin*

*Women at high risk for preeclampsia should receive low-dose aspirin at 81 mg/day. There is strong evidence of reduced risk of preeclampsia and its complications in women who are at high risk for preeclampsia, including women with preeclampsia during a prior pregnancy, chronic kidney disease, autoimmune disorder/antiphospholipid antibodies, preexisting type 1 or type 2 diabetes or chronic (preexisting) hypertension. More evidence is needed to ascertain the benefit of low-dose aspirin therapy for women with other risk factors for preeclampsia, although risk is increased if more than one risk factor is present. Aspirin (ASA) prophylaxis is not recommended for women who are at low risk for preeclampsia, including low-risk nulliparous women, as there is no evidence for the benefit of ASA in reducing preeclampsia risk in low-risk women. There is expert consensus that aspirin therapy should begin as early as possible for maximal benefit and should continue to delivery, supported by evidence that has shown that the most benefit in risk reduction may be achieved if aspirin therapy is begun before 16 weeks gestation.*

There is general consensus across guidelines that women at risk for preeclampsia should receive low-dose aspirin (ASA). Low-dose aspirin has been most extensively studied in women with high-risk factors including multifetal pregnancy, chronic (preexisting) hypertension and/or previous preeclampsia. Most guidelines, including those of the World Health Organization (WHO), recommend low-dose aspirin for women at high risk for preeclampsia based on strong evidence of reduced risk of preeclampsia and its complications in women at high risk.<sup>44</sup> Women at high risk for preeclampsia include women with HDP during a prior pregnancy, chronic kidney disease, autoimmune disorder, preexisting type 1 or type 2 diabetes or chronic (preexisting) hypertension. More evidence is needed to ascertain the benefit of low-dose aspirin therapy for women with

moderate risk factors for preeclampsia. There is no clear evidence to differentiate among individual moderate risk factors, but a higher risk for preeclampsia is associated with the presence of more than one moderate risk factor. SOGC guidelines recommend low-dose aspirin for women with one high-risk factor or more than one moderate risk factor. Low-dose aspirin is commonly defined as 75 mg/day. Although a range of aspirin dosages from 50-150mg/day has been investigated, there is no clear evidence for a dosage cutoff or evidence to recommend higher dosages. Given available preparations, low-dose aspirin in high-risk women should be administered at a dosage of 81 mg/day. Enteric coated aspirin should be avoided.

There is expert consensus that aspirin therapy should begin as early as possible for maximal benefit and should continue to delivery, supported by evidence that has shown the most benefit in risk reduction may be achieved if aspirin therapy is begun before 16 weeks gestation. The WHO recommends initiation prior to 20 weeks gestation. There is good evidence to support continuing aspirin therapy to delivery, and no reported increased bleeding complications with therapy. SOGC guidelines cite fair evidence from randomized controlled trials to recommend administration of aspirin prophylaxis at bedtime.

#### *b. Other pharmaceuticals*

*There is no evidence to recommend pharmaceuticals other than low-dose aspirin in the prevention of preeclampsia or its complications.*

Other than low-dose aspirin, there are no pharmaceuticals recommended in current guidelines for the prevention of preeclampsia or its complications. Antihypertensive therapy specifically to prevent preeclampsia is not recommended.

There is limited evidence regarding the benefit of low-molecular-weight heparin (LMWH), and there is insufficient evidence to recommend it for preventing preeclampsia, even among women with thrombophilia or previous preeclampsia. Other pharmaceutical agents for which evidence is limited include nitric oxide donors, diuretics and progesterone; none of these are recommended in guidelines, and diuretics are specifically not recommended in WHO guidelines for the prevention of preeclampsia or its complications.

#### *c. Dietary calcium supplementation*

*Adequate calcium intake (1300 mg/day for women age 14-18 and 1000 mg/day for women over age 18) is necessary for maternal health, and women with low dietary intake of calcium should receive calcium supplementation. There is no clear evidence for the benefit of calcium for the reduction of the risk of preeclampsia in the general US population. There is no evidence to support recommending other supplements for the prevention of preeclampsia.*

Many supplements that have been investigated for potential benefit in decreasing the risk of hypertensive disorders of pregnancy are known to be of general benefit in pregnancy. Though calcium may be of general benefit for pregnant women, evidence has been mixed regarding the benefit of calcium supplementation for reducing the risk of preeclampsia. Calcium in the prevention of

preeclampsia has been identified as a key area for research in NICE guidelines, since current evidence is lacking due to variability in study populations. The greatest effect of calcium supplementation has been shown in high-risk women with poor intake, and has included a small decrease in the incidence of preeclampsia, and also a decrease in maternal death and serious morbidity.<sup>45</sup>

While ACOG guidelines published in 2002 indicate that there is no evidence for the benefit of calcium for the reduction of the risk of preeclampsia, the more recent SOGC and SOMANZ guidelines recommend calcium supplementation for women at risk who have low dietary calcium intake. Recommendations are based on randomized, controlled trials and include at least 1g/d supplementation orally for women with low dietary intake of calcium, defined as  $\leq 600$  mg/d). WHO guidelines recommend supplementation with 1.5-2 grams elemental calcium per day for pregnant women, particularly those at high risk for preeclampsia, in areas where dietary calcium intake is low.

#### *d. Other dietary supplements*

*There is no evidence to support recommending supplements other than calcium for the prevention of preeclampsia.*

There is no evidence for the benefit of magnesium in the prevention of preeclampsia, and it is not recommended for this purpose. Other supplements that are specifically not recommended based on strong evidence include vitamin C and E, and prostaglandin precursors such as fish oils or algal oils. Although Vitamins C and E had previously shown promise, as noted in the ACOG preeclampsia practice bulletin, there is now good quality evidence that Vitamin C and E have no effect on prevention of preeclampsia, and indeed some adverse effects have been noted; therefore, Vitamin C and E are not recommended for the prevention of preeclampsia. There is insufficient evidence to recommend garlic, zinc, pyridoxine or selenium. WHO guidelines do not recommend Vitamin D supplementation for the prevention of preeclampsia and its complications.

Although of general periconceptual benefit in the prevention of neural tube and other anomalies, there is poor evidence for the use of folic acid in the prevention of HDP.

#### *e. Anticipatory guidance*

*Pregnant women at risk for preeclampsia should be provided with anticipatory guidance regarding symptoms of preeclampsia to be reported to the physician, midwife, nurse practitioner or physician assistant.*

Only NICE guidelines include a recommendation to provide anticipatory guidance relating to symptoms of preeclampsia, including severe headache, vision problems (blurring, flashing) and severe pain below the ribs. While not explicit in other guidelines, identification of the signs and symptoms to be reported to the physician or midwife is an essential part of patient education in general. It is important that women at risk for preeclampsia be alerted to symptoms of preeclampsia and advised when to contact their health care provider.

## *f. Diet/lifestyle*

*A healthy lifestyle is generally recommended for pregnant women, including moderate exercise.*

*Appropriate weight gain based on pre-pregnancy BMI as per Institute of Medicine (IOM) guidelines is recommended.*

A healthy lifestyle is generally recommended for pregnant women and is important for a woman's long term health. ACOG-AAP guidelines recommend providing all pregnant women with information regarding balanced nutrition for maternal and infant health, and ACOG-AAP guidelines recommend nutrition consultation for obese women. Calorie restriction during pregnancy for overweight or obese women is not recommended, as it has not been associated with a decreased incidence of preeclampsia or gestational hypertension, and there are concerns that calorie restriction may contribute to starvation ketosis in the fetus and resultant neurodevelopmental problems.

There is consensus across guidelines that salt restriction is not recommended solely to prevent gestational hypertension or preeclampsia, since there is no clear evidence to support its effectiveness in high-risk women.<sup>46,47</sup> There is good evidence against recommending dietary salt restriction in low-risk women. A reexamination of the Institute of Medicine guidelines for weight gain during pregnancy published in 2009 established a range of appropriate weight gain based on pre-pregnancy Body Mass Index (BMI), and includes a relatively narrow range of weight gain for obese women.<sup>48</sup> The IOM noted that women whose weight gain exceeds recommended ranges may have an increased risk of gestational hypertension and preeclampsia, but the evidence is limited and of fair to poor quality. Therefore, associations of these conditions and gestational weight gain are not clear. The alterations in the normal maternal plasma volume expansion and vascular permeability seen in preeclampsia confound the monitoring of weight gain in women with preeclampsia.

Advice on rest, exercise and work for women at risk for preeclampsia is the same as the advice generally given for healthy pregnant women; moderate exercise is recommended. There are observational studies suggesting there may be an association between exercise and reduced preeclampsia risk in low-risk women, but no specific evidence to recommend exercise to low-risk women to prevent preeclampsia. However, low to moderate intensity exercise is of benefit for general health. The 2002 ACOG Committee Opinion on exercise during pregnancy identifies preeclampsia and gestational hypertension as absolute contraindications to aerobic exercise in pregnancy and poorly controlled chronic (preexisting) hypertension as a relative contraindication to aerobic exercise in pregnancy.<sup>49</sup> SOGC guidelines cite insufficient evidence for exercise in high-risk women.

There is insufficient evidence to recommend rest for women at risk for preeclampsia. SOGC guidelines cite conflicting evidence for increased rest at home in the third trimester for women at risk. WHO guidelines do not recommend rest at home for the prevention of preeclampsia in women at risk. Other lifestyle factors that have been investigated for the prevention of HDP, such as abstention from alcohol and tobacco, do not have specific evidence for a reduction of the risk of preeclampsia but have other known benefits in pregnancy.

### *g. Referrals for at risk*

There is no clear evidence for the benefit of specialty referrals for women at risk for preeclampsia. ACOG-AAP guidelines recommend consultation with a maternal- fetal medicine subspecialist based on underlying comorbidities that are risk factors for preeclampsia, specifically chronic (preexisting) hypertension with renal or heart disease and chronic renal disease with serum creatinine level of  $\geq 3$  mg/dL with or without hypertension. OB consultation is recommended in ACOG-AAP guidelines for women with diastolic blood pressures  $> 90$ mmHg, chronic (preexisting) hypertension without renal or heart disease and chronic renal disease with serum creatinine  $< 3$  mg/dL. SOGC guidelines recommend offering OB consultation for women with risk markers for preeclampsia.

## **7. Ambulatory care of HDP**

### *a. Preconception/initial visit counseling and evaluation*

*Women with chronic (preexisting) hypertension should be provided with preconception counseling, including counseling regarding treatment strategies, medication risks and alternatives for those planning pregnancy. Renin-angiotensin-aldosterone system (RAAS) inhibitor drugs, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are contraindicated in all trimesters of pregnancy. Women should be changed from RAAS inhibitor drugs to alternative therapy upon discovery of intrauterine pregnancy. For women planning pregnancy, RAAS drugs should be discontinued if an effective alternative exists. Women with HDP should be provided with education regarding their condition and self-management.*

There is consensus across guidelines that preconception counseling should be provided to women with chronic (preexisting) hypertension, including counseling regarding treatment strategies, medication risks and alternatives for those planning pregnancy. There is only limited evidence for most antihypertensive agents in pregnancy. There has been uniform agreement across guidelines that women should be advised of an increased risk of congenital abnormality with use of drugs that act on the renin-angiotensin-aldosterone system (RAAS) during pregnancy, and alternative therapy should be initiated for pregnant women who are taking RAAS drugs. These drugs include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and direct renin inhibitors. The ACOG practice bulletin *Chronic Hypertension in Pregnancy* includes a level A recommendation that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are contraindicated in all trimesters of pregnancy. This recommendation is based on evidence of an association of ACE/ARB therapy with teratogenic effects. This association was further explored by Li *et al.* in a 2011 population-based study of ACE inhibitor use in the first trimester of pregnancy and the risk of malformation.<sup>50</sup> This study revealed that there was an increased risk of congenital heart defects in offspring of women with hypertension treated with ACE inhibitors in the first trimester compared to normals (the control group had neither hypertension or use of ACE inhibitor). However, this risk did not differ from the risk for women with hypertension and no antihypertensive therapy or the risk for women using other antihypertensives in the first trimester.

The authors concluded that the risk for malformation was likely due to the underlying hypertensive condition rather than ACE inhibitor therapy in the first trimester. This finding provides some reassurance for women who become pregnant while taking ACE inhibitors. This study did not address ACE inhibitor use in the second and third trimesters, for which a category D (known fetal risk) classification from the US Food and Drug Administration has previously been assigned. The FDA currently notes that when used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus, and that when pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible. Therefore, since there is some evidence that there may be no added risk from RAAS inhibitors during the first trimester of pregnancy, but risk is clearly present in the second and third trimesters, women should be changed from RAAS inhibitors to alternative therapy upon discovery of intrauterine pregnancy.

The ACOG practice bulletin for chronic hypertension notes consensus and expert opinion that women with chronic (preexisting) hypertension should be evaluated for end-organ damage, which increases the risk of adverse outcomes, and possible secondary causes for hypertension, ideally before conception. The JNC report and SOGC guidelines also recommend a preconception evaluation for possible secondary causes of hypertension and for end-organ dysfunction for women with chronic (preexisting) hypertension. The ACOG *Chronic Hypertension in Pregnancy* practice bulletin notes that renal artery stenosis should be considered in women younger than 30 years with severe hypertension who have not been previously evaluated, especially if there is no family history of hypertension. The JNC notes the high morbidity and mortality of pheochromocytoma if not diagnosed antepartum, and the need to evaluate those women for whom suspicion is high. ACOG recommends evaluation for pheochromocytoma for women with paroxysmal hypertension, frequent hypertensive crises, seizure disorders, anxiety attacks, palpitations or headaches.

Women with HDP should be educated about their condition, including self management and signs or symptoms of concern. It is important to note that ACOG recommends that all health encounters during a woman's reproductive years, particularly those that are a part of preconception care, should include counseling on appropriate health behaviors to optimize pregnancy outcomes.

#### **b. Diet**

*Appropriate weight gain according to Institute of Medicine (IOM) guidelines is recommended. There is insufficient evidence regarding salt restriction in women with chronic (preexisting) hypertension.*

Appropriate weight gain for healthy pregnancy outcomes has been defined by the Institute of Medicine (IOM). Dietary salt restriction is not recommended for gestational hypertension, and there is insufficient evidence to recommend dietary salt restriction for women with chronic (preexisting) hypertension. However, the JNC notes that despite sparse data, many experts advise salt restriction to 2.4g sodium daily for women with chronic (preexisting) hypertension as is recommended for primary hypertension in the general population, and NICE guidelines also base recommendations on general adult hypertension guidance. Salt restriction has a variable effect on blood pressure among individuals. Women with chronic (preexisting) hypertension who are on a DASH (Dietary Approaches to Stop Hypertension) diet are advised to continue it in SOGC guidelines, although there is no definitive evidence to support this recommendation.



Weight reduction and calorie restriction are not generally recommended for overweight and obese women with HDP.

### *c. Lifestyle*

*A healthy lifestyle is recommended for women with HDP. Moderate exercise is often part of the care plan for women with well-controlled chronic (preexisting) hypertension. There is insufficient evidence for a recommendation regarding optimal activity levels for women newly diagnosed with gestational hypertension. Aerobic exercise is not recommended for women with preeclampsia.*

Physical activity is part of a healthy lifestyle and there is insufficient evidence to recommend rest or activity limitation for women with HDP. However, the 2002 ACOG Committee Opinion on exercise during pregnancy recommends restricting aerobic exercise in women who develop preeclampsia or gestational hypertension, and the JNC for women with chronic (preexisting) hypertension, based on theoretical concerns regarding its potentially negative impact on placental blood flow and consequent increased risk of preeclampsia.

The JNC notes that it is particularly important to strongly discourage the use of alcohol and tobacco by women with HDP.

### *d. Blood pressure threshold and targets for treatment*

#### **i. Non-severe hypertension**

*Non-severe hypertension: There is no definitive evidence for optimal blood pressure targets in hypertensive disorders in pregnancy; there is a particular lack of clear evidence regarding the optimal management of women with non-severe hypertension. Some experts in the U.S., including the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in their Seventh Report, have recommended treating women with chronic (preexisting) hypertension and no evidence of end-organ damage whose blood pressure is 150-160 mmHg systolic or 100-110 mmHg diastolic.*

The goal of blood pressure management in hypertensive disorders in pregnancy is to optimize pregnancy outcome, which requires consideration of minimizing maternal risk while maintaining placental/fetal perfusion. Intervention decisions for abnormal blood pressure readings are dependent on consideration of gestational age. There is no definitive evidence for optimal blood pressure targets in hypertensive disorders in pregnancy; there is a particular lack of clarity regarding the optimal management of women with non-severe hypertension (systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-109 mmHg). There is some evidence that implementing antihypertensive therapy for non-severe hypertension may decrease the relative risk of maternal severe hypertension, but there is no evidence for a positive impact on adverse maternal or perinatal outcomes such as stroke, preterm birth or perinatal death. Furthermore, there is some evidence to suggest that antihypertensive therapy for non-severe hypertension and the resultant decrease in blood pressure therapy may cause some harm, such as an increased risk of small for gestational age or low birthweight births.<sup>51</sup>

The threshold for administering antihypertensive therapy for women with non-severe chronic (preexisting) hypertension is not clear from existing evidence, and it is generally acknowledged that more evidence is needed. There is limited, good quality evidence against treating mild or moderate hypertension. There is insufficient evidence regarding the benefit of pharmacological treatment of non-severe chronic (preexisting) hypertension in the prevention of maternal stroke or other maternal morbidity or in the prevention of adverse neonatal outcomes. The JNC report cites evidence that there is a linear relationship between the fall in blood pressure induced by treatment and an increase in the proportion of small for gestational age (SGA) births in women with chronic (preexisting) hypertension. The JNC notes that women with Stage 1 blood pressure (140-159/90-99 mmHg) are at low risk for developing cardiovascular complications during pregnancy and are candidates for lifestyle modification rather than antihypertensive therapy. This recommendation is supported by the fact that blood pressure usually falls during the first half of pregnancy, which may facilitate control with reduced or no medication; this observation is also cited in SOGC guidelines. Further, JNC guidelines cite the lack of evidence of improved neonatal outcomes with pharmacological treatment. The ACOG practice bulletin for chronic (preexisting) hypertension in pregnancy suggests that it is reasonable to withhold antihypertensive therapy, and stop or reduce medication for those women already taking antihypertensive therapy, if blood pressure is less than 150/100 mmHg, and there are no complicating factors such as cardiovascular or renal disease. For women with target organ damage or who required multiple antihypertensive agents for blood pressure control prior to pregnancy, the JNC recommends continuing antihypertensive medication to maintain blood pressure control.

The JNC report advocates reinstating antihypertensive therapy for any woman with chronic (preexisting) hypertension when blood pressure reaches systolic readings of 150-160 mmHg or diastolic of 100-110 mmHg.<sup>52</sup> The recommendation for instituting treatment at this threshold is geared toward preventing severe hypertension during pregnancy, since there are reports of high rates of fetal loss and maternal mortality among women with severe chronic (preexisting) hypertension in the first trimester. This threshold for treatment is also cited by NICE guidelines for both chronic (preexisting) and gestational hypertension. ACOG stresses that women with severe chronic (preexisting) hypertension (systolic blood pressure 160 mmHg or greater or diastolic blood pressure 110 mmHg or greater) should have antihypertensive therapy initiated or continued to reduce the risk of maternal stroke.

There is lack of clarity in the literature regarding optimal targets for blood pressure control if treatment is instituted. Based on expert consensus, SOGC guidelines cite a blood pressure target of 130-155/80-105 mmHg for both chronic (preexisting) and gestational hypertension if there are no comorbid conditions, although noting that it is not critical to maintain normal blood pressure over the few months that compromise the duration of pregnancy. NICE guidelines cite a target of less than 150/100 mmHg. Both NICE and SOGC guidelines identify a lower limit of diastolic blood pressure of 80 mmHg for any woman being treated for hypertension, based on a concern that controlling blood pressure to lower levels will limit uteroplacental perfusion. For women with chronic (preexisting) hypertension with target organ damage, such as renal disease, SOGC guidelines recommend tighter control, with a target of blood pressure 130-139/80-89 mmHg based on expert consensus. For women with gestational hypertension and comorbid

conditions that increase cardiovascular risk, tighter control is controversial due to the known risk of IUGR; however, SOGC guidelines cite the same target for these women of 130-139/80-89 mmHg. Referenced comorbid conditions include those for which there is a compelling reason for more aggressive therapy beyond improving short term pregnancy outcomes, such as major cardiovascular risk factors including preexisting diabetes, vascular disease or renal disease. A 2011 Cochrane review of two small randomized controlled trials revealed that there was no difference in the incidence of severe preeclampsia between groups of women with low-risk gestational or chronic (preexisting) hypertension whose blood pressure was tightly controlled (blood pressure < 140 mmHg systolic and < 90 mmHg diastolic) compared to those whose blood pressure was very tightly controlled (blood pressure ≤ 130mmHg systolic and ≤ 80mmHg diastolic), and no difference in perinatal deaths or other fetal adverse outcomes. However, there were no cases of stroke, eclampsia or maternal deaths in these studies.<sup>53</sup> For women with non-severe hypertension and preeclampsia, SOGC guidelines do not specify targets, noting that consideration must be given to maternal and fetal clinical conditions.

## **ii. Severe hypertension**

*Acute management should be initiated for severe hypertension, defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 110 mmHg or both.*

There is consensus across guidelines for the need to acutely manage severe hypertension, defined as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mmHg or both, with the goal of preventing maternal stroke and avoiding intrauterine growth restriction (IUGR). The ACOG Committee Opinion on therapy for acute, severe hypertension notes that acute onset of persistent, severe systolic or diastolic hypertension in pregnant or postpartum women with preeclampsia or eclampsia constitutes a hypertensive emergency.<sup>54</sup> Women presenting with acute onset, severe hypertension in an office setting should be rapidly referred to a hospital setting for treatment. The JNC report notes that it is important to treat severe chronic (preexisting) hypertension in the first trimester since there are high rates of fetal loss and risk of maternal mortality in these patients.<sup>55</sup>

There is a lack of clear evidence regarding the goals of therapy in acute hypertension management. Targets for acute management across guidelines include lowering blood pressure to less than severe levels (less than 160/110 mmHg), with caution to avoid a precipitous or extreme drop in blood pressure. The ACOG Committee Opinion on therapy for acute, severe hypertension recommends a blood pressure control goal of 140-160/90-100 mmHg to avoid prolonged exposure to severe systolic hypertension and loss of maternal cerebral vascular autoregulation. The target for severe hypertension cited by NICE guidelines, < 150/100 mmHg but not lower than 80 mmHg diastolic, does not differ from the NICE target for non-severe hypertension.

## **e. Antihypertensive agents for non-acute blood pressure management**

*In the absence of contraindications, labetalol is preferred for management of hypertension in pregnancy. If labetalol is contraindicated, extended-release nifedipine is commonly used in pregnant women with chronic (preexisting) hypertension. Methyl dopa has also been used in HDP. Women with chronic*

*(preexisting) hypertension who are well controlled on diuretics prior to pregnancy do not need to have the diuretic discontinued during pregnancy. Atenolol is not recommended for use during pregnancy due to association with IUGR. Discussion with Maternal Fetal Medicine regarding optimal blood pressure management for women with chronic (preexisting) hypertension may be helpful.*

There is insufficient evidence to identify a single preferred agent for non-acute blood pressure management. However, there is consistency across guidelines regarding the acceptability of oral labetalol, nifedipine and methyldopa for non-acute treatment of hypertension in pregnancy, based on good quality evidence. Labetalol, a combined  $\alpha$  and  $\beta$  receptor blocker, and methyldopa, a centrally acting  $\alpha$  agonist, are most frequently cited as preferred agents. However, labetalol is preferred due to fewer adverse effects than methyldopa, and is recommended by ACOG as a good option for first line treatment of chronic (preexisting) hypertension in pregnancy. ACOG and the JNC cite reports of stable uteroplacental flow and fetal hemodynamics, as well as an absence of reports of long term adverse developmental effects in children, as reasons that methyldopa is preferred by many clinicians. However, the use of methyldopa has been associated with serious adverse effects, including hepatitis, hemolytic anemia, depression, central nervous system sedation and a lupus-like syndrome.<sup>56</sup> Oral labetalol is considered first line by NICE, with a recommendation to consider alternatives methyldopa and nifedipine only after considering maternal, fetal and neonatal side effect profiles.

RAAS active drugs, including ACE inhibitors, ARB and renin inhibitors, have been associated with fetal abnormalities, although the evidence is of poor quality. All guidelines recommend discontinuing these agents and not initiating them during pregnancy.

SOGC guidelines cite the acceptability of the beta blockers acebutolol, metoprolol, pindolol and propranolol, while SOMANZ guidelines note the possible association of IUGR with highly selective beta blockers. Atenolol has been associated with low birth weight when used from early pregnancy, and it is not recommended for use during pregnancy. A possible association of metoprolol and IUGR has also been reported, and metoprolol may also exacerbate asthma.<sup>57</sup>

The evidence for long acting calcium channel blockers is more limited than the evidence for labetalol, but they appear to be safe.<sup>58</sup> Nifedipine has been the most commonly studied. ACOG notes a theoretical concern regarding potential synergy between magnesium and other calcium channel blockers with resultant severe hypotension. SOGC guidelines recommend that prazosin not be used based on an association with stillbirth in one trial. Some of the reviewed guidelines recommend against using diuretics, due to their contribution to a restriction of the normal plasma volume expansion of pregnancy; ACOG and the JNC report note that they are not first line agents but probably safe. Other possible adverse effects of thiazide diuretics include hypokalemia and carbohydrate intolerance. The ACOG practice bulletin for chronic (preexisting) hypertension lists hydrochlorothiazide, as well as hydralazine, as adjunctive agents among oral antihypertensives used commonly in pregnancy. A summary of standard and maximum dose ranges of common agents is noted below.

## Commonly used antihypertensive agents for non-acute management of chronic (preexisting) hypertension in pregnancy\*

Agent	Dosage range	Caution/comment
Labetalol	Standard dose: 200-800 mg orally per day in 2-3 divided doses  Maximum dosage: 2,400 mg per day	Should be avoided in women with cardiac conduction abnormalities, systolic heart failure or asthma.
Nifedipine (extended-release)	Standard dose: 30-60 mg orally per day Maximum dosage: 120 mg per day	Ensure correct form of nifedipine prescribed; <b>short acting nifedipine is not recommended due to the risk of hypotension.</b> There is concern for severe hypotension if nifedipine is continued with intravenous magnesium.
Methyldopa	Standard dose: 250-1000 mg orally per day in 2-3 divided doses  Maximum dosage: 3000 mg per day	Associated with hepatitis, hemolytic anemia, depression, and sedation.

\*Modified from American Congress of Obstetricians and Gynecologists. *Chronic hypertension in Pregnancy. Practice Bulletin number 125. Obstetrics and Gynecology 2012; 119 (2 Part 1): 396-407.*

Acute management of severe hypertension is addressed below in section 8, Inpatient prenatal care of HDP.

### *f. Maternal surveillance: blood pressure monitoring*

*Although there is no definitive evidence, the use of daily home monitoring should be individualized and is encouraged, and the use of home monitoring can lead to improved self-management for women with HDP.*

Optimal maternal monitoring frequency is not clearly defined, but the JNC report notes that close clinical and lab monitoring of women with hypertension is essential to ensure early identification of preeclampsia. As noted in SOMANZ guidelines, increased vigilance for accelerated hypertension, preeclampsia, growth restriction, abruption, preterm labor and stillbirth is necessary in the third trimester. Guidelines are consistent in noting that the routine antenatal visit schedule is not adequate for women with chronic (preexisting) hypertension, and that additional visits should be scheduled based on individual need. Close monitoring is essential for women with gestational hypertension as well, since many will develop proteinuria (preeclampsia). NICE guidelines recommend monitoring of blood pressure twice weekly for women with moderate hypertension (150-159/100-109 mmHg), women presenting with mild hypertension (140-149/90-99 mmHg) before 32 weeks or women at high risk for preeclampsia. SOGC guidelines also differentiate monitoring recommendations based on gestational age at onset of hypertension, with twice weekly monitoring of women with onset at less than 34 weeks gestation. For women with severe hypertension who have been discharged after blood pressure was effectively controlled in the hospital, SOGC guidelines recommend at least twice weekly monitoring.

The role of home blood pressure monitoring in maternal surveillance for women with HDP is not clearly defined. Studies have shown that women can accurately measure blood pressure at home using automated devices, but results of published observational studies for maternal and perinatal outcomes lack clarity due to differing definitions of associated home care programs and variability of assessments. A Cochrane review of the evidence found no randomized controlled trial evidence to support the use of ambulatory blood pressure monitoring during pregnancy, although noting

that observational studies suggests that it may be of use in assessing blood pressure in pregnancy.<sup>32</sup> In women with HDP, the role of home blood pressure surveillance is unclear. Based on the level of blood pressure control and other comorbid conditions, use of daily home monitoring should be individualized, and may be appropriate for some patients. Monitoring of blood pressure at least twice a week for women with HDP undergoing home blood pressure surveillance should be considered. Daily monitoring may be appropriate for some patients.

#### *g. Maternal surveillance: laboratory testing*

*Women with HDP should have periodic, definitive proteinuria testing (24 hour urine collection or spot urinary protein: creatinine ratio to quantify the amount of proteinuria) as indicated.*

For women with confirmed hypertensive disorders without preeclampsia, definitive proteinuria testing is recommended. SOGC guidelines recommend proteinuria testing using spot urinary protein: creatinine ratio or 24-hour urine collection if there is a suspicion of preeclampsia, including for women who are normotensive with symptoms or signs suggestive of preeclampsia, and for hypertensive pregnant women with a rising blood pressure. Neither SOGC nor ACOG, which recommends periodic testing with spot urine protein: creatinine ratio, cite a specific frequency of proteinuria testing for women with hypertensive disorders. NICE guidelines recommend the use of an automated reagent strip reading device or urinary protein: creatinine ratio twice weekly for women with non-severe hypertension presenting before 32 weeks and other women at high risk of preeclampsia.

In women with confirmed HDP, testing should be conducted for end-organ dysfunction. Other than proteinuria testing, there is insufficient evidence to define which lab assessments are most useful in monitoring women with hypertensive disorders of pregnancy, and the validity of tests alone or in combination has not been reported. There is poor quality evidence regarding the predictive value of specific positive tests, although negative tests can be useful.<sup>33</sup> In addition to routine antenatal lab testing, most guidelines recommend that women with suspected preeclampsia should be evaluated with a complete blood count (hemoglobin, white blood cell count and differential, platelet count, blood film), electrolytes and renal function (serum creatinine), and liver function tests (transaminases, bilirubin). SOGC guidelines also recommend coagulation studies (INR and aPTT, fibrinogen) and serum uric acid, glucose and urinalysis, with additional baseline labs as indicated. ACOG notes that elevated serum uric acid may be particularly useful in distinguishing preeclampsia in women with chronic (preexisting) hypertension who first present late in pregnancy.

SOGC guidelines note that there is no clear evidence to define the frequency of surveillance if preeclampsia is suspected, but cite changes in maternal or fetal clinical status as reasonable indications to repeat tests. NICE guidelines recommend repeat testing if there is ongoing concern, and these guidelines specify weekly testing for women presenting with severe hypertension.

#### *h. Fetal surveillance: tests of fetal well being*

There is no definitive evidence regarding the most appropriate way to conduct fetal surveillance testing for women with HDP. Fetal growth should be assessed with ultrasonography in all women with HDP. Non-stress test, biophysical profile, deepest amniotic fluid pocket assessment and

umbilical artery Doppler velocimetry are commonly used tests, but there is no evidence to determine which test or group of tests is most appropriate for fetal surveillance. Fetal testing should be conducted in the context of a coordinated system, with involvement of obstetricians and maternal-fetal medicine subspecialists based on the patient's degree of control and risk.

ACOG-AAP *Guidelines for Perinatal Care* note the lack of randomized clinical trials regarding the effect of prenatal tests of fetal well being on outcomes. ACOG and other guidelines note that fetal surveillance has become central to the care of high-risk pregnancies, and hypertensive disorders in pregnancy are an indication for initiating tests of fetal well being. Evidence is lacking regarding how to conduct fetal surveillance in women with HDP, such as which tests should be performed and when they should be initiated. ACOG notes that testing should be individualized, and NICE guidelines recommend development of an individual care plan for women with HDP that includes the nature and timing of fetal monitoring. It is essential that fetal testing be conducted in the context of a coordinated system, with involvement of obstetricians and maternal-fetal medicine subspecialists as indicated.

Due to a lack of randomized controlled trials, there is no evidence that any single test of fetal well being is superior to others. Tests are of low specificity, and the meaning of abnormal results at early gestational ages is unclear. Therefore, tests should be corroborated when possible to avoid unnecessary intervention. Commonly recommended tests across guidelines include non-stress test (NST), biophysical profile (BPP) without non-stress test, ultrasound assessment of fetal growth, amniotic fluid assessment (deepest amniotic fluid pocket measurement), and umbilical artery Doppler velocimetry.

NST is the most common antepartum screening test; it is easily performed on an outpatient basis and requires minimal staff. BPP has a lower false positive rate than NST alone, and is supplanting contraction stress test as follow up to a nonreactive NST. BPP includes the individual components of NST, fetal breathing movements, fetal movement, fetal tone, and quantification of amniotic fluid volume. ACOG recommends NST or BPP frequently if IUGR is suspected or for women with preeclampsia. Modified BPP that includes NST and assessment of amniotic fluid depth for oligohydramnios appears to be as predictive as other approaches.<sup>34</sup>

SOGC cites evidence to favor deepest amniotic fluid pocket over amniotic fluid index for assessing amniotic fluid volume. Fetal growth should be monitored with ultrasonography assessments in women with hypertension. Although not a good screening test in the general population, umbilical artery Doppler velocimetry can be used for women at high risk of IUGR in combination with other biophysical tests, and it has been shown to reduce the need for fetal intervention, improve neonatal outcome and predict adverse perinatal outcomes.<sup>35</sup> The ACOG practice bulletin for chronic (preexisting) hypertension indicates that the use of umbilical vessel Doppler velocimetry is appropriate for women with chronic (preexisting) hypertension. For women with early onset preeclampsia, which is thought to be placental mediated, uterine artery Doppler may be particularly useful for predicting complications.<sup>36</sup> There is a lack of evidence for the timing or frequency of umbilical artery Doppler velocimetry, and it is of limited value after 36 weeks gestation.

SOGC guidelines also include fetal movement counts in fetal surveillance. ACOG guidelines indicate that maternal perception of fetal movement may precede fetal demise, but the effect of maternal perception on outcomes is unclear. There is no defined normal cutoff of fetal movement counts, and maternal perception of a relative decrease may be more important.

ACOG notes that the prognosis for survival if action is taken for abnormal results of fetal tests of well-being must be considered in the timing of initiation of testing, as well as severity of maternal disease and risk of fetal death. ACOG recommends initiation of fetal tests of well-being at 32-34 weeks as appropriate for most pregnancies, with initiation at 26-28 weeks for multiple gestation or very high risk conditions. NICE guidelines recommend initiation at 28-30 weeks, or 2 weeks before the gestational age of onset of previous episodes of HDP if earlier.

#### *i. Frequency of fetal testing and monitoring*

*There is no definitive evidence regarding the most appropriate timing of initiation or interval of testing in women with HDP. It is reasonable to initiate fetal testing beginning no later than 32 weeks and to conduct fetal tests of well-being once to twice weekly in women with HDP. Surveillance for fetal growth should be conducted with ultrasonography at least monthly for women with HDP, and ultrasound should be initiated earlier than 32 weeks for fetal indications such as evidence of IUGR or maternal indications such as comorbid conditions, for example, diabetes.*

NICE guidelines recommend repeat fetal testing 4 weeks after initiation. ACOG-AAP guidelines recommend repeating NST, BPP or both weekly through delivery once initiated if results are reassuring and twice weekly for very high-risk women or for changes in maternal condition. The ACOG practice bulletin for chronic hypertension notes that monitoring of women with chronic (preexisting) hypertension may include twice weekly NST or BPP. The recommendation for weekly testing is based on the low likelihood of intrauterine fetal death in the 7 days following a reassuring test in most clinical conditions. However, ACOG-AAP guidelines suggest twice weekly testing may be indicated for high-risk conditions, which include gestational hypertension and IUGR.

#### *j. Referrals/consultations*

*Consultation/referral to an obstetrician/gynecologist is recommended for women with HDP. Maternal-fetal medicine telephone consultation is always available with the regional perinatal center. Consider maternal/neonatal needs and availability of ICU when considering transfer to a regional perinatal center. Control of severe hypertension and seizure prophylaxis must be initiated at the referring hospital prior to maternal transport.*

NICE guidelines recommend a specialist for women with secondary chronic (preexisting) hypertension (by consensus) and assessment by a professional trained in management of HDP for women with preeclampsia. ACOG-AAP guidelines recommend consultation with a maternal-fetal medicine subspecialist for women with chronic (preexisting) hypertension and renal or heart disease, and for severe preeclampsia remote from term. The ACOG practice bulletin Chronic Hypertension in Pregnancy suggests consideration of consultation for women with chronic (preexisting) hypertension and superimposed preeclampsia. Obstetric or maternal fetal medicine consultation/referral for



high-risk hypertensive disorders in pregnancy is encouraged and should be considered. Maternal-fetal medicine telephone consultation is available with the regional perinatal center. ACOG notes that severe preeclampsia remote from term is best managed in a tertiary care setting. Maternal and neonatal needs should be considered when evaluating the need for transfer to a regional perinatal center (RPC), as well as factors such as availability of ICU care.

## 8. Inpatient prenatal care of HDP-severe hypertension and preeclampsia

### *a. Indications for inpatient care*

*Inpatient care is generally recommended for all women with severe hypertension or preeclampsia. Hospitals should have written protocols to identify indications for outpatient care and to outline how home monitoring will be conducted. Patients with HDP being discharged to home should have formal written instructions for how their outpatient monitoring and management will be conducted.*

Inpatient care is recommended for women with identified severe hypertension or preeclampsia across guidelines. ACOG, SOGC and SOMANZ guidelines all advise consideration of the rare home management for non-severe preeclampsia after initial inpatient care, and for women hospitalized for severe hypertension after control of blood pressure if seriously remote from term. NICE guidelines recommend that hospitalization continue for women with severe hypertension until blood pressure is 159/109 mmHg or lower. ACOG guidelines note that after hospitalization and serial assessment of maternal and fetal condition, mild preeclampsia remote from term may be managed with careful home observation, with mild preeclampsia defined as blood pressure less than 160/110 mmHg, proteinuria less than 5g/d, and absence of oliguria or other maternal/fetal symptoms or signs. Home management should include access to health care providers and frequent maternal and fetal evaluation. Women undergoing home observation should be hospitalized if they are noted to have any progression or manifestation of severe disease by lab findings, symptoms or signs, or if they have difficulty with compliance. Hospitals should have written protocols to identify which patients are candidates for home monitoring and to define how home monitoring will be conducted.

ACOG further advises that severe preeclampsia remote from term is best managed in a tertiary care setting or in consultation with an obstetrician trained and experienced in high-risk pregnancies, such as a maternal-fetal medicine subspecialist.

### *b. Critical care*

SOMANZ guidelines recommend admission to critical care for intensive monitoring and management for women with HDP and organ failure, severe pulmonary edema or sepsis, intractable hypertension, anuria or renal failure, repeated seizure, massive blood loss with DIC, neurologic impairment requiring ventilation, or critical abdominal pathology.

### *c. Communications*

*Hospitals should have written protocols for management of HDP that are available to all care team members.*

Clear communication among care team members is essential for optimal, safe and consistent management of women with HDP. SOGC, NICE and SOMANZ guidelines all recommend that facilities develop protocols that can be accessed by all staff to ensure consistent, quality care. Guidelines recommend that facilities have protocols in place that include general management protocols for preeclampsia, protocols for severe hypertension management, and indications for seizure prophylaxis in preeclampsia. SOMANZ guidelines recommend that OB units post protocols for the administration of LMWH when epidural anesthesia or analgesia is administered.

ACOG-AAP guidelines recommend informing the obstetrician, midwife or nurse practitioner of any woman presenting to labor and delivery who is found to have hypertension on initial evaluation. Other communications among team members recommended in guidelines include informing anesthesia when women with preeclampsia are admitted, and discussion among the patient and neonatal, obstetric and anesthesia team members if birth before 34 weeks is considered. Written care plans with parameters for maternal and fetal surveillance and maternal follow-up are advocated in NICE guidelines.

Hospitals should have written protocols that are evidence-based for management of HDP, including protocols for treatment of severe hypertension, eclamptic seizures, fluid management, thromboprophylaxis, and home monitoring. Notification procedures should be part of written protocols, and written plans for discharge should be part of the discharge process.

### *d. Bedrest*

Although JNC guidelines recommend hospitalization for preeclampsia for bedrest, most guidelines recommend against strict bedrest for inpatient care of women with HDP. The role of bedrest in treatment of preeclampsia has been identified as a priority area for research by the SOGC. SOGC and SOMANZ guidelines cite fair evidence against recommending strict bedrest for women with preeclampsia who are hospitalized, with no difference in maternal or perinatal outcomes found compared to some bedrest. SOGC guidelines note insufficient evidence for the usefulness of bedrest in all other women with HDP. NICE guidelines cite one small randomized controlled trial (RCT) that showed no benefit from hospital bedrest for pregnant women with chronic (preexisting) hypertension in reducing the risk of preeclampsia, but NICE and SOGC guidelines suggest that some hospital bedrest may be useful for women with gestational hypertension without preeclampsia when compared with unrestricted activity at home, based on an observed reduced risk of severe hypertension with hospitalization plus bedrest. Prolonged bedrest can increase the risk of venous thromboembolism. Thromboprophylaxis may be considered when bedrest is prescribed.

### *e. Acute hypertension management*

*Severe hypertension, systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 110$  mmHg or both, requires urgent management. Intravenous labetalol is recommended for initial therapy for severe hypertension. Hydralazine is also acceptable for initial therapy for severe hypertension.*

There is general consensus in guidelines that acute management should be instituted for severe hypertension (systolic blood pressure  $\geq 160$  mmHg or diastolic  $\geq 110$  mmHg or both), and that blood pressure should be lowered to systolic  $< 160$  mmHg and diastolic  $< 110$  mmHg. Hospitalized patients with preeclampsia who are identified with either systolic blood pressure of 160 mmHg or diastolic blood pressure of 110 mmHg should ideally receive an intravenous (IV) antihypertensive agent within 15 minutes. The goal for treatment of severe hypertension is to decrease maternal morbidity and mortality, since antihypertensive treatment has not been shown to affect perinatal outcome and may negatively impact uteroplacental blood flow. Most women presenting with severe hypertension will have had a recently normal blood pressure, and the commonly abrupt, marked increase in blood pressure heightens the urgency of treating severe hypertension in pregnant women even in the absence of symptoms. The ACOG Committee Opinion on management of acute severe hypertension recommends a target blood pressure of 140-160/90-100 mmHg. Women undergoing acute hypertension management require monitoring of blood pressure response and of maternal/fetal status. Continuous maternal blood pressure and fetal heart rate monitoring are indicated, since all short acting agents have been shown in observational studies to be associated with maternal hypotension in women with preeclampsia. There are no controlled studies for the rapidity of blood pressure reduction, but care must be taken to avoid maternal hypotension or a precipitous decrease, since this could result in impaired placental perfusion. Blood pressure should be controlled prior to delivery.

There is a consistent recommendation across guidelines that labetalol intravenously (IV) is recommended for initial therapy for severe hypertension. ACOG guidelines note that labetalol and hydralazine have been shown to be equally effective; the 2011 ACOG Committee Opinion for treatment of acute, severe hypertension recommends use of one or both of these agents as first line therapy. Hydralazine has been associated with more severe adverse effects than other agents based on results of a meta-analysis. Parenteral hydralazine causes severe maternal hypotension and significant tachycardia, particularly in volume-depleted women, and has been associated with marked, severe fetal tachycardia. Therefore, hydralazine should only be used in a volume-repleted patient and only if there is a clear contraindication to labetalol. It should be noted that the same meta-analysis showed an association of labetalol and increased risk of neonatal bradycardia. Labetalol should be avoided in women with cardiac conduction abnormalities, systolic heart failure or asthma, and monitoring should be conducted for possible neonatal bradycardia. The ACOG committee opinion for acute severe hypertension notes that labetalol can be administered orally if IV access has not been established and treatment is urgently needed, and the ACOG practice bulletin for chronic hypertension in pregnancy includes hydralazine intramuscularly (IM) as an option for urgent control of severe acute hypertension.

ACOG indicates that there is less evidence regarding calcium channel blockers for acute, severe hypertension, though other guidelines cite good evidence to support the use of nifedipine capsules for acute blood pressure management in women with severe hypertension. The ACOG practice bulletin for chronic hypertension includes oral nifedipine as a possible agent for urgent control of severe, acute hypertension in pregnancy, noting possible interference with labor as an adverse effect. The JNC report notes that short acting nifedipine is not FDA approved for managing hypertension. Nifedipine used concurrently with magnesium can cause a precipitous drop in blood pressure. There is a high risk of precipitous drop in blood pressure with nifedipine in the preeclamptic patient.

ACOG has developed sample order sets for the initial management of acute, severe hypertension in pregnant or postpartum women with preeclampsia or eclampsia in the ACOG Committee Opinion 514, *“Emergent Therapy for Acute Onset, Severe Hypertension with Preeclampsia or Eclampsia”* (December 2011) that include the following medication dosage and monitoring protocols:

Set 1: Labetalol first protocol

- Notify OB provider when patient presents with severe HTN (systolic  $\geq$  160 mmHg or diastolic  $>$  110 mmHg)
- Initiate appropriate fetal surveillance
- Labetalol 20 mg IV over 2 min; recheck BP in 10 min; if still above either threshold then:
- Labetalol 40 mg IV over 2 min; recheck BP in 10 min; if still above either threshold then:
- Labetalol 80 mg IV over 2 min; recheck BP in 10 min; if still above either threshold then:
- Hydralazine 10 mg IV over 2 min; recheck BP in 20 min; if still above either threshold then:
- Emergency consultation with maternal fetal medicine (MFM), anesthesia, internal medicine, critical care specialist.
- Give additional antihypertensive medication per specific order.
- Once the aforementioned BP thresholds are achieved, repeat BP measurement every 10 minutes for 1 hour, then every 15 minutes for 1 hour, then every 30 minutes for 1 hour, and then every hour for 4 hours.
- Institute additional BP timing per specific order.

Set 2: Hydralazine first protocol

- Notify OB provider when patient presents with severe HTN (systolic  $\geq$  160 mmHg or diastolic  $\geq$  110 mmHg)
- Initiate appropriate fetal surveillance
- Hydralazine 5 or 10 mg IV over 2 min; recheck BP in 20 min; if still above either threshold then:
- Hydralazine 10 mg IV over 2 min; recheck BP in 20 min; if still above either threshold then:
- Labetalol 20 mg IV over 2 min; recheck BP in 10 min; if still above either threshold then:
- Labetalol 40 mg IV over 2 min and;
- Obtain emergency consultation with MFM, anesthesia, internal medicine, critical care specialist.
- Give additional antihypertensive medication per specific order.
- Once the aforementioned BP thresholds are achieved, repeat BP measurement every 10 minutes for 1 hour, then every 15 minutes for 1 hour, then every 30 minutes for 1 hour, and then every hour for 4 hours
- Institute additional BP timing per specific order.

Magnesium sulfate is not recommended as an antihypertensive agent. SOGC guidelines cite limited evidence (observational) that describes no or only a transient decrease in blood pressure 30 minutes following IV magnesium sulfate administration. Staff should be aware of the potential for

a transient decrease in blood pressure when administering antihypertensive agents in conjunction with magnesium sulfate. SOGC guidelines note that there is < 1% risk of neuromuscular blockade if magnesium sulfate is co-administered with nifedipine based on one single center controlled study and a literature synthesis, for which 10 mg of IV calcium gluconate can be administered for reversal. ACOG notes that this potential effect was not observed in one large retrospective study.

For women who fail to respond to first line agents, the 2011 ACOG Committee Opinion for acute, severe hypertension recommend emergent consultation with anesthesia, maternal fetal medicine or critical care for second line management decisions, which can include labetalol or nicardipine by infusion pump, and nitroprusside for extreme emergencies. The JNC report and SOGC guidelines also include sodium nitroprusside to be used rarely when other agents fail, at 0.25 µg/kg/min to a maximum of 5 µg/kg/min. Nitroprusside should be used for the shortest amount of time possible, due to the risk of fetal cyanide poisoning and increased intracerebral pressure with worsening cerebral edema.

#### *f. Inpatient maternal surveillance*

There is no definitive evidence for the frequency of inpatient blood pressure monitoring; SOGC guidelines recommend monitoring at least four times daily for severe hypertension. NICE notes that frequency depends on severity and risk factors, with four times a day routine for non-severe hypertension and increased frequency for severe. The 2011 ACOG Committee Opinion for acute, severe hypertension therapy recommends blood pressure monitoring every 10 minutes for one hour once blood pressure is controlled, then every 15 minutes for the next hour, then every 30 minutes for the next hour, and then every hour for four hours.

Recommendations for maternal laboratory and fetal surveillance testing vary across guidelines. ACOG recommends individualized testing based on condition severity and progression, with frequent monitoring of women with preeclampsia for worsening preeclampsia; in some cases, this may include daily lab and fetal surveillance. For women hospitalized with severe hypertension without proteinuria, quantification of proteinuria is recommended. ACOG and NICE guidelines recommend against repeating quantification after significant proteinuria is identified.

Other maternal lab monitoring consistently recommended in guidelines includes monitoring of complete blood count (hemoglobin, white blood cell count and differential, platelet count, blood film), electrolytes and renal function (serum creatinine), and liver functions (transaminases, bilirubin). SOGC guidelines also recommend coagulation studies (INR and aPTT, fibrinogen) and serum uric acid, glucose and urinalysis, with additional baseline labs as indicated. All guidelines support monitoring these parameters with frequency based on severity but at least weekly. SOMANZ guidelines recommend LDH if falling hemoglobin is noted, and SOGC guidelines recommend monitoring of serum uric acid. NICE guidelines note that rising uric acid has been associated with severe preeclampsia but does not have added value to the monitoring of platelet count, serum creatinine and transaminases.

Women with preeclampsia are at risk for pulmonary edema, and undiagnosed pulmonary edema has been identified as a leading cause of preventable maternal death.<sup>59</sup> Women with preeclampsia reporting shortness of breath should undergo careful evaluation, including immediate chest X-ray.

For women with early development of severe preeclampsia, ACOG and SOMANZ guidelines recommend evaluation for lupus anticoagulant and anticardiolipin antibodies.

#### *g. Invasive hemodynamic monitoring*

Invasive hemodynamic monitoring is not routinely done for women with HDP. ACOG and SOGC guidelines note that invasive monitoring may be useful in critical cases such as acute renal failure or hemodynamic instability to monitor response to treatment based on limited evidence.

#### *h. Fetal surveillance*

There is consensus across guidelines to recommend continuous fetal monitoring for women with severe hypertension. Although serial surveillance of fetal well being is generally recommended, there is no specific evidence for the type and frequency of tests. For severe preeclampsia, SOGC guidelines recommend monitoring fetal movement count, NST, BPP, deepest amniotic fluid pocket, ultrasound assessment of fetal growth and umbilical artery Doppler velocimetry, with frequency based on ongoing concern. These guidelines suggest weekly Doppler interrogation of the umbilical artery for evaluation of IUGR in women with gestational hypertension and preeclampsia. ACOG monitoring recommendations for severe preeclampsia include daily fetal movement assessments and weekly NST or BPP, with twice weekly NST or BPP for IUGR or oligohydramnios, or more frequent assessments depending on severity and progression.

#### *i. Delivery timing/expectant management*

*Determination of delivery timing in women with HDP is a complex decision that requires consideration of gestational age, degree of hypertension control, and patterns of maternal and fetal adverse conditions. Preeclampsia is a maternal indication for delivery, and delivery should take place by 37 weeks. Delivery should not be deferred to 39 weeks for women with preeclampsia. Delivery at 37 weeks for mild preeclampsia is an indicated delivery and is not considered elective. Delivery should not be deferred to await antenatal steroid administration if delivery is warranted for severe maternal indications.*

Determination of delivery timing in women with HDP is a complex decision that requires consideration of gestational age, degree of hypertension control, and patterns of maternal and fetal adverse conditions such as HELLP syndrome, deteriorating renal function, and fetal distress or IUGR.<sup>37</sup> The ACOG practice bulletin for chronic hypertension notes that chronic (preexisting) hypertension with superimposed preeclampsia is particularly complex. Gestational age is a major driver of decisions regarding expectant management for women with preeclampsia, since there is evidence of an association of delivery before 34 weeks with neonatal morbidity, but the impact on maternal risk is less clearly defined in published trials. Two small trials cited by SOGC have suggested that expectant management of women with preeclampsia at less than 32-34 weeks gestation may decrease the risk of NICU admission, respiratory distress syndrome, and necrotizing enterocolitis. Guidelines recommend expectant management before 34 weeks after evaluation of fetal and maternal status and weighing of maternal risk factors such as severe hypertension refractory to treatment; SOGC guidelines suggest expectant management should only take place in perinatal centers capable of caring for very preterm neonates.

ACOG guidelines note that severe preeclampsia usually warrants delivery, and eclampsia and HELLP syndrome are indications for delivery. The ACOG practice bulletin for chronic hypertension notes that it is prudent to perform delivery in women with chronic (preexisting) hypertension with superimposed preeclampsia at 34 weeks, as in women with severe preeclampsia. If birth is offered before 34 weeks for maternal or fetal indications, antenatal steroids should be administered, and some guidelines recommend discussion with neonatal and anesthesia teams. NICE guidelines recommend documentation of maternal (biochemical, hematologic, and clinical) and fetal thresholds for elective birth before 34 weeks in women with preeclampsia.

SOGC guidelines note that there is insufficient evidence to make recommendations about the benefit of expectant management for women at 34-36 weeks gestation with non-severe preeclampsia, though there is no expected perinatal benefit if pregnancy is prolonged. NICE guidelines recommend offering birth to women with preeclampsia and mild or moderate hypertension at 34-36 weeks gestation based on maternal and fetal status, risk factors, and NICU availability. Guidelines generally recommend offering birth immediately or within 24-28 hours for women with severe or non-severe preeclampsia at  $\geq 37$  weeks gestation.

Evidence from the HYPITAT trial cited in NICE guidelines revealed that there were no maternal or neonatal disadvantage to delivery for these women, but progression of preeclampsia and resultant adverse consequences are a risk if delivery is not offered. There is no evidence for biochemical or hematological thresholds for delivery.

#### *j. Antenatal steroids*

*Antenatal steroids should be considered for women at risk for preterm delivery who present between 24 and 34 weeks gestation.*

Antenatal steroids should be considered for women at risk for preterm delivery who present between 24 and 34 weeks gestation. There is strong evidence to recommend steroids for all women presenting with preeclampsia before 34 weeks gestation. The evidence is less clear regarding antenatal steroids for women presenting with gestational hypertension without evidence of preeclampsia at less than 34 weeks gestation; although one third of these women will develop preeclampsia, it is unlikely that they will deliver within 7 days of presentation. SOGC guidelines recommend consideration of antenatal steroids for women with gestational hypertension without signs or symptoms of preeclampsia who present at less than 34 weeks gestation if delivery is contemplated within the next 7 days based on expert consensus, and some guidelines recommend discussion with the neonatal team.

## **9. Inpatient care specific to preeclampsia**

### *a. Severity classification*

Severity classification of preeclampsia affects management decisions. Criteria for severe preeclampsia described in guidelines include severe hypertension, maternal symptoms, maternal biochemical

and hematological impairment, and fetal compromise. ACOG parameters should be used to define severe preeclampsia. It should be noted that several of these parameters are based on level C (expert consensus) evidence. These parameters include one or more of the following:

- Blood pressure  $\geq$  160/110 on two occasions 6 hours apart while patient on bedrest
- Proteinuria 5g or higher on 24 hour urine or 3+ or greater on two random urine samples 4 hours apart
- Oliguria (<500mL in 24 hours)
- Cerebral or visual disturbance
- Pulmonary edema or cyanosis
- Epigastric or right upper quadrant pain
- Impaired liver function
- Thrombocytopenia or evidence of hemolysis
- Fetal growth restriction

These parameters are for the most part consistent with those cited in other guidelines. NICE guidelines note that although recommended as a criterion for severe preeclampsia, there is weak evidence for the association of >5 g/d of proteinuria and adverse outcomes.

SOGC guidelines also define preeclampsia with onset before 34 weeks' gestation as severe preeclampsia.

### *b. Seizure prophylaxis*

*Seizure prophylaxis with magnesium sulfate is recommended for women with severe preeclampsia.*

*Seizure prophylaxis may also be considered for women with preeclampsia that is not classified as severe.*

Guidelines uniformly recommend magnesium sulfate in severe preeclampsia to prevent seizures; however, as noted above, severe preeclampsia definitions are not all consistent. ACOG guidelines note that respiration and deep tendon reflexes and urine output should be monitored for women receiving magnesium sulfate. Seizure prophylaxis should be considered for all women with preeclampsia who are in labor.

There is no definitive evidence for seizure prophylaxis in women with non-severe preeclampsia. Although there is a reported reduced risk of seizure with magnesium sulfate prophylaxis in non-severe preeclampsia, there have also been reports of an increase in cesarean delivery and other adverse maternal effects; therefore, the overall benefit of magnesium sulfate in non-severe preeclampsia is unclear. SOGC guidelines recommend consideration of magnesium sulfate in non-severe preeclampsia.

WHO guidelines recommend a full regimen of magnesium sulfate for prevention as well as treatment.

### *c. Thromboprophylaxis*

*Preeclampsia and associated risk factors, such as obesity and immobility, increase the risk for thromboembolic disease. These risks for thromboembolic disease should be considered when determining the need for prophylaxis.*



Recommendations for thromboprophylaxis differ among guidelines. ACOG–AAP guidelines recommend thromboprophylaxis with low-dose heparin pre and postpartum for women with a history of thrombosis related to pregnancy or thrombosis with underlying thrombophilia. The Royal College of Obstetricians and Gynaecologists Guideline for Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium recommends assessment of risk for venous thromboembolism (VTE) and antenatal prophylaxis with low-molecular-weight heparin (LMWH) as early in pregnancy as possible for women with the following risk factors: previous recurrent VTE, previous unprovoked or estrogen or pregnancy-related VTE, previous VTE and a history of VTE in a first degree relative or documented thrombophilia.<sup>60</sup> This guideline, which is used by many New York hospitals, also recommends consideration of thromboprophylaxis antenatally for women with three or more current or persistent risk factors that include preeclampsia and risk factors for preeclampsia, such as medical comorbidity, obesity, older age and multifetal pregnancy. SOGC guidelines also note that preeclampsia and preeclampsia risk factors such as obesity, older age and thrombophilia increase the risk for thromboembolic disease, as do other factors that may be pertinent for women with preeclampsia, such as bedrest for more than 4 days prior to delivery and cesarean delivery. SOGC guidelines recommend consideration of thromboprophylaxis when bedrest has been prescribed. SOMANZ guidelines recommend consideration of compression stockings for hospitalized women. Both SOGC and SOMANZ guidelines recommend consideration of postpartum thromboprophylaxis for women with preeclampsia unless it is contraindicated. Royal College of Obstetricians and Gynaecologists recommend postpartum thromboprophylaxis for women with risk factors that include class three obesity (BMI > 40kg/m<sup>2</sup>), women undergoing emergency cesarean delivery, and women with two or more persistent risk factors such as preeclampsia, medical comorbidity, obesity, and smoking. Post partum low-molecular-weight heparin (LMWH) should not be administered until two hours after epidural catheter removal.

#### *d. Referral/consultation*

ACOG AAP guidelines recommend management of severe preeclampsia in a tertiary care setting or in consultation with a maternal-fetal medicine subspecialist. SOGC guidelines recommend mandatory OB consultation for women with severe preeclampsia, and advise subspecialty consultation.

## **10. Eclampsia/HELLP syndrome**

Eclampsia and HELLP syndrome are two severe manifestations of preeclampsia that require additional management considerations.

### *a. Management of seizures in eclampsia*

*Seizures in eclampsia should be treated with magnesium sulfate.*

Magnesium sulfate is first line treatment for eclampsia, and it is administered by an IV loading dose followed by IV infusion. Guideline-recommended dosages for magnesium sulfate administration

for eclampsia range from 4 grams to 6 grams in 100cc delivered IV over 15 minutes, followed by an IV infusion of 1-2 grams per hour. Blood pressure, respiratory rate, urine output and deep tendon reflexes should be monitored during magnesium sulfate administration. Repeat boluses of 2-4 grams can be administered for recurrent seizures. Other agents are considered in SOGC guidelines only if magnesium sulfate is ineffective or contraindicated, and include phenytoin and benzodiazepines.

#### *b. Delivery timing eclampsia*

Considerations for delivery timing in eclampsia include assessment of stability with regard to blood pressure, urinary output and fetal heart rate. A consensus recommendation is delivery two hours after stability is achieved.

#### *c. Transfusion for HELLP syndrome*

SOGC guidelines cite expert consensus that platelet transfusion is indicated when platelet count is  $<50 \times 10^9/L$  and falling, and/or there is coagulopathy. Some experts recommend platelet transfusion for platelet count  $<40 \times 10^9$  prior to intubation for cesarean section. Platelet transfusion is recommended prior to delivery for any woman with HELLP syndrome and platelet count  $<20 \times 10^9/L$ .

HELLP syndrome has been shown to occur in approximately 20% of women with severe preeclampsia. SOGC guidelines recommend platelet transfusion when platelet count is  $<50 \times 10^9/L$  and falling, and/or there is coagulopathy based on expert consensus. SOGC guidelines recommend consideration of platelet transfusion for women with platelet count less than  $20 \times 10^9/L$  prior to vaginal delivery or cesarean section based on expert consensus of risk of profound hemorrhage. Prophylactic platelet transfusion is not recommended, even prior to cesarean delivery, if platelet count is  $>50 \times 10^9/L$  and there is no excessive bleeding or evidence of platelet dysfunction according to SOGC guidelines, based on fair evidence. Some experts have recommended platelet transfusion for platelet count  $<40 \times 10^9$  prior to intubation for cesarean section.<sup>61</sup>

#### *d. Other therapy for HELLP syndrome*

*There is no clear evidence for the use of corticosteroids in HELLP syndrome.*

The use of corticosteroids for HELLP syndrome is not well defined in the literature. Only SOGC guidelines recommend consideration of corticosteroids for HELLP syndrome for women with platelet counts less than  $50 \times 10^9/L$  based on expert opinion; other guidelines, including those of the WHO, do not recommend the use of corticosteroids in HELLP syndrome. SOGC guidelines note insufficient evidence for plasma exchange or plasmapheresis, noting that observational studies have suggested improved hematological and biochemical indicators, but small RCTs have found no maternal or perinatal outcome improvement.

## 11. Delivery-intrapartum care for women with HDP

### a. Mode of delivery

*Vaginal delivery is preferred unless there is another indication for cesarean section.*

For women with any HDP, vaginal delivery is preferred unless cesarean delivery is required for other indications. SOGC cites strong evidence for cervical ripening if the cervix is unfavorable and vaginal delivery is planned, based on pregnancy experience in normotensive women.

Third stage management with oxytocin is recommended to avoid hemorrhage due to the risk of thrombocytopenia and coagulopathy in preeclampsia. Oxytocin should be administered in slow, small doses to minimize significant hemodynamic effects.

### b. Intrapartum

There is consensus across guidelines that antihypertensive therapy should be continued through labor and delivery to maintain blood pressure at less than 160/110. There is a lack of good quality RCTs regarding antihypertensive treatment after birth.

### c. Anesthesia concerns

*Regional anesthesia is preferred in women with HDP unless it is contraindicated by coagulopathy or other condition.*

All reviewed guidelines note that regional anesthesia is preferred in women with HDP unless it is contraindicated by coagulopathy or other condition. All regional techniques appear safe with appropriate fluid management; low-dose aspirin is not a contraindication to regional anesthesia if the platelet count is adequate and there is no coagulopathy. Regional anesthesia should not be administered to women treated with LMWH for 12 hours after a prophylactic dose, and 24 hours after a therapeutic dose due to the possibility of a small, but increased risk for the development of epidural hematoma in these patients. SOGC cites a threshold platelet count for regional anesthesia of  $>75 \times 10^9/L$  unless there is coagulopathy, falling platelets, or co-administration of an anti-platelet agent (ASA) or anticoagulant (heparin). Regional anesthesia is generally safe when platelet count is  $>75 \times 10^9/L$  and generally contraindicated when platelet count is  $<50 \times 10^9/L$ . For cesarean delivery, if there are no contraindications, epidural, spinal and combined spinal-epidural anesthesia is all noted to be acceptable in SOGC guidelines.

General anesthesia may pose a risk to women with chronic (preexisting) hypertension who have severe hypertension or superimposed preeclampsia due to a hypertensive response to intubation and possible increased risk for laryngeal edema. Women with HDP may have an increased likelihood of difficult or failed intubation than the general population. SOMANZ guidelines note that general anesthesia may be indicated by fetal or maternal conditions, and requires early anesthesia notification, aspiration prophylaxis, and attenuation of pressor responses.

#### *d. Analgesia*

SOMANZ guidelines recommend early insertion of an epidural catheter for pain if there is no contraindication, so that the option for regional anesthesia can be maintained if conditions change rapidly. Epidural analgesia is a useful adjunct for hypertension control and for improving renal and uteroplacental flow, since epidural analgesia can blunt pain-induced increases in blood pressure that can be exaggerated in women with preeclampsia. SOMANZ guidelines recommend patient controlled fentanyl or remifentanyl analgesia if epidural is not possible. SOGC and SOMANZ guidelines recommend avoiding non-steroidal anti-inflammatory drugs (NSAIDs) post partum if hypertension is difficult to control, or if there is oliguria, elevated creatinine or platelets less than  $50 \times 10^9/L$ . These agents are commonly given for analgesia and can contribute to hypertension, elevated creatinine or renal failure.

#### *e. Fluid balance*

*Women with preeclampsia have reduced plasma volume and routine fluid restriction in all such women may not be appropriate. Optimizing fluid balance prior to delivery is essential, and fluid balance should be carefully monitored in women with HDP. Fluid management for these patients, including an intravenous (IV) fluid bolus prior to administration of regional anesthesia, should be directed by an anesthesiologist with expertise in this area.*

Preeclampsia is associated with vasospasm, hemoconcentration, capillary leak and alteration in the normal volume expansion seen in pregnancy, complicating fluid management in women with preeclampsia. Women with preeclampsia have reduced plasma volume, associated with reduced serum albumin.<sup>62</sup> Some women with preeclampsia are at increased risk for pulmonary edema, which has been associated with excess fluid administration, and pulmonary edema is a major cause of maternal mortality in this population. There is no clear evidence for optimal fluid management in women with preeclampsia.

The ACOG practice bulletin for chronic hypertension notes that women with chronic (preexisting) hypertension and cardiovascular or renal disease may be more susceptible to fluid overload and pulmonary edema, and therefore require particular attention to fluid balance. ACOG and NICE guidelines recommend hourly intake and output monitoring before delivery, and note that invasive monitoring is rarely needed.

Women with preeclampsia are at risk for hypotension following regional anesthesia/analgesia (both spinal and epidural) because they are intravascularly depleted, and steps should be taken to avoid this complication. Fluid management for these patients, including an IV fluid bolus prior to administration of regional anesthesia, should be directed by an anesthesiologist with expertise in this area. The anesthesiologist should also be responsible for management of any hypotension following regional anesthesia and should provide appropriate monitoring guidelines.

ACOG-AAP Guidelines for Perinatal Care note that intrapartum oliguria is common, especially with oxytocin usage, and recommend up to three boluses of 500 cc of crystalloid if urine output is less than 30 cc/hr for 2 consecutive hours during labor. If oliguria persists, more accurate determination of volume status may be required.

Recommendations for postpartum oliguria vary across guidelines. SOGC guidelines recommend tolerating oliguria (<15 mL/hr) for at least the first six hours post partum in women without preexisting renal disease or rising creatinine. ACOG-AAP guidelines note, however, that postpartum oliguria is usually due to hypovolemia and recommend initial volume replacement for oliguria with 500 cc of crystalloid over 20 minutes; with consideration of packed red blood cells if oliguria persists and the woman is anemic.

## 12. Postpartum and follow-up

### *a. Postpartum evaluation/surveillance*

*Close monitoring of women with HDP is essential in the postpartum period. Many women with preeclampsia can deteriorate postpartum. Preeclampsia and eclampsia can develop in the postpartum period, and blood pressure in women with chronic (preexisting) hypertension is often unstable for 1-2 weeks postpartum. Blood pressure should be monitored at least every 4 hours postpartum, and women should not be discharged until blood pressure has been well controlled for at least 24 hours. The follow-up plan for monitoring of women with HDP should be clear in discharge instructions. Peak postpartum blood pressure occurs between days 3-5 after birth. Blood pressure should be measured at least once in the 3-5 day postpartum period.*

Though close follow up is essential, there is no clear evidence for the frequency of post partum follow-up visits for women with HDP. Frequency should be clinically driven, and occur at least at the same frequency as antenatal visits. Prior to discharge, NICE guidelines recommend a written care plan to include who will provide follow-up care and the frequency of BP monitoring needed.

Close monitoring of blood pressure is essential in the post partum period; many women with preeclampsia can deteriorate postpartum, and preeclampsia and eclampsia can develop in the post partum period. Blood pressure in women with chronic (preexisting) hypertension is often unstable for 1-2 weeks post partum. Blood pressure, proteinuria and other adverse conditions may worsen in the first few days post partum, especially in women with severe disease. Women should be evaluated in the first few days post partum for symptoms such as headache and epigastric pain, as well as blood pressure and evidence of adverse conditions. NICE guidelines recommend monitoring daily for the first two days after birth, with particular attention to monitoring high-risk women such as those with antenatal preeclampsia with preterm delivery, high BUN or uric acid levels.

Peak postpartum blood pressure occurs between day 3 -5 after birth, and hypertension may develop de novo in this timeframe; blood pressure should be measured at least once in this timeframe. SOGC recommends maternal surveillance at least once in the first three days postpartum for women with preeclampsia and as indicated if treatment is changed, with continuation of monitoring every other day until blood pressure is normal.

Postpartum surveillance should include confirmation that the end-organ dysfunction of preeclampsia has resolved. NICE guidelines recommend monitoring platelet count, transaminases, and serum creatinine in the 48-72 hours after birth for women with preeclampsia, to be repeated as clinically indicated. Derangement should resolve at 6 weeks post partum.

### *b. Postpartum antihypertensive therapy*

There is no reliable data to guide whether or not to continue antenatal antihypertensive therapy and which agent is preferred.

Antihypertensive therapy may be restarted postpartum, especially in women with severe preeclampsia and those who have delivered preterm according to SOGC guidelines. WHO guidelines recommend continuing antihypertensive treatment postpartum in women treated with antihypertensive drugs antenatally and treating women with severe postpartum hypertension with antihypertensive drugs. While there is generally consensus that severe hypertension should be treated to keep blood pressure < 160/110 mmHg, there is insufficient evidence for treating non-severe hypertension postpartum. The JNC report suggests consideration of withholding antihypertensives for breastfeeding women with blood pressure 140-159/90-99 mmHg, with close monitoring for the first few months while nursing. For women with gestational hypertension on antihypertensives, NICE guidelines recommend reducing and stopping antihypertensive treatment if possible, with consideration of reduction of antihypertensives if blood pressure is < 140/90 mmHg. For women with gestational hypertension who were not previously treated with antihypertensives, NICE guidelines recommend initiating therapy postpartum for blood pressure higher than 149/99 mmHg.

For chronic (preexisting) hypertension, NICE guidelines suggest that target blood pressures should be the same as long term targets for the general population, with aim to keep blood pressure less than 140/90 mmHg. This target is the same as the definition of control in the JNC report for general populations. Comorbid conditions should be considered in the treatment of non-severe hypertension. SOGC guidelines suggest that antihypertensive therapy may be used to treat non-severe post partum hypertension, particularly in women with comorbidities, and that in certain populations (diabetes, chronic kidney disease or prior stroke) a lower target of < 130/80 mmHg may be indicated.

Women with preeclampsia usually require longer antihypertensive therapy than women with gestational hypertension, but requirements vary. Although hypertension usually resolves by 6 weeks postpartum in gestational hypertension, it may persist up to 3 months or longer in severe preeclampsia.

Women who are breastfeeding should be offered information regarding antihypertensive agents. SOGC guidelines note that antihypertensive agents are usually acceptable for breastfeeding women, although all agents are excreted in breast milk. However, there is little data on long term effects or the effect of maternal antihypertensive therapy on low birthweight or preterm infants. Labetalol and propranolol are preferred if beta blockers are indicated. The JNC recommends against ACE/ARB therapy based on reports of adverse fetal and neonatal effects and insufficient evidence of safety. NICE guidelines cite insufficient evidence on the safety of ARBs, amlodipine, and ACE inhibitors other than enalapril and captopril, although other guidelines indicate the acceptability of enalapril, captopril and quinapril during breastfeeding. Diuretics can decrease lactation, and should be avoided in breastfeeding women. NICE guidelines recommend discontinuation of methyldopa if it is prescribed for women with chronic (preexisting) hypertension during pregnancy within 2 days of birth, with resumption of antenatal treatment to avoid the risk of depression.

### *c. Follow up review/testing*

Long term treatment of women with HDP should be reviewed at 2 weeks post partum for those who remain on antihypertensives. NICE recommends a medical review for women with HDP who remain on antihypertensives two weeks after discharge, since many women with gestational hypertension may actually have a preexisting hypertensive disorder. SOGC guidelines recommend that women with severe preeclampsia, especially those who presented or delivered before 34 weeks, should be screened for pre-existing hypertension, underlying renal disease and thrombophilia.

SOGC guidelines recommend follow-up of women with chronic (preexisting) hypertension that includes urinalysis, serum sodium, potassium and creatinine, fasting glucose, fasting total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and 12 lead EKG if not done previously. SOGC guidelines note that previously normotensive women with a hypertensive disorder in pregnancy may benefit from assessment of cardiovascular risk markers.

NICE guidelines recommend a specialist for women with gestational hypertension who still need antihypertensives at their postnatal review or have ongoing proteinuria or other non- resolved abnormal indices. SOMANZ guidelines recommend that women with HDP should have annual blood pressure checks and cardiovascular risk assessment, including lipids and glucose, at least every five years.

### *d. Risk communication/lifestyle counseling*

*Women with HDP should be advised of the risk for recurrent HDP and of future cardiovascular risk. It is important to note that ACOG recommends that all health encounters during a woman's reproductive years, particularly those that are part of preconception care, should include counseling on appropriate health behaviors to optimize pregnancy outcomes and prevent maternal mortality.*

Women should be advised of the risk for future hypertensive disorders using plain language. All women with HDP are at risk for future preeclampsia, and are at increased risk of future hypertension and its complications. Hypertension recurs in 20-50% of subsequent pregnancies of women with HDP, particularly in women with early onset of hypertension in pregnancy, a history of chronic (preexisting) hypertension, or hypertension persisting beyond 5 weeks postpartum.<sup>38</sup>

The risk of recurrent preeclampsia is based on severity, gestation at onset, and additional maternal risk factors (chronic (preexisting) hypertension, diabetes). NICE guidelines advocate advising women with preeclampsia of the risk of future gestational hypertension and preeclampsia, which is more likely for women with severe preeclampsia, HELLP syndrome, eclampsia, or complications that led to birth before 34 or 28 weeks.

Women with preeclampsia have a greater tendency to develop chronic hypertension than women with normotensive pregnancies. There are large scale epidemiologic studies showing women with gestational hypertension and especially preeclampsia to have increased risk of developing chronic hypertension, renal disease and cardiovascular and cerebrovascular morbidity and mortality. Due to the long term risk of women with HDP, specific cardiovascular risk factors should be addressed and recommendations made for addressing them with dietary and lifestyle modification, including DASH diet, exercise, maintenance of ideal body weight and avoidance of tobacco. American Heart

Association *Guidelines for the Prevention of Cardiovascular Disease in Women* note that relative to other women, women with preeclampsia have been shown to have nearly a two fold increase in risk for ischemic heart disease, stroke and venous thromboembolic disease in the five to fifteen years after the pregnancy.<sup>63</sup> These guidelines suggest that the physiologic changes of pregnancy may unmask early or preexisting endothelial dysfunction and vascular or metabolic disease, and therefore recommend postpartum referral to a primary care physician or cardiologist for women with preeclampsia for management of cardiovascular risk factors.

Women should be counseled regarding family planning to prevent pregnancy. Hospital staff and health care providers should ensure all women have a method of birth control prior to discharge from the hospital post partum. Women should be informed that intervals between pregnancies of < 2 years or > 10 years are both associated with recurrent preeclampsia. Higher BMI categories are associated with increased complications and adverse outcomes, including risk for HDP. Overweight women should be encouraged to attain healthy BMI to decrease future pregnancy risk and improve long term health. There is strong epidemiologic evidence that weight gain between pregnancies is associated with an increased risk for preeclampsia, even in non-obese women. Avoidance of interpregnancy weight gain for high-risk women is recommended in SOGC guidelines. For those with severe obesity, surgical management has reduced the risk of gestational hypertension in subsequent pregnancies in a small group of women, as noted in SOGC and IOM guidelines. It is important to note that ACOG recommends that all health encounters during a woman's reproductive years, particularly those that are a part of preconception care, should include counseling on appropriate health behaviors to optimize pregnancy outcomes and prevent maternal mortality.

### **13. Continuous Quality Improvement**

SOMANZ guidelines recommend that hospitals monitor outcomes of women with HDP, including maternal mortality, composite severe adverse maternal outcomes, perinatal mortality, and rate of NICU admission of term babies.



## Glossary of acronyms

ACE	angiotensin-converting enzyme
ACOG	American Congress of Obstetricians and Gynecologists
AAP	American Academy of Pediatrics
ARB	Angiotensin Receptor Blocker
HDP	Hypertensive Disorders in Pregnancy
IOM	Institute of Medicine
IUGR	Intrauterine Growth Restriction
IV	Intravenously
JNC	Joint National Committee
LMWH	Low-molecular-weight Heparin
MgSO <sub>4</sub>	Magnesium sulfate
MMR	Maternal Mortality Review
NHBPEP	National High Blood Pressure Education Program
NICE	Royal College of Obstetricians and Gynaecologists, National Institute for Health and Clinical Excellence
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NYSDOH	New York State Department of Health
SOGC	Society of Obstetricians and Gynaecologists of Canada
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand

## *Appendix A* • Hypertensive Disorders in Pregnancy

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