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Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy

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Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy

This guideline has been reviewed and approved by the Hypertension Guideline Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: This guideline summarizes the quality of the evidence to date and provides a reasonable approach to the diagnosis, evaluation, and treatment of the hypertensive disorders of pregnancy (HDP).

Evidence: The literature reviewed included the original HDP guidelines and their reference lists and an update from 1995. Using key words, Medline was searched for literature published between 1995 and 2007. Articles were restricted to those published in French or English. Recommendations were evaluated using the criteria of the Canadian Task Force on Preventive Health Care (Table 1).

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Key Words: Hypertension, blood pressure, pregnancy, preeclampsia, maternal outcome, perinatal outcome

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

∗The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[9]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[9]

CHAPTER 1: DIAGNOSIS AND CLASSIFICATION

Recommendations: Measurement of BP

1. BP should be measured with the woman in the sitting position with the arm at the level of the heart. (II-2A)
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used. (II-2A)
3. Korotkoff phase V should be used to designate diastolic BP. (I-A)
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements. (III–B)
5. BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in preeclampsia. (II-2A)
6. Automated BP machines may underestimate BP in women with preeclampsia, and comparison of readings using mercury sphygmomanometry or an aneroid device is recommended. (II-2A)
7. Ambulatory BP monitoring (by 24-hour or home measurement) may be useful to detect isolated office (white coat) hypertension. (II-2B)
8. Patients should be instructed in proper BP measurement technique if they are to perform home BP monitoring. (III-B)

Recommendations: Diagnosis of Hypertension

1. The diagnosis of hypertension should be based on office or in-hospital BP measurements. (II-2B)
2. Hypertension in pregnancy should be defined as a diastolic BP of ≥ 90 mmHg, based on the average of at least two measurements, taken using the same arm. (II-2B)
3. Women with a systolic BP of ≥ 140 mmHg should be followed closely for development of diastolic hypertension. (II-2B)
4. Severe hypertension should be defined as a systolic BP of ≥ 160 mmHg or a diastolic BP of ≥ 110 mmHg. (II-2B)
5. For non-severe hypertension, serial BP measurements should be recorded before a diagnosis of hypertension is made. (II-2B)
6. For severe hypertension, a repeat measurement should be taken for confirmation in 15 minutes. (III-B)
7. Isolated office (white coat) hypertension should be defined as office diastolic BP of ≥ 90 mmHg, but home BP of < 135/85 mmHg. (III-B)

Recommendations: Measurement of Proteinuria

1. All pregnant women should be assessed for proteinuria. (II-2B)
2. Urinary dipstick testing may be used for screening for proteinuria when the suspicion of preeclampsia is low. (II-2B)
3. More definitive testing for proteinuria (by urinary protein: creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of preeclampsia, including in hypertensive pregnant women with rising BP or in normotensive pregnant women with symptoms or signs suggestive of preeclampsia. (II-2A)

Recommendations: Diagnosis of Clinically Significant Proteinuria

1. Proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥ 2+. (II-2A)
2. Proteinuria should be defined as ≥ 0.3g/d in a 24-hour urine collection or ≥ 30 mg/mmol urinary creatinine in a spot (random) urine sample. (II-2B)
3. There is insufficient information to make a recommendation about the accuracy of the urinary albumin: creatinine ratio. (II-2 I)

Recommendations: Classification of HDP

1. Hypertensive disorders of pregnancy should be classified as pre-existing or gestational hypertension on the basis of different diagnostic and therapeutic factors. (II-2B)
2. The presence or absence of preeclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes. (II-2B)
3. In women with pre-existing hypertension, preeclampsia should be defined as resistant hypertension, new or worsening proteinuria, *or* one or more of the other adverse conditions. (II-2B)
4. In women with gestational hypertension, preeclampsia should be defined as new-onset proteinuria *or* one or more of the other adverse conditions. (II-2B)
5. Severe preeclampsia should be defined as preeclampsia with onset before 34 weeks' gestation, with heavy proteinuria or with one or more adverse conditions. (II-2B)
6. The term PIH (pregnancy-induced hypertension) should be abandoned, as its meaning in clinical practice is unclear. (III-D)

Recommendations: Investigations to Classify HDP

1. For women with pre-existing hypertension, serum creatinine, serum potassium, and urinalysis should be performed in early pregnancy if not previously documented. (II-2B)
2. Among women with pre-existing hypertension, additional baseline laboratory testing may be based on other considerations deemed important by health care providers. (III-C)
3. Women with suspected preeclampsia should undergo the maternal laboratory (II-2B) and fetal (II-1B) testing described in Table 3.
4. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about preeclampsia (e.g., change in maternal and/or fetal condition). (III-C)
5. Uterine artery Doppler velocimetry may be useful among hypertensive pregnant women to support a placental origin for hypertension, proteinuria, and/or adverse conditions. (II-2B)
6. Umbilical artery Doppler velocimetry may be useful to support a placental origin for intrauterine fetal growth restriction. (II-2B)

CHAPTER 2: PREDICTION, PREVENTION, AND PROGNOSIS OF PREECLAMPSIA

Recommendations: Predicting Preeclampsia

1. At booking for antenatal care, women with markers of increased risk for preeclampsia should be offered obstetric consultation. (II-2B)
2. Women at increased risk of preeclampsia should be considered for risk stratification involving a multivariable clinical and laboratory approach. (II-2B)

Recommendations: Preventing Preeclampsia and its Complications in Women at Low Risk

1. Calcium supplementation (of at least 1g/d, orally) is recommended for women with low dietary intake of calcium (< 600 mg/d). (I-A)
2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, (II-2E) exercise for maintenance of fitness, (I-A) periconceptual use of a folate-containing multivitamin for prevention of neural tube defects, (I-A) and smoking cessation for prevention of low birthweight and preterm birth. (I-E)
3. The following may be useful: periconceptual use of a folate-containing multivitamin, (I-B) or exercise. (II-2B)

4. The following are **not** recommended for preeclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursors, (I-C) or supplementation with magnesium, (I-C) or zinc. (I-C)

5. The following are **not** recommended: dietary salt restriction during pregnancy, (I-D) calorie restriction during pregnancy for overweight women, (I-D) low-dose aspirin, (I-E) vitamins C and E (based on current evidence), (I-E) or thiazide diuretics. (I-E)

6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, (II-2I) workload or stress reduction, (II-2I) supplementation with iron with/without folate, (I-I) or pyridoxine. (I-I).

Recommendations: Preventing Preeclampsia and its Complications in Women at Increased Risk

1. Low-dose aspirin (I-A) and calcium supplementation (of at least 1 g/d) are recommended for women with low calcium intake, (I-A) and the following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of preeclampsia): abstention from alcohol, (II-2 E) periconceptual use of a folate-containing multivitamin, (I-A) and smoking cessation. (I-E)

2. Low-dose aspirin (75–100 mg/d)(III-B) should be administered at bedtime, (I-B) starting pre-pregnancy or from diagnosis of pregnancy but before 16 weeks' gestation, (III-B) and continuing until delivery. (I-A)

3. The following may be useful: avoidance of inter-pregnancy weight gain, (II-2E) increased rest at home in the third trimester, (I-C) and reduction of workload or stress. (III-C)

4. The following are **not** recommended for preeclampsia prevention but may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-C) and magnesium supplementation. (I-C)

5. The following are **not** recommended: calorie restriction in overweight women during pregnancy, (I-D) weight maintenance in obese women during pregnancy, (III-D) antihypertensive therapy specifically to prevent preeclampsia, (I-D) vitamins C and E. (I-E)

6. There is insufficient evidence to make a recommendation about the usefulness of the following: dietary salt restriction during pregnancy, (III-I) the heart-healthy diet (III-I); exercise (I-I); heparin, even among women with thrombophilia and/or previous preeclampsia (based on current evidence) (II-2 I); selenium (I-I); garlic (I-I); zinc, (III-I) pyridoxine, (III-I) iron (with or without folate), (III-I) or multivitamins with/without micronutrients. (III-I)

Recommendations: Prognosis (Maternal and Fetal) in Preeclampsia

1. Serial surveillance of maternal well-being is recommended, both antenatally and post partum. (II-3B)

2. The frequency of maternal surveillance should be at least once per week antenatally, and at least once in the first three days post partum. (III-C)

3. Serial surveillance of fetal well-being is recommended. (II-2B)

4. Antenatal fetal surveillance should include umbilical artery Doppler velocimetry. (I-A)

5. Women who develop gestational hypertension with neither proteinuria nor adverse conditions before 34 weeks should be followed closely for maternal and perinatal complications. (II-2B)

CHAPTER 3: TREATMENT OF THE HYPERTENSIVE DISORDERS OF PREGNANCY

Antenatal Treatment

Recommendations: Dietary changes

1. New dietary salt restriction is not recommended. (II-2D).

2. There is insufficient evidence to make a recommendation about the usefulness of the following: ongoing salt restriction among women with pre-existing hypertension, (III-I) heart-healthy diet, (III-I) and calorie restriction for obese women. (III-I)

Recommendations: Lifestyle changes

1. There is insufficient evidence to make a recommendation about the usefulness of: exercise, (III-I) workload reduction, (III-I) or stress reduction. (III-I)

2. For women with gestational hypertension (without preeclampsia), some bed rest in hospital (compared with unrestricted activity at home) may be useful. (I-B)

3. For women with preeclampsia who are hospitalized, strict bed rest is **not** recommended. (I-D)

4. For all other women with HDP, the evidence is insufficient to make a recommendation about the usefulness of bed rest, which may nevertheless, be advised based on practical considerations. (III-C)

Recommendations: Place of care

1. In-patient care should be provided for women with severe hypertension or severe preeclampsia. (II-2B)

2. A component of care through hospital day units (I-B) or home care (II-2B) can be considered for women with non-severe preeclampsia or non-severe (pre-existing or gestational) hypertension.

Recommendations: Antihypertensive therapy for severe hypertension (BP of > 160 mmHg systolic or ≥ 110 mmHg diastolic)

1. BP should be lowered to <160 mmHg systolic and < 110 mmHg diastolic. (II-2B)

2. Initial antihypertensive therapy should be with labetalol, (I-A) nifedipine capsules, (I-A) nifedipine PA tablets, (I-B) or hydralazine. (I-A)

3. $MgSO_4$ is not recommended as an antihypertensive agent. (II-2 D)

4. Continuous FHR monitoring is advised until BP is stable. (III-I)

5. Nifedipine and $MgSO_4$ can be used contemporaneously. (II-2B)

Recommendations: Antihypertensive therapy for non-severe hypertension (BP of 140–159/90–109 mmHg)

1. For women without comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130–155 mmHg and diastolic BP at 80–105 mmHg. (III-C)

2. For women with comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130–139 mmHg and diastolic BP at 80–89 mmHg. (III-C)

3. Initial therapy can be with one of a variety of antihypertensive agents available in Canada: methyldopa, (I-A) labetalol, (I-A) other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol), (I-B) and calcium channel blockers (nifedipine). (I-A)

4. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should not be used. (II-2E)

5. Atenolol and prazosin are not recommended. (I-D)

Recommendations: Corticosteroids for acceleration of fetal pulmonary maturity

1. Antenatal corticosteroid therapy should be considered for all women who present with preeclampsia before 34 weeks' gestation. (I-A)
2. Antenatal corticosteroid therapy may be considered for women who present at < 34 weeks' with gestational hypertension (despite the absence of proteinuria or adverse conditions) if delivery is contemplated within the next 7 days. (III-I)

Recommendations: Mode of delivery

1. For women with any HDP, vaginal delivery should be considered unless a Caesarean section is required for the usual obstetric indications. (II-2B)
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery. (I-A)
3. Antihypertensive treatment should be continued throughout labour and delivery to maintain systolic BP at <160 mmHg and diastolic BP at < 110 mmHg. (II-2B)
4. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopenia or coagulopathy. (I-A)
5. Ergometrine should not be given in any form. (II-3D)

Recommendations: Anaesthesia, including fluid administration

1. The anaesthesiologist should be informed when a woman with preeclampsia is admitted to delivery suite. (II-3B)
2. A platelet count should be performed in all women with HDP on admission to the delivery suite, but tests of platelet function are not recommended. (III-C)
3. Regional analgesia and/or anaesthesia are appropriate in women with a platelet count > 75 x 10^9/L, unless there is a coagulopathy, falling platelet concentration, or co-administration of an antiplatelet agent (e.g., ASA) or anticoagulant (e.g., heparin). (III-B)
4. Regional anaesthesia is an appropriate choice for women who are taking low-dose ASA in the absence of coagulopathy and in the presence of an adequate platelet count. (I-A)
5. Regional anaesthesia is an appropriate choice for women on low-molecular weight heparin 12 hours after a prophylactic dose or 24 hours after a therapeutic dose. (III-B)
6. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of pain. (I-A)
7. A fixed intravenous fluid bolus should not be administered prior to regional analgesia and/ or anaesthesia. (I-D)
8. Small doses of phenylephrine or ephedrine may be used to prevent or treat hypotension during regional anaesthesia. (I-A)
9. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean section: epidural, spinal, combined spinal-epidural, and general anaesthesia. (I-A)
10. Intravenous and oral fluid intake should be minimized in women with preeclampsia, to avoid pulmonary edema. (II-1B)
11. Fluid administration should not be routinely administered to treat oliguria (< 15 mL/hr). (III-D)
12. For persistent oliguria, neither dopamine nor furosemide is recommended. (I-D)
13. Central venous access is not routinely recommended, and if a central venous catheter is inserted, it should be used to monitor trends and not absolute values. (II-2D)
14. Pulmonary artery catheterization is not recommended unless there is a specific associated indication, (III-D) and then only in a high dependency unit setting. (III-B)

Recommendations: Aspects of care specific to women with pre-existing hypertension

1. Pre-conceptual counselling for women with pre-existing hypertension is recommended. (III-I)
2. Discontinue ACE inhibitors and ARBs pre-pregnancy (or as soon as pregnancy is diagnosed). (II-2D)
3. If antihypertensive agent(s) are to be discontinued or changed to allow treatment to continue during pregnancy, then consider changing the agent(s) pre-pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months). (III-I)
4. Consider discontinuing atenolol when pregnancy is diagnosed. (I-D)
5. A variety of antihypertensive drugs may be used in the first trimester of pregnancy (e.g., methyldopa, labetalol, and nifedipine). (II-2B)

Recommendations: Timing of delivery of women with preeclampsia

1. Obstetric consultation is mandatory in women with severe preeclampsia. (III-B)
2. For women at < 34 weeks' gestation, expectant management of preeclampsia (severe or non-severe) may be considered, but only in perinatal centres capable of caring for very preterm infants. (I-C)
3. For women at 34–36 weeks' gestation with non-severe preeclampsia, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management. (III-I)
4. For women at $\geq 37^0$ weeks' gestation with preeclampsia (severe or non-severe), immediate delivery should be considered. (III-B)

Recommendations: Magnesium sulphate ($MgSO_4$) for eclampsia prophylaxis or treatment

1. $MgSO_4$ is recommended for first-line treatment of eclampsia. (I-A)
2. $MgSO_4$ is recommended as prophylaxis against eclampsia in women with severe preeclampsia. (I-A)
3. $MgSO_4$ may be considered for women with non-severe preeclampsia. (I-C)
4. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to $MgSO_4$ or it is ineffective. (I-E)

Recommendations: Plasma volume expansion for preeclampsia

1. Plasma volume expansion is not recommended for women with preeclampsia. (I-E)

Recommendations: Therapies for HELLP syndrome

1. Prophylactic transfusion of platelets is not recommended, even prior to Caesarean section, when platelet count is > 50 $\times$ 10^9/L and there is no excessive bleeding or platelet dysfunction. (II-2D)
2. Consideration should be given to ordering blood products, including platelets, when platelet count is < 50 $\times$ 10^9/L, platelet count is falling rapidly, and/or there is coagulopathy. (III-I)
3. Platelet transfusion should be strongly considered prior to vaginal delivery when platelet count is < 20 $\times$ 10^9/L. (III-B)
4. Platelet transfusion is recommended prior to Caesarean section, when platelet count is < 20 $\times$ 10^9/L. (III-B)

5. Corticosteriods may be considered for women with a platelet count $< 50 \times 10^9$/L. (III-I)
6. There is insufficient evidence to make a recommendation regarding the usefulness of plasma exchange or plasmapheresis. (III-I)

Recommendations: Other therapies for treatment of preeclampsia

1. Women with preeclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity. (I-A)
2. Thromboprophylaxis may be considered when bed rest is prescribed. (II-2C)
3. Low-dose aspirin is not recommended for treatment of preeclampsia. (I-E)
4. There is insufficient evidence to make recommendations about the usefulness of treatment with the following: activated protein C, (III-I) antithrombin, (I-I) heparin, (III-I) L-arginine, (I-I) long-term epidural anaesthesia, (I-I) N-acetylcysteine, (I-I) probenecid, (I-I) or sildenafil nitrate. (III-I)

Postpartum Treatment

Recommendations: Care in the six weeks post partum

1. BP should be measured during the time of peak postpartum BP, at days three to six after delivery. (III-B)
2. Antihypertensive therapy may be restarted post partum, particularly in women with severe preeclampsia and those who have delivered preterm. (II-2 I)
3. Severe postpartum hypertension should be treated with antihypertensive therapy, to keep systolic BP < 160 mmHg and diastolic BP < 110 mmHg. (II-2B)
4. Antihypertensive therapy may be used to treat non-severe postpartum hypertension, particularly in women with comorbidities. (III-I)
5. Antihypertensive agents acceptable for use in breastfeeding include the following: nifedipine XL, labetalol, methyldopa, captopril, and enalapril. (III-B)
6. There should be confirmation that end-organ dysfunction of preeclampsia has resolved. (III-I)
7. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be given post partum if hypertension is difficult to control or if there is oliguria, an elevated creatinine (i.e., ≥ 100 μM), or platelets $< 50 \times 10^9$/L. (III-I)
8. Postpartum thromboprophylaxis may be considered in women with preeclampsia, particularly following antenatal bed rest for more than four days or after Caesarean section. (III-I)
9. LMWH should not be administered post partum until at least two hours after epidural catheter removal. (III-B)

Recommendations: Care beyond six weeks post partum

1. Women with a history of severe preeclampsia (particularly those who presented or delivered before 34 weeks' gestation) should be screened for pre-existing hypertension, (II-2B) underlying renal disease, (II-2B) and thrombophilia. (II-2C)
2. Women should be informed that intervals between pregnancies of < 2 or ≥ 10 years are both associated with recurrent preeclampsia. (II-2D)
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future pregnancy (II-2A) and for long-term health. (I-A)
4. Women with pre-existing hypertension should undergo the following investigations (if not done previously): urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting total cholesterol and high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides; and standard 12-lead electrocardiography. (III-I)
5. Women who are normotensive but who have had an HDP, may benefit from assessment of traditional cardiovascular risk markers. (II-2B)
6. All women who have had an HDP should pursue a healthy diet and lifestyle. (I-B)

INTRODUCTION

The hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity in Canada[1] and internationally.[2,3] In 1994, the Canadian Hypertension Society initiated a consensus project on the diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. The resulting guidelines, published in the CMAJ in 1997[4–6] and endorsed by the Society of Obstetricians and Gynaecologists of Canada, were instrumental in changing the classification of the hypertensive disorders of pregnancy, adding "adverse conditions" of maternal and perinatal morbidity. The guidelines have been widely cited, and they informed the updates of the American[7] and Australasian[8] guidelines, both published in 2000. In 2005, the SOGC, with representation from the CHS (AL) and from the British Columbia Perinatal Health Program (formerly the British Columbia Reproductive Care Program or BCRCP). initiated a process to update the Canadian guidelines.

These guidelines summarize the quality of the evidence to date and provide a reasonable approach to the diagnosis, evaluation, and treatment of HDP. There are still many areas where evidence is insufficient to guide clinical practice. These deficiencies need to be addressed in future research studies.

METHODS

Canadian obstetricians and internists knowledgeable about HDP and guideline development participated in the project. Invitations to participate took into account geographical representation, previous involvement in developing HDP guidelines, ongoing interest and expertise in HDP, and membership in CHS and/or SOGC.

The literature reviewed included the original HDP guidelines[4–6] and their reference lists and an update from 1995. Each subgroup leader provided the CHS with key words for a subgroup literature search of MEDLINE (1995–2005). Searches were subsequently updated by subgroup members in 2006. Articles were restricted to those published in French or English. The key words used are listed in the Appendix. The concepts explored for pregnancy and hypertension were diagnosis, evaluation, classification, prediction (using clinical and laboratory markers), prevention, prognosis, treatment of hypertension, other treatments of the hypertensive disorders, general management issues (such as mode of delivery and anaesthetic considerations), and postpartum follow-up (for subsequent pregnancies and long-term health).

A focus was placed on consideration of RCTs for therapy and evaluation of substantive clinical outcomes (rather than surrogate markers such as laboratory values). The final grading of the recommendations was done using methodological criteria from the Canadian Task Force on Preventive Health Care (Table 1).[9] The resulting document was reviewed by the Guidelines and Perinatal Committees of SOGC, the British Columbia Perinatal Health Program, and the obstetric section of the Canadian Anesthesiologists' Society.

ABBREVIATIONS

ACE	angiotensin converting enzyme
ADH	antidiuretic hormone
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASSHP	Australasian Society for the Study of Hypertension in Pregnancy
BMI	body mass index
Booking	first antenatal visit, usually early in pregnancy
BP	blood pressure
CHEP	Canadian Hypertension Education Program
CHS	Canadian Hypertension Society
CS	Caesarean section
CT	computed axial tomography
CVP	central venous pressure
DASH	Dietary Approaches to Stop Hypertension
FHR	fetal heart rate
hCG	human chorionic gonadotropin
HDP	hypertensive disorders of pregnancy
INR	international normalized ratio
ISSHP	International Society for the Study of Hypertension in Pregnancy
LMWH	low molecular weight heparin
MRI	magnetic resonance imaging
RBC	red blood cell
RCT	randomized controlled trial
S/D	systolic/diastolic
SGA	small for gestational age
UACR	urinary albumin: creatinine ratio

Appendix. Key words used with "pregnancy" to search MEDLINE (limited to French or English)

Pregnancy AND	AND
{hypertension, hypertensive disorders of pregnancy, pregnancy-induced hypertension, preeclampsia, pregnancy toxemias, gestational hypertension, systolic blood pressure, diastolic blood pressure, OR mean blood pressure}	{diagnosis, definition, classification, prediction, prognosis, severity, maternal mortality, maternal morbidity, perinatal mortality, perinatology, perinatal morbidity}
{hypertension, hypertensive disorders of pregnancy, pregnancy-induced hypertension, preeclampsia, pregnancy toxemias, OR gestational hypertension}	{reproductive technology, weight gain, multiple pregnancy, inter-pregnancy interval, gestational trophoblasic disease, new partner, primigravid, nulliparity, obesity, smoking, diabetes mellitus, dyslipidemia, thrombophilia, previous preeclampsia, maternal age, ethnicity, OR socioeconomic status}
{hypertension, hypertensive disorders of pregnancy, pregnancy-induced hypertension, preeclampsia, pregnancy toxemias, OR gestational hypertension}	{platelets, Hb, Hct, MCV, MPV to platelet ratio, fibrinogen, BUN, creatinine, uric acid, creatinine clearance, PT, aPTT, INR, AST, ALT, LDH, GGT, liver function tests, umbilical artery Doppler, MCA Doppler, diastolic to systolic ratio, MSS, AFP, PAI, PAPP-A, PlGF, hCG, inhibin, activin, sFlt-1, OR vWF}
{measurement} AND	{systolic blood pressure, diastolic blood pressure, OR mean blood pressure measurement} AND {mercury sphygmomanometer, aneuroid sphygmomanometer, electronic device, ambulatory, clinic, OR hospital}
{measurement} AND	{proteinuria, 24 hour urine collection, urinary dipstick, protein to creatinine ratio, OR albumin to creatinine ratio}
{hypertension, hypertensive disorders of pregnancy, pregnancy-induced hypertension, preeclampsia, pregnancy toxemias, OR gestational hypertension}	{diet, exercise, bedrest, micronutrient, vitamin, anti-oxidant, aspirin, heparin, TED stockings, elastic compression stockings, pneumatic compression stockings, thromboprophylaxis, anticoagulants, prostaglandin precursor, prophylaxis}
{hypertension, hypertensive disorders of pregnancy, pregnancy-induced hypertension, preeclampsia, pregnancy toxemias, OR gestational hypertension}	{antihypertensives, antihypertensive agent, hospitalization, antepartum home care program, obstetrical day unit, outpatient, timing of delivery, mode of delivery, fluid administration, plasma volume expansion, plasmapheresis, transfusion, corticosteroids, betamethasone, dexamethasone, magnesium sulphate (or sulfate), anticonvulsants, antiseizure medication, phenytoin (or dilatin), diazepam (or valium), benzodiazepines, postpartum . postnatal, puerperal, puerpium, cardiovascular disease, cerebrovascular disease, renal disease}

AFP: alphafetoprotein; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; GGT: gamma glutamic acid transferase; Hb: hemoglobin; hCG: human chorionic gonadotropin; Hct: hematocrit; INR: international normalized ratio; LDH: lactate dehydrogenase; MCA Doppler: middle cerebral artery Doppler; MCV: mean cell volume; MPV: mean platelet volume to platelet ratio; MSS: maternal serum screening; PAI: plasminogen activator inhibitor; PAPP-A: pregnancy-associated plasma protein A; PlGF: placental growth factor; PT: prothrombin time); sFlt-1: soluble fms-like tyrosine kinase; TEDS: thromboembolic deterrent stockings); vWF: von Willebrand factor

Diagnosis and Classification

The classification of the hypertensive disorders of pregnancy is based on the two most common manifestations of preeclampsia: hypertension and proteinuria. Accordingly, the measurement of blood pressure and proteinuria and the diagnosis of hypertension and clinically significant proteinuria are described in detail.

MEASUREMENT OF BP

Recommendations

1. BP should be measured with the woman in the sitting position with the arm at the level of the heart. (II-2A)
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used. (II-2A)
3. Korotkoff phase V should be used to designate diastolic BP. (I-A)
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements. (III-B)
5. BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in preeclampsia. (II-2A)
6. Automated BP machines may underestimate BP in women with preeclampsia, and comparison of readings using mercury sphygmomanometry or an aneroid device is recommended. (II-2A)
7. Ambulatory BP monitoring (by 24-hour or home measurement) may be useful to detect isolated office (white coat) hypertension. (II-2B)
8. Patients should be instructed on proper BP measurement technique if they are to perform home BP monitoring. (III-B)

Comments

We have focused on measurement issues that are specific to pregnancy. The reader should refer to the most recent CHEP document for general guidelines.[10]

BP measurement should follow standardized technique, as outside pregnancy.[10]

It is preferable to have women rest for five minutes. In particular, Korotkoff phase V should be used for designation of diastolic BP, as it is more reliable,[11] and with its use (compared with use of phase IV), pregnancy outcome is similar.[12] This recommendation replaces the previous recommendation to use both phase IV and phase V. Phase IV (muffling) should be used for diastolic BP only if Korotkoff sounds are audible as the level approaches 0 mmHg. A cuff that is too small (i.e., such that the white lines do not cross) will overestimate sBP by 7–13 mmHg and dBP by 5–10 mmHg. A cuff should never be placed over clothing. Women should be in the sitting position that gives the highest BP; supine positioning has the potential to cause hypotension, and left lateral positioning has the potential to give the lowest BP value, because the right arm is frequently elevated above the level of the heart during BP measurement.[13] Any arm-to-arm differences should be documented, and if the BP is consistently higher in one arm, that arm should be used for all BP measurements.[14]

BP can be measured using a mercury sphygmomanometer, aneroid device, or automated (usually oscillometric) BP device, as mercury sphygmomanometers have been eliminated from many institutions. When choosing a BP measurement device, considerations include observer error, validation, disease specificity, and the need for regular recalibration.

Recalibration involves comparing readings taken with a given device with readings taken with a mercury manometer. Aneroid devices must be recalibrated every two years against mercury devices. This is performed by the biomedical department of hospitals but must be arranged separately by those practitioners with private offices.

Validation is undertaken to determine the accuracy of a device, at all levels of BP readings, on several occasions and for women with different HDPs.[15] Validation must be done particularly in women with preeclampsia for two reasons. First, the detection of preeclampsia is the major purpose of BP measurement in pregnancy. Second, women with pre-existing hypertension have approximately a 20% risk of preeclampsia,[16–20] and women with gestational hypertension may develop typical preeclampsia.[21–26] Automated BP measurement devices will eliminate observer error. However, only some devices have been validated in pregnancy[15] and in preeclampsia, specifically.[27] Automated devices may underestimate BP in preeclampsia by an average of 5 mmHg in systolic and diastolic, but there is wide variation.[28]

Most errors in office BP measurements are operator dependent and correctable. [14] However, ambulatory

measurements have gained popularity. Twenty-four-hour ambulatory BP monitoring or serial BP measurements in an obstetrical day unit may identify women who have isolated office hypertension. Compared with persistently hypertensive women, women with isolated office hypertension are at lower risk of maternal and perinatal complications.[29–33] However, 24-hour ambulatory BP monitoring is of only modest use for an individual woman because of negative predictive values that only modestly decrease the risk of adverse outcomes such as severe hypertension, preterm delivery, and admission to the neonatal intensive care unit.[29,32,33] Home BP monitoring is widely available, economical, comfortable, and easy to repeat when disease evolution is suspected, and pregnant women prefer it to 24-hour ambulatory BP monitoring.[34] However, values have not been validated against adverse pregnancy outcomes.

Therefore, at present, there is insufficient information to define the role of either method of ambulatory BP monitoring in hypertensive (or normotensive) pregnancy. To date, no RCT has been performed to assess the impact of any type of ambulatory BP measurement on maternal or perinatal outcomes.[35]

DIAGNOSIS OF HYPERTENSION

Recommendations

1. The diagnosis of hypertension should be based on office or in-hospital BP measurements. (II-2B)
2. Hypertension in pregnancy should be defined as a diastolic BP of ≥ 90 mmHg, based on the average of at least two measurements, taken using the same arm. (II-2B)
3. Women with a systolic BP of ≥ 140 mmHg should be followed closely for development of diastolic hypertension. (II-2B)
4. Severe hypertension should be defined as a systolic BP of ≥ 160 mmHg or a diastolic BP of ≥ 110 mmHg. (II-2B)
5. For non-severe hypertension, serial BP measurements should be recorded before a diagnosis of hypertension is made. (II-2B)
6. For severe hypertension, a repeat measurement should be taken for confirmation in 15 minutes. (III-B)
7. Isolated office (white coat) hypertension should be defined as office dBP of ≥ 90 mmHg, but home BP of < 135/85 mmHg. (III-B)

Comments

The definition of hypertension in pregnancy is dBP ≥ 90 mmHg by office measurement. A dBP of 90 mmHg identifies a level above which perinatal morbidity is increased in non-proteinuric hypertension, and dBP is a better predictor of adverse pregnancy outcomes than is sBP.[32,36] Non-severely elevated BP should be confirmed by repeat measurement, preferably on more than one visit, as 30% to 70% of women with an office BP of ≥ 140/90 mmHg have normal BP on subsequent measurements on the same visit, after serial measurement in an obstetrical day unit, or after home BP monitoring.[30,32,33,37] Whether the BP is repeated over hours, days, or weeks will depend on the underlying HDP.

Systolic BP was previously excluded from the definition of hypertension in pregnancy for several reasons. First, it is subject to more variation than is dBP. Second, it is usually increased along with dBP.[38] Third, there is the potential for overlabelling and seeing women more frequently than necessary. However, even an intermittently elevated sBP is a risk marker for later development of gestational hypertension,[39] so elevated sBP should trigger closer follow-up and investigation as appropriate.

Defining severe hypertension as a systolic BP ≥ 160 mmHg (instead of ≥ 170 mmHg) is based on the fact that sBP ≥ 160 mmHg is associated with an increased risk of stroke in pregnancy.[40,41]

A relative rise in BP is not part of the definition of hypertension, given that it is within the variation in BP seen in all trimesters of pregnancy, and there is a high false positive rate for suspected preeclampsia.[42] Mean arterial pressure is not part of the definition of hypertension in pregnancy as it is cumbersome to calculate.

If home BP monitoring is used to identify women with isolated office hypertension, then ideally, normal home BP values should be confirmed by 24-hour ambulatory BP monitoring. As criteria for normality have varied, use of the widely accepted threshold (outside pregnancy) of < 135/85 mmHg for normal home BP measurements is recommended[10] (see discussion in *BP measurement*).

MEASUREMENT OF PROTEINURIA

Recommendations

1. All pregnant women should be assessed for proteinuria. (II-2B)
2. Urinary dipstick testing may be used for screening for proteinuria when the suspicion of preeclampsia is low. (II-2B)
3. More definitive testing for proteinuria (by urinary protein: creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of preeclampsia, including in hypertensive pregnant women with rising

BP or in normotensive pregnant women with symptoms or signs suggestive of preeclampsia. (II-2A)

Comments

Most testing for urinary protein is performed to screen for preeclampsia in hypertensive women or those at increased risk of preeclampsia, although urinary protein screening is used in early pregnancy to detect pre-existing renal disease. The current recommendations have been revised to reflect the critical fact that proteinuria is but one diagnostic criterion for preeclampsia. The end-organ complications of preeclampsia may occur in the absence of proteinuria; for example, 20% of women who develop eclampsia will have had only hypertension in the week preceding their seizure, 10% will have had only proteinuria, and 10% will have had neither.[43] There is also the need for both efficiency and economy in clinical care.

There are many options for diagnosis of proteinuria, including urinary dipstick testing, urinary protein: creatinine ratio, and various timed urine collections (most commonly, 24-hour). We do not know the method that best identifies women at increased risk of maternal and/or perinatal complications. However, in a retrospective study, increasing number of pluses of urinary dipstick proteinuria was associated with increasing risk of adverse maternal outcomes.[44] Most research has focussed on methods that best match the quantification of urinary protein by 24-hour urine collection, considered to be the gold standard. However, 24-hour urine collection is time-consuming, inconvenient, and often not complete (as assessed by collection of 13–18% of the ideal body weight as urinary creatinine [mmol/d]).[45] For diagnosis of proteinuria, these logistical considerations have prompted the National Kidney Foundation to abandon timed collections in favour of the spot urine samples.

DIAGNOSIS OF CLINICALLY SIGNIFICANT PROTEINURIA

Recommendations

1. Proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥ 2+. (II-2A)

2. Proteinuria should be defined as ≥ 0.3g/d in a 24-hour urine collection or ≥ 30 mg/mmol urinary creatinine in a spot (random) urine sample. (II-2B)

3. There is insufficient information to make a recommendation about the accuracy of the urinary albumin: creatinine ratio. (II-2 I)

Comments

The upper limit of normal 24-hour urine protein excretion is 0.3 g/d and is based on a 95% CI for urinary protein in pregnancy. It is used by convention; however, a urinary protein measurement of ≥ 0.5g/d may be a better predictor of adverse clinical outcome.[46]

The urinary protein: creatinine ratio has been accepted for diagnosis by the International and Australasian pregnancy hypertension societies. Ideally, this test should be performed in the morning but not on the first voided urine; however, timing may not be critical in pregnancy.[47] The reported cut-off varies from 17 to 57 mg/mmol (median 26 mg/mmol) in 10 studies (1079 hypertensive women).[48–57] For a cut-off of 30 mg/mmol urinary creatinine (as recommended by the ASSHP), and among women with a HDP specifically, the sensitivities and specificities were 0.85 (95% CI 0.78– 0.91) and 0.76 (0.73–0.78), respectively.[58] Efforts are underway to improve the standardization of urinary protein and serum creatinine measurement across laboratories.[59]

Urinary dipstick testing is inexpensive, easy, and widely used. Its usefulness is uncertain for screening either women with hypertension or those who are at increased risk of preeclampsia. A negative or trace value should not be ignored in a woman with new hypertension or symptoms or signs suggestive of preeclampsia; 12% of negative/trace results will be false negatives as assessed against 24-hour proteinuria of 0.3 g/d,[60] and, regardless, these women may have preeclampsia without proteinuria.

For the detection of significant proteinuria, urinary albumin: creatinine ratio (UACR) generally performed well (in comparison with 24-hour urinary protein excretion) in three prospective studies[61–63] but not in a fourth[64] (321 hypertensive women). More information is needed before clinical use of the urinary ACR can be recommended.

It is not clear that there is a role for the quantification of proteinuria in pregnancy for purposes of prognostication, which is discussed under *Prediction, Prevention, and Prognosis of Preeclampsia*. If quantification is sought, then 24-hour urine collection should be used as the U PCR is less reliable at high levels of proteinuria.

CLASSIFICATION OF HDP

Recommendations

1. Hypertensive disorders of pregnancy should be classified as pre-existing or gestational hypertension on the basis of different diagnostic and therapeutic factors. (II-2B)

2. The presence or absence of preeclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes. (II-2B)

3. In women with pre-existing hypertension, preeclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, *or* one or more of the other adverse conditions. (II-2B)

4. In women with gestational hypertension, preeclampsia should be defined as new-onset proteinuria *or* one or more of the other adverse conditions. (II-2B)
5. Severe preeclampsia should be defined as preeclampsia with onset before 34 weeks' gestation, with heavy proteinuria or with one or more adverse conditions. (II-2B)
6. The term PIH (pregnancy-induced hypertension) should be abandoned, as its meaning in clinical practice is unclear. (III-D)

Comments

The purpose of classification is to facilitate communication among caregivers, and to create meaningful groups with different prognoses, considerations for surveillance, and/or outcomes. To this end, the classification system for the hypertensive disorders of pregnancy has been simplified.

According to population-based data, approximately 1% of pregnancies are complicated by pre-existing hypertension, 5% to 6% by gestational hypertension without proteinuria, and 1% to 2% by preeclampsia.[65] It can be expected that these numbers will increase given the trend towards an older and more obese obstetric population.

Hypertension is classified as pre-existing or gestational (Table 2). Pre-existing hypertension pre-dates pregnancy or appears before 20 weeks, and gestational hypertension appears at or after 20 weeks. For both pre-existing and gestational hypertension, there are two subgroups: (1) with comorbid conditions and (2) with preeclampsia, defined by three criteria: hypertension, proteinuria, and adverse conditions. Edema and weight gain remain excluded from the definition of preeclampsia. Edema, even facial, is neither sensitive nor specific for preeclampsia.[66,67] Neither edema nor weight gain is significantly associated with perinatal mortality and morbidity.[36,66] This liberal definition of preeclampsia is meant to signal a need for heightened maternal and fetal surveillance, recognizing that not all of the adverse conditions have equal weight (e.g., eclampsia has different significance from persistent, new/unusual headache).

Severe preeclampsia is defined as preeclampsia with onset before 34 weeks' gestation, with heavy proteinuria (3–5 g/d according to other international guidelines), or with one or more adverse conditions. This definition is consistent with American guidelines[7] and those from the ISSHP,[66] with the exception of the gestational age criterion (see *Prediction, Prevention, and Prognosis of Preeclampsia* and *Place of Care,* and specific therapy). Although the magnitude of proteinuria has not been consistently associated with worse maternal or perinatal prognosis, proteinuria is retained in the definition of severe preeclampsia for face validity, until there are definitive data to indicate that heavy proteinuria should be removed.

Table 2. Classification of the hypertensive disorders of pregnancy*

Primary diagnosis	Definition of preeclampsia†
Pre-existing hypertension	
With comorbid conditions‡	
With preeclampsia → (after 20 weeks' gestation)	Resistant hypertension, *or* New or worsening proteinuria, *or* One/more adverse condition(s)§
Gestational hypertension	
With comorbid conditions‡	
With preeclampsia → (after 20 weeks' gestation)	New proteinuria, *or* One/more adverse condition(s)§

* Women may be classified into more than one subgroup.

† Severe preeclampsia corresponds to preeclampsia: with onset before 34 weeks' gestation, with heavy proteinuria (3–5 g/d according to other international guidelines), or with one or more adverse conditions.

‡Comorbid conditions, such as type I or II diabetes mellitus, renal disease, or an indication for antihypertensive therapy outside pregnancy.

§Other adverse conditions consist of maternal symptoms (persistent or new/unusual headache, visual disturbances, persistent abdominal or right upper quadrant pain, severe nausea or vomiting, chest pain or dyspnea), maternal signs of end-organ dysfunction (eclampsia, severe hypertension, pulmonary edema, or suspected placental abruption), abnormal maternal laboratory testing (elevated serum creatinine [according to local laboratory criteria]; elevated AST, ALT or LDH [according to local laboratory criteria] with symptoms; platelet count <100x109/L; or serum albumin < 20 g/L), or fetal morbidity (oligohydramnios, intrauterine growth restriction, absent or reversed end-diastolic flow in the umbilical artery by Doppler velocimetry, or intrauterine fetal death).

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase

Women with pre-existing hypertension have a 10% to 20% risk of developing preeclampsia, defined by resistant hypertension, new/worsening proteinuria, or one or more adverse condition (Table 2).[16–20] Women with certain comorbidities (e.g., renal disease or pre-existing diabetes mellitus) at also at increased risk.[68] Women with gestational hypertension with onset before 34 weeks (as opposed to onset at ≥ 34 weeks) are more likely to develop preeclampsia, with rates of about 35%.[21–26]

With Comorbid Conditions

"With comorbid conditions" refers to conditions that are strong indications for more aggressive antihypertensive therapy outside pregnancy,[69] and as such, they warrant special BP treatment thresholds and goals in pregnancy. Comorbid conditions are highlighted because they constitute indications for antihypertensive therapy over the short-term, outside pregnancy. These are usually major cardiovascular risk factors, such as type I or II (but not gestational) diabetes, renal parenchymal or vascular disease, or cerebrovascular disease.

With Preeclampsia

The term, preeclampsia has been re-introduced for its brevity and because of its international use. It corresponds to the following previous terms

- pre-existing hypertension with superimposed gestational hypertension, proteinuria and/or an adverse condition or conditions
- gestational hypertension with proteinuria
- gestational hypertension (without proteinuria) with one or more of the adverse conditions.

The changes have been made for clarity. First, the term "superimposed" is not used, but the criteria for the diagnosis of preeclampsia in women with pre-existing hypertension have been clarified. Resistant hypertension is hypertension that requires three antihypertensive medications for control of blood pressure after 20 weeks' gestation. Second, the classification emphasizes that there is significant clinical overlap, that women may meet criteria for more than one subgroup, and that evolution may occur over time. A final diagnosis of the type of HDP is retrospective, following the postpartum period.

All hypertension societies regard preeclampsia as a hypertensive disorder most commonly defined by new-onset proteinuria, and, potentially, other end-organ dysfunction. A restrictive definition of preeclampsia is gestational hypertension with proteinuria, and this is often used by the research community and endorsed for this purpose by the ISSHP.[66] An inclusive definition of preeclampsia is gestational hypertension with proteinuria or typical end-organ dysfunction. Both these guidelines and those of the ASSHP use this inclusive definition.[8] Although the American guidelines use a restrictive definition of preeclampsia, they also state that end-organ dysfunction makes the diagnosis of preeclampsia "highly suspect."[7]

Adverse conditions reflect preeclampsia-related direct fetal complications (e.g., oligohydramnios), direct maternal systemic end-organ complications (e.g., eclampsia), or conditions that significantly heighten the risk of maternal complications (e.g., serum albumin < 20 g/L) (Table 2).

The adverse conditions have been modified. Elevated creatinine has been added. Both oliguria and proteinuria > 3 g/d have been removed. Oliguria is non-specific and has many causes, including high ADH levels after stress or surgery. Also, the diagnosis may prompt fluid administration, and pulmonary edema from fluid administration is a major cause of death in women with preeclampsia.[2] Oliguria (< 15 mL/hr) should be tolerated, at least over the first six hours post partum, in women who do not have pre-existing renal disease. Although there is a continuum of risk between greater proteinuria and more adverse outcomes,[63,66,70] there is no clear cut-off. (Use of urinary protein quantification for prognostication in preeclampsia is discussed under *Prediction, Prevention, and Prognosis of Preeclampsia.*) A threshold for low serum albumin of < 20 g/L has been used as the point at which edema develops from hypoproteinemia alone.[71–73]

Hyperuricemia has not been included as an adverse condition, but was considered because its association with perinatal complications is at least as strong as that of proteinuria.[66,74] To date, serum uric acid has not predicted adverse maternal outcomes in preeclampsia.[75]

Gestational age has not been listed as an adverse condition. However, onset of hypertension at < 34 weeks is a risk marker for evolution of gestational hypertension to preeclampsia and is associated with an increased risk of maternal and perinatal complications.[21–26]

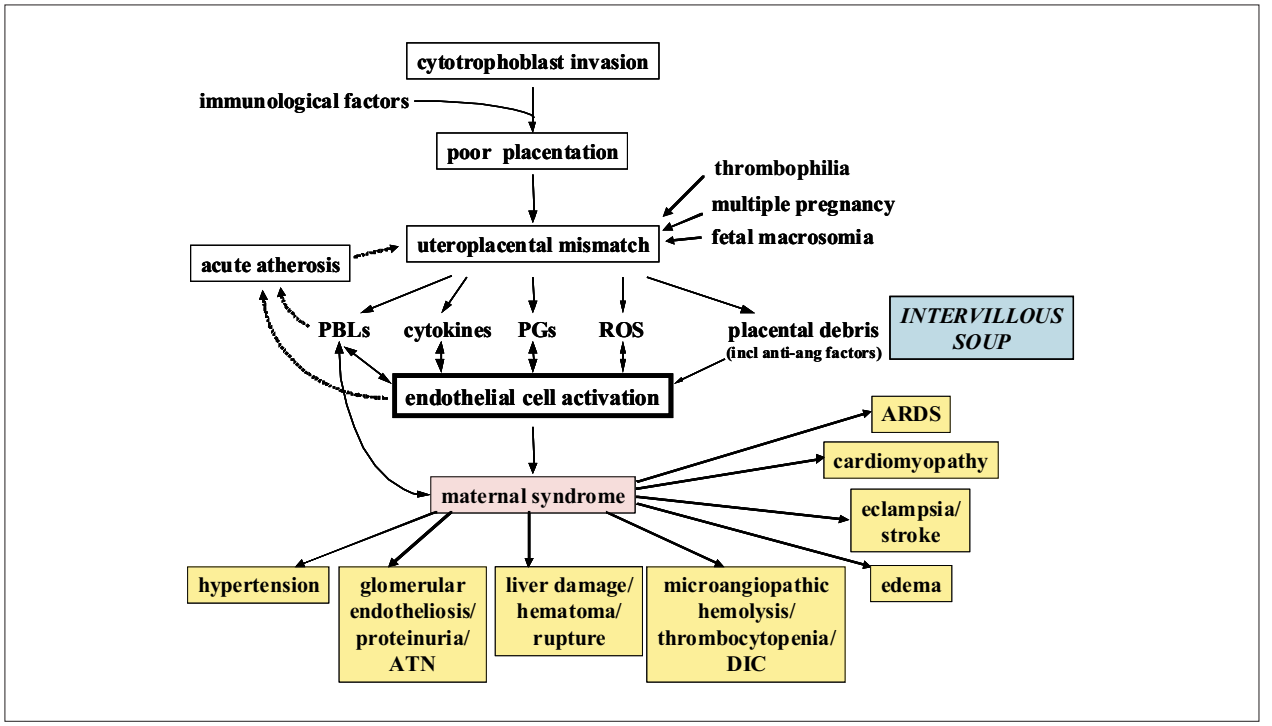
Preeclampsia Is Not Just Hypertension

Understanding the pathogenesis of preeclampsia is key to understanding the multi-system and varied clinical manifestations of preeclampsia. The most popular theory for the pathogenesis of preeclampsia describes a two-stage process, which ultimately results in a mismatch between uteroplacental supply and fetal demands, leading to maternal endothelial cell dysfunction and the maternal (and fetal) manifestations of preeclampsia (Figure).[76] For details, see the reviews by Roberts et al.[77,78]

The most common maternal manifestations are those that are used to define preeclampsia clinically: hypertension and proteinuria. Other manifestations include visual scintillations and scotomata that reflect occipital cortical ischemia, persistent headache that indicates cerebral ischemia and/or edema, epigastric or right upper quadrant pain that reflects capsular irritation secondary to hepatic necrosis and/or hematoma, and dyspnea and/or chest pain that indicate non-cardiogenic pulmonary edema. None of these is specific to preeclampsia.

There are a few specific comments that should be made about maternal signs. Stroke may occur at a systolic BP of 160 mmHg or more, lower than previously thought.[2,41] Stroke and, to a lesser extent, pulmonary edema are the leading causes of maternal death in preeclampsia.[2] The sensitivity and specificity of complications are unknown for clonus or hyperreflexia (which is common in pregnancy). Jaundice is a late finding, reflecting disseminated intravascular coagulation or another diagnosis (e.g., acute fatty liver of pregnancy). The seizures of eclampsia are usually isolated; when women have been imaged before and after eclampsia, CT or MRI studies have usually shown ischemia followed by edema.[79–85]

Figure. The pathogenesis of the maternal syndrome of preeclampsia (modified from von Dadelszen et al.)[76]



anti-ang factors: anti-angiogenic factors (e.g., s-Flt-1:PlGF ratio); ARDS: acute respiratory distress syndrome; ATN: acute tubular necrosis; DIC: disseminated intravascular coagulation; incl: including; PBLs: peripheral blood leukocytes; PGs: eicosanoids (e.g., TXA1:PGI2 ratio); ROS: reactive oxygen species

Fetal manifestations may occur with, precede, or occur in the absence of maternal manifestations.[86] The fetal syndrome consists of oligohydramnios (i.e., low amniotic fluid), intrauterine fetal growth restriction, abnormal Doppler velocimetry of the umbilical artery (as measured by S/D ratio, pulsatility index or resistance index), decreased resistance to flow in the fetal middle cerebral artery (reflecting redistribution of blood flow to the central nervous system), an abnormal waveform in the ductus venosus, and/or stillbirth. Up to 30% of preeclampsia pregnancies are complicated by IUGR, reflected by reduced fetal growth velocity,[87] and usually asymmetrical growth, although growth can be symmetrically reduced with severe placental disease or actually excessive.[88]

INVESTIGATIONS TO CLASSIFY HDP

The investigations relating to preeclampsia cover diagnosis. For women who already have a diagnosis of preeclampsia, surveillance is be covered under *Prognosis of Preeclampsia.*

Recommendations

1. For women with pre-existing hypertension, serum creatinine, serum potassium, and urinalysis should be performed in early pregnancy if not previously documented. (II-2B)
2. Among women with pre-existing hypertension, additional baseline laboratory testing may be based on other considerations deemed important by health care providers. (III-C)
3. Women with suspected preeclampsia should undergo the maternal laboratory (II-2B) and fetal (II-1B) testing described in Table 3.
4. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about preeclampsia (e.g., change in maternal and/or fetal condition). (III-C)
5. Uterine artery Doppler velocimetry may be useful among hypertensive pregnant women to support a placental origin for hypertension, proteinuria, and/or adverse conditions. (II-2B)
6. Umbilical artery Doppler velocimetry may be useful to support a placental origin for intrauterine fetal growth restriction. (II-2B)

Comments

Pre-existing Hypertension

Women with pre-existing hypertension will most likely (> 95%) have essential hypertension, but secondary causes should be considered. A basic work-up has been suggested for women for whom suspicion of a secondary cause is low. (See the CHEP document for a more extensive discussion.[10]) Because conditions such as obesity, associated non-alcoholic steatohepatitis, or immune

Table 3. Investigations to diagnose or monitor maternal and fetal well-being in preeclampsia

Investigations for diagnosis	Investigations for prognosis	Description in women with preeclampsia
	Maternal	
Hemoglobin	Hemoglobin	Higher (due to hemoconcentration) unless there is microangiopathic hemolytic anemia[89-92]
WBC and differential	WBC and differential	Higher (largely due to exaggerated neutrophilia)[89,93]
Platelet count	Platelet count	Lower
Blood film		Microangiopathy with RBC fragments[94,95]
INR and aPTT	*INR and aPTT**	Higher with DIC
Fibrinogen	*Fibrinogen**	Lower
Serum creatinine	Serum creatinine	Higher (due to hemoconcentration and/or renal failure)
Serum uric acid	Serum uric acid	Higher[96]
Glucose		Low in acute fatty liver of pregnancy
AST	AST	Higher
ALT	ALT	Higher
LDH	LDH	Higher
Albumin	Albumin	Lower
Bilirubin	Bilirubin	Higher (unconjugated from hemolysis or conjugated from liver dysfunction)
Urinalysis (routine and microscopy)		
Proteinuria (assessed by urinary protein dipstick, spot or 24 hr)	Proteinuria	Higher (discussed elsewhere)
	Fetal	
Fetal movement count	Fetal movement count	Decreased
Non-stress test	Non-stress test	Non-reassuring FHR
Biophysical profile	Biophysical profile	Lower score (associated with adverse perinatal outcomes, but due to deepest amniotic fluid pocket)[97,98]
Deepest amniotic fluid pocket	Deepest amniotic fluid pocket	Lower
Ultrasonographic assessment of fetal growth	Ultrasonographic assessment of fetal growth	Usually asymmetrical intrauterine fetal growth
Umbilical artery Doppler	Umbilical artery Doppler	Increased resistance, absent or reversed end-diastolic flow

* Tests of coagulation are recommended if there is thrombocytopenia or placental abruption. APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase; DIC: disseminated intravascular coagulation; INR: international normalized ratio; LDH: lactate dehydrogenase; RBC: red blood cells; WBC: white blood cell.

thrombocytopenia may make interpretation of bloodwork for preeclampsia end-organ dysfunction difficult later in pregnancy, it may be appropriate to conduct additional baseline testing in women with these conditions early in pregnancy.

When Preeclampsia is Suspected

Women with suspected preeclampsia should undergo testing (outlined in Table 3[89–98]) for end-organ dysfunction that is characteristic of this condition or to rule out important differential diagnoses (e.g., acute fatty liver of pregnancy). The validity of the various tests in Table 3, alone or in combination, has not been established. Uterine artery Doppler velocimetry may be useful in hypertensive pregnant women to support a placental origin for the hypertension, proteinuria, and/or adverse conditions[99]; obstetric consultation would then be warranted. Umbilical artery Doppler velocimetry may be useful. Absent or reversed end-diastolic flow in the umbilical artery would be more consistent with placental dysfunction than with decreased biological growth potential, uncertain dates, or aneuploidy as a cause of IUGR.[99–103]

Preeclampsia may be a disease in evolution, with clinical manifestations unfolding in a serial fashion. When there is ongoing suspicion of preeclampsia, the nature and frequency of serial surveillance are unclear, but a change in clinical status for mother or baby would be a reasonable indication for repeat testing.

Prediction, Prevention, and Prognosis of Preeclampsia

PREDICTING PREECLAMPSIA

There is no single predictor of preeclampsia among women at either low or increased risk of preeclampsia.

Recommendations

1. At booking for antenatal care, women with markers of increased risk for preeclampsia should be offered obstetric consultation. (II-2B)
2. Women at increased risk of preeclampsia should be considered for risk stratification involving a multivariable clinical and laboratory approach. (II-2B)

Comments

There are many risk markers for preeclampsia, which include maternal demographics; past medical, obstetric, and family histories; and current pregnancy characteristics (Table 4[103–129]). Many markers of preeclampsia risk are known at booking for antenatal care, and these increase the risk of preeclampsia two- to four-fold.[68] These markers are shaded in grey in Table 4, and the strongest among them are previous preeclampsia and anti-phospholipid antibodies. For the other markers in Table 4, the strength of the association with preeclampsia is less well established or less consistent, or the marker pertains to information that becomes available in the second or third trimesters.

In the UK, the strongest clinical markers of preeclampsia risk that are identifiable at antenatal booking (i.e., those shaded in Table 4), have been recommended as a means of screening for preeclampsia in the community (the preeclampsia community guidelines, PRECOG).[108] It is recommended that women should be offered subspecialty referral if they have one of the bolded (and shaded markers) or two or more of the unbolded (and shaded markers) (grade D) (Table 4).

The markers of preeclampsia risk that become available in the second and third trimesters are based on the pathophysiological changes that characterize preeclampsia and precede clinical disease. Risk markers that are best characterized are presented in Table 4. Many have been evaluated, and they include measures of the following: placental perfusion and vascular resistance (e.g., mean second trimester BP, intravenous infusion of angiotensin-II, roll-over test, 24-hour ambulatory BP monitoring, Doppler ultrasound); cardiac output and systemic vascular resistance; fetoplacental unit endocrinology (e.g., alpha fetoprotein, hCG); renal function (e.g., serum uric acid or microalbuminuria); endothelial function and endothelial-platelet interaction (e.g., platelet count, antiphospholipid antibodies, or homocysteine); oxidative stress (e.g., serum lipids); and circulating anti-angiogenic factors.[130,131] None of these (individually) have sufficient sensitivity and predictive values to be useful clinically, even among women at increased risk.

As there is no single test that predicts preeclampsia with sufficient accuracy to be clinically useful,[132] interest has grown in the development of multivariable models that include both clinical and laboratory predictors, available at booking and thereafter in pregnancy.[133] Women at increased risk of preeclampsia may benefit from this type of risk stratification. Table 5 presents an example of such a multivariable approach to risk stratification that distinguishes between population risk (5–7%), low risk (7–29%), intermediate risk (30–50%), and high risk (> 60%) of preeclampsia in the current pregnancy so that antenatal care can be planned accordingly.

PREVENTING PREECLAMPSIA AND ITS COMPLICATIONS

There is a considerable literature devoted to the prevention of preeclampsia. However, there is some controversy over whether or not prevention of preeclampsia per se is a worthy goal, rather than the prevention of the complications of preeclampsia. Non-severe gestational hypertension (or preeclampsia specifically) may have some adaptive function.[134] For example, neonatal morbidity is lower and neurodevelopmental outcome better among SGA babies whose mothers become hypertensive than among those whose mothers do not.[135] Therefore, we have based our recommendations on both the prevention of preeclampsia and/or the prevention of its associated complications.

Using the PRECOG criteria, women are stratified, at booking, as being at low or increased risk of preeclampsia on the basis of the presence (Table 4) of one of the bolded (and shaded) markers, or two or more of the unbolded (and shaded) markers (expert opinion).[108] This approach does

Table 4. Risk markers for preeclampsia*

First trimester markers			Second or third trimester markers
Demographics	Past history	Current pregnancy	
	Previous preeclampsia	Multiple pregnancy	
	Anti-phospholipid antibodies		
	Pre-existing medical condition(s)		
	Pre-existing hypertension or booking diastolic BP ≥ 90 mmHg		
	Pre-existing renal disease or booking proteinuria		
	Pre-existing diabetes mellitus		
Maternal age ≥ 40 years	Obesity (BMI ≥ 35 kg/m^2)	First ongoing pregnancy	
	Family history of preeclampsia (mother or sister)	Inter-pregnancy interval ≥ 10 years	
		Booking sBP ≥ 130 mmHg, or booking dBP ≥ 80 mmHg	
Ethnicity: *Nordic, Black, South Asian or Pacific Island*	Non-smoking	Inter-pregnancy interval < 2 years	Elevated BP†
Lower socioeconomic status	Heritable thrombophilias‡[103-106]	Reproductive technologies§	Abnormal MSS‖
	Increased pre-pregnancy triglycerides	New partner	Abnormal uterine artery Doppler velocimetry¶
	Family history of early-onset cardiovascular disease[107]	Gestational trophoblastic disease	Cardiac output > 7.4L/min
	Cocaine and metamphetamine use	Excessive weight gain in pregnancy	Elevated uric acid
		Infection during pregnancy (e.g., UTI, periodontal disease)	Investigational laboratory markers#

*Those risk markers of greatest importance are highlighted in shades of grey. Women at increased risk (who should be considered for specialty referral) are those with one of the bolded (and shaded) factors, or two or more of the unbolded (and shaded) markers.[108]

†Elevated BP is defined as dBP ≥ 110 mmHg before 20 weeks,68 2nd trimester mean arterial pressure of ≥ 85 mmHg, or a 2nd trimester sBP ≥ 120mmHg.[109] Standardized cut-offs for 24-hour ambulatory BP or home BP monitoring have not been established.

‡Heritable thrombophilia includes Factor V Leiden gene mutation and Protein S deficiency.

§Subfertility and its treatment (especially the use of donor eggs, sperm and/or gametes), after correction for multiple gestations.

‖Decreased first trimester PAPP-A (pregnancy-associated plasma protein A) ≤ 5th centile,[110] unexplained increased second trimester AFP (alphafetoprotein),[111-116] increased second trimester hCG,[114-117] increased first or second trimester inhibin A,[113,118-121] increased second trimester activin.[122]

¶Abnormality is practically defined at 22-24 weeks as bilateral notching with mean resistance index (RI) > 0.55 (i.e., > 50th centile), unilaternal notching with mean RI > 0.65 (> 90th centile), or no notching with mean RI > 0.70 (> 95th centile).[123]

#Investigational markers include elevated sFlt-1/P1GF (soluble fms-like tyrosine kinase, placental growth factor),124-126 PAI-1/PAI-2 (plasminogen activator inhibitor),[124,127] von Willebrand factor,[128] and leptin.[122,125,129]

MSS: maternal serum screening; UTI: urinary tract infection

not recognize nulliparous women as requiring specialist consultation unless another risk marker for preeclampsia is present.

Preventing Preeclampsia and its Complications in Women at Low Risk

Recommendations

1. Calcium supplementation (of at least 1g/d, orally) is recommended for women with low dietary intake of calcium (< 600 mg/d). (I-A)

2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, (II-2E) exercise for maintenance of fitness, (I-A) periconceptual use of a folate-containing multivitamin for prevention of neural tube defects, (I-A) and smoking cessation for prevention of low birthweight and preterm birth. (I-E)

3. The following may be useful: periconceptual use of a folate-containing multivitamin, (I-B) or exercise. (II-2B)

4. The following are **not** recommended for preeclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursors, (I- C) or supplementation with magnesium, (I-C) or zinc. (I-C)

5. The following are **not** recommended: dietary salt restriction during pregnancy, (I-D) calorie restriction during pregnancy for overweight women, (I-D) low-dose

Table 5. Risk stratification for preeclampsia and intensity of antenatal care: EMMA Clinic, Vancouver

Risk	Nature of previous PET	No. of abnormal MSS analytes	Uterine artery Dopplers	Routine antenatal care PLUS
Population risk	Mild or late-onset PET	0	Normal	—
Low risk	Mild or late-onset PET	1	Normal	Education +
	Severe or early-onset PET	0	Normal	Single follow-up growth scan in early 3rd trimester
Medium risk	Mild or late-onset PET	2	Normal	Education +
	Severe or early-onset PET	1	Normal	Single follow-up growth scan in early 3rd trimester +
				Serial bloodwork and clinic visit every 4 weeks +
				Ultrasound* from 20 weeks
High risk	Mild or late-onset preeclampsia	≥ 3	Normal	Education +
	Severe or early-onset PET	2	Normal	Single follow-up growth scan in early 3rd trimester +
	Severe or early-onset PET	0–1	Persistent uterine artery notching or high resistance uterine artery flow at 22–26 weeks	Serial bloodwork and clinic visit every 2 weeks +
				Ultrasound† from 20 weeks

*For growth, amniotic fluid index and umbilical artery Doppler monthly.

†For growth, amniotic fluid index and umbilical artery Doppler every two weeks.

EMMA: estimate of maternal markers of adverse outcome; MSS: maternal serum screening; PET: preeclamptic toxemia

aspirin, (I-E) vitamins C and E (based on current evidence), (I-E) or thiazide diuretics. (I-E)

6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, (II-2I) workload or stress reduction, (II-2I) supplementation with iron with/without folate, (I-I) or pyridoxine. (I-I).

Comments

Abstention From Alcohol

There are no trials on the effect of alcohol abstention on the incidence of HDPs, although reduced consumption is recommended to reduce BP in non-pregnant individuals.[69] There is no proven safe level of alcohol consumption in pregnancy.[136]

Aspirin (Low-Dose)

Low dose aspirin does not decrease the incidence of preeclampsia in low risk nulliparous women (RR 0.93; 95% CI 0.81–1.08).[137–141]

Calcium

There is an inverse relationship between dietary calcium intake and BP in the general population.[142] Low calcium intake (< 600 mg/day, corresponding to less than two dairy servings per day) may do harm by causing vasoconstriction, either through increasing magnesium levels or by stimulating release of parathyroid hormone or renin, thereby increasing vascular smooth muscle intracellular calcium.[143] Oral calcium supplementation (of at least 1g/d) decreases the incidence of preeclampsia (RR 0.68; 95% CI 0.49–0.94) (7 trials including the American CPEP trial,[144] 14 619 women), due to a small decrease among women with low calcium intake (RR 0.81; 95% CI 0.67–0.99) (4 trials, 9775 women).[142] Maternal death or serious morbidity was also reduced (RR 0.80; 95% CI 0.65–0.97) (1 trial, 8312 women).[145] The use of calcium supplementation may have been discouraged by the results of the largest (low-risk) CPEP trial, in which calcium supplementation was not effective in a low-risk, nulliparous population with adequate dietary calcium.[144] There were no documented adverse effects of calcium supplementation.[142] An alternative to supplementation may be an increase in dietary calcium intake, by 3 to 4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

Dietary Changes

Dietary salt restriction (with confirmed compliance) does not affect the incidence of gestational hypertension or preeclampsia specifically (RR 1.11; 95% CI 0.46–2.66) (2 trials, 603 women).[146]

A heart-healthy diet has been associated with a lower risk of preeclampsia in a case-control study.[147] No trials of this intervention were identified.

Energy or protein restriction for women who are overweight or for those with excessive weight gain in pregnancy did not result in a decreased incidence of preeclampsia or gestational hypertension (3 trials, 384 women).[148] There are theoretical concerns about the effect of starvation ketosis on fetal neurodevelopment.[149]

Folate-Containing Multivitamins

Periconceptual use of a folate-containing multivitamin is recommended for all women for primary prevention of neural tube and, possibly, other congenital anomalies, including cardiovascular and limb defects.[150] Periconceptual and ongoing regular use of multivitamins has been associated with primary prevention of gestational hypertension (1 trial, 138 women)[151] and preeclampsia in women with a body mass index < 25 kg/m^2 (prospective cohort, 1835 women).[152] (See below for use of vitamins C and E for women at increased risk of preeclampsia.)

Lifestyle Changes

Observational studies have associated exercise (and greater intensity of exercise) with a reduced risk of preeclampsia.[153–158] Potential mechanisms include a decrease in BP, in lipids, and in proinflammatory cytokines.[159] We were unable to identify trials of exercise for preeclampsia prevention among women at low risk. However, exercise of low to moderate intensity is beneficial for general health reasons to maintain or improve physical fitness (11 trials, 472 women).[160] Overweight women who exercised from early pregnancy had improved exercise capacity without demonstrated differences in substantive clinical outcomes (1 trial, 132 women).[161]

Preeclampsia is associated with greater workload[157,162] and stress,[163] even among women at low risk, but the quality of the evidence does not allow for firm conclusions.[164] Although workload reduction is a common obstetric intervention, we were unable to identify randomized studies of workload or stress reduction on the incidence of preeclampsia. These are unlikely to be forthcoming given the nature of the interventions.

Micronutrients Other Than Calcium

Micronutrient deficiencies other than calcium are often found in pregnancy, but women at risk are difficult to identify clinically. Deficiencies of magnesium, zinc, and pyridoxine have been associated with an increase in HDP and/or their complications.[165–167]

Magnesium is an essential mineral involved in protein synthesis and electrical potentials of muscle membranes and nerves. Magnesium supplementation (various preparations), primarily in women at low risk, did not affect the incidence of a HDP, but did decrease preterm birth (RR 0.73; 95% CI 0.57–0.94), low birthweight (RR 0.67; 95% CI 0.46–0.96), and incidence of SGA infants (RR 0.70; 95% CI 0.53–0.93) (7 trials, 2689 women).[166] However, no conclusions can be drawn because only one included trial was of high quality.

Zinc plays a critical role in protein synthesis and nucleic acid metabolism. Zinc supplementation (20–90 mg elemental zinc) primarily in women at low risk did not affect the incidence of a HDP, although decreases in preterm delivery (RR 0.73; 95% CI 0.54–0.98) and CS (RR 0.69; 95% CI 0.49–0.96) reached statistical significance (7 trials, 1962 women).[165]

Prostaglandin Precursors

Diets rich in marine oils are associated with a reduced risk of preeclampsia.[168] Marine and other oils (e.g., evening primrose oil) are rich in prostaglandin precursors and may be beneficial by reducing inflammation and vasoconstriction. These oils (referred to as prostaglandin precursors for brevity) did not decrease the risk of preeclampsia in mixed populations that included both low and high risk women (RR 0.86; 95% CI 0.59–1.27) (6 trials, 2783 women).[168] However, birth before 34 weeks was marginally decreased (RR 0.69; 95% CI 0.49–0.99). Although marine oil supplementation may be useful, increased dietary intake of fish for the purpose of fish oil consumption, is not recommended because of concerns about contaminants such as mercury.[169]

Smoking Cessation

Smoking is associated with a reduced risk of preeclampsia in observational studies. However, smoking cessation is recommended to decrease low birthweight (RR 0.81; 95% CI 0.70–0.94) and preterm birth (RR 0.84; 95% CI 0.72–0.98) (57 trials, 28 431 women).[170] Various approaches have been tried. An ongoing RCT is evaluating the effectiveness and safety of nicotine replacement therapy in pregnancy.[171]

Thiazide Diuretics

Thiazide diuretics did not decrease preeclampsia (RR 0.68; 95% CI 0.45–1.03) or other substantive outcomes in women at low risk of preeclampsia (5 trials, 1836 women).[172] Maternal side effects were more common than among women who took placebo, but there was no increase in any other substantive adverse maternal or perinatal outcome.

Vitamins C and E

Preeclampsia is associated with oxidative stress. However, in an adequately powered RCT of vitamins C (1000 mg/d) and E (400 IU/d) in nulliparous women at low risk, vitamins C and E therapy from 14–22 weeks showed no reduction in the incidence of preeclampsia (1 trial, 1877 women).[173] In a secondary analysis of these data, vitamins C and E actually increased the incidence of preeclampsia defined as gestational hypertension with proteinuria. The (low-risk arm of the) INTAPP trial of vitamins C and E before 18 weeks was stopped early, but data are pending.[174] The NIH CAPPS Trial of vitamins C and E from 9 to 16 weeks in low-risk primigravid women is ongoing.[175]

Other interventions for Which no Recommendation can be Made

Interest in supplementation with iron and/or folate (beyond 10 weeks' gestation) stems from the importance of anemia in developing countries and further progressive anemia associated with pregnancy. There is insufficient evidence on the effect on preeclampsia of either routine (vs. no routine) iron supplementation (usually 60–100 mg elemental iron/day) on preeclampsia (1 trial, 47 women) or routine iron with/without folic acid supplementation (1 trial, 48 women).[176]

Pyridoxine has many roles, including neurological development and function. Although in five trials (1646 women), pyridoxine supplementation did not decrease the risk of preeclampsia, the trials were of poor quality with poor reporting of substantive outcomes, making it impossible to draw conclusions.[167]

We were unable to identify trials administering the following agents for primary prevention of preeclampsia: garlic, vitamin A, selenium, copper, and iodine.

Preventing Preeclampsia and its Complications in Women at Increased Risk

Prevention of preeclampsia has been extensively studied in women at increased risk, defined most commonly as maternal age < 18 years, positive roll-over test (reflecting increased sensitivity to angiotensin-II but not longer performed clinically), multiple pregnancy, pre-existing hypertension, and/or previous preeclampsia.

Recommendations

1. Low-dose aspirin (I-A) and calcium supplementation (of at least 1 g/d) are recommended for women with low calcium intake, (I-A) and the following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of preeclampsia): abstention from alcohol, (II-2E) periconceptual use of a folate-containing multivitamin, (I-A) and smoking cessation. (I-E)
2. Low-dose aspirin (75–100 mg/d)(III-B) should be administered at bedtime, (I-B) starting pre-pregnancy or from diagnosis of pregnancy but before 16 weeks' gestation, (III-B) and continuing until delivery. (I-A)
3. The following may be useful: avoidance of inter-pregnancy weight gain, (II-2E) increased rest at home in the third trimester, (I-C) and reduction of workload or stress. (III-C)
4. The following are **not** recommended for preeclampsia prevention but may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-C) and magnesium supplementation. (I-C)
5. The following are **not** recommended: calorie restriction in overweight women during pregnancy, (I-D) weight maintenance in obese women during pregnancy, (III-D) antihypertensive therapy specifically to prevent preeclampsia, (I-D) vitamins C and E. (I-E)
6. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet (III-I); exercise (I-I); heparin, even among women with thrombophilia and/or previous preeclampsia (based on current evidence) (II-2 I); selenium (I-I); garlic (I-I); zinc, pyridoxine, iron (with or without folate), or multivitamins with/without micronutrients. (all III-I)

Comments

Antihypertensive Therapy

Antihypertensive therapy does not prevent preeclampsia (RR 0.99; 95% CI 0.84–1.18) or the associated adverse perinatal outcomes, but it decreases by half the incidence of development of severe hypertension among women with mild hypertension (RR 0.52; 95% CI 0.41–0.64) (24 trials, 2815 women).[177] Antihypertensive therapy cannot be recommended for preeclampsia prevention until it can be demonstrated that the decrease in maternal blood pressure is not outweighed by a negative impact on perinatal outcomes.[25,178,179] (Antihypertensive therapy for treatment of elevated BP is discussed under *Treatment of the Hypertensive Disorders of Pregnancy*.)

Aspirin (Low Dose)

In women at increased risk of preeclampsia, low-dose aspirin results in a small decrease in: preeclampsia (RR 0.85; 95% CI 0.78–0.92; NNT 69; 95% CI 51–109 women; 43 trials, 33 439 women for this outcome), preterm delivery (RR 0.92, 95% CI 0.88–0.97; NNT 83; 95% CI 50–238 women), and perinatal death (RR 0.86, 95% CI 0.75–0.98; NNT 227; 95% CI 128–909 women) (51 trials, 36 500 women overall).[180] There is no evidence of short- or long-term adverse

effects on the mother or newborn. Aspirin does not increase miscarriage risk.[181]

Who should receive aspirin and in what dose is unclear. Subgroup analyses in meta-analyses of aspirin trials appear to indicate that aspirin may be more effective for women at greatest baseline risk when it is started before 16 weeks' gestation and when aspirin is used at a higher dose.[180,182,183] This may be because some women are more resistant than others to the effects of aspirin,[184] and/or a dose of at least 75 mg/d may be necessary to inhibit both platelet and placental thromboxane. However, a dose of 100 mg/d may affect fetal prostacyclin synthesis.[185] One RCT found that taking aspirin at bedtime resulted in lower BP than taking aspirin in the morning.[180,186] Aspirin may be continued until delivery[187] (see *Anaesthesia and Fluid Administration*).

Calcium

Oral calcium supplementation (of at least 1g/d) decreases the incidence of preeclampsia (RR 0.22; 95% CI 0.12–0.42) and preterm delivery (RR 0.45; 95% CI 0.24–0.83) (5 trials, 587 women).[142] Three trials were conducted in low calcium intake populations. No trial included women with previous preeclampsia. There were no documented adverse effects of calcium supplementation. An alternative to supplementation may be an increase in dietary calcium intake, by 3 to 4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

Dietary Changes

We were unable to identify trials of dietary salt restriction on the incidence of preeclampsia among women at increased risk. Women with pre-existing hypertension who are already following a DASH diet may continue this diet during pregnancy, but there is no evidence to support this practice.

We were unable to identify trials of a heart-healthy diet for preeclampsia prevention.

Obesity is both a major public health problem and a risk marker for preeclampsia. No effect on gestational hypertension (or preeclampsia specifically) has been demonstrated when overweight women have received dietary counselling during pregnancy to curb the rate of weight gain (3 trials, 384 women).[148] No trials have addressed the impact of pre-pregnancy or early pregnancy weight reduction on preeclampsia; there are theoretical concerns about the impact of starvation ketosis on fetal neurodevelopment.[149]

Folate-Containing Multivitamin

Periconceptual and ongoing regular use of multivitamins was associated with higher birthweight centiles in a secondary analysis of the VIP (vitamin C and E trial) in the UK.[188] Periconceptual use of a folate-containing multivitamin is recommended for all women of child-bearing age for prevention of neural tube and, possibly, other birth defects.

Heparin

Enthusiasm for the use of heparin to prevent preeclampsia and other adverse placental complications comes from the effective use of unfractionated heparin for women with antiphospholipid syndrome and recurrent pregnancy loss.[189] It is unclear whether or not heparin does more harm than good for women with a history of preeclampsia, even in women with an inherited or acquired thrombophilia. There are no completed trials of heparin for preeclampsia prevention in women with thrombophilia.[190] The only trial in women without thrombophilia enrolled 80 women with the angiotensin-converting enzyme DD polymorphism. In this trial, LMWH (dalteparin 5000 IU/d) decreased preeclampsia recurrence by 75%.[191] Potential benefits of thromboprophylaxis must be weighed against the cost, inconvenience, and possible side effects of treatment. Practitioners are encouraged to enrol their patients in clinical trials (e.g., TIPPS[192]).

Lifestyle Changes

There is robust epidemiological data that weight gain between pregnancies (even in non-obese women) is associated with significantly more preeclampsia and other pregnancy complications, such as CS and gestational diabetes.[193]

Physical activity is associated with a reduced incidence of preeclampsia.[159,194] No impact of exercise was seen on gestational hypertension or preeclampsia (2 trials, 45 women)[194]; there is one ongoing high quality of trial of moderate intensity exercise in women with previous preeclampsia.[195] In women at increased risk of preeclampsia, it is not known whether exercise (to improve or maintain fitness) is of greater benefit than risk.

Physically demanding work is associated with a higher risk of gestational hypertension and preeclampsia (OR 1.60; 95% CI 1.30–1.96; 4 observational studies, 5837 women).[162] Although workload reduction is a common obstetric intervention, we were unable to identify randomized studies of workload or stress reduction on the incidence of preeclampsia. These are unlikely to be forthcoming given the nature of the interventions.

Increased rest at home (varying from 30 minutes to 6 hours/day) in the third trimester of pregnancy decreased the incidence of preeclampsia (RR 0.05; 95% CI 0.00–0.83 for increased rest alone; RR 0.13; 95% CI 0.03–0.51 for rest plus a nutrient supplement) (2 trials, 106 women).[196] Other substantive outcomes (such as adverse effects of rest and women's views) were not reported. There is a lack of clarity

about the definition of bed rest and uncertainty about whether women comply with activity restriction.[197]

Micronutrients Other Than Calcium

Magnesium supplementation (various preparations) administered to a mixed population of women at low and high risk in (7 trials, 2689 women) did not decrease the risk of preeclampsia, but decreases were seen in preterm birth (RR 0.73; 95% CI 0.57–0.94), low birth weight (RR 0.67; 95% CI 0.46–0.96), and incidence of SGA infants (RR 0.70, 95% CI 0.53–0.93).[166] However, no conclusions can be drawn because only one included trial was of high quality.

In one trial (100 women), selenium supplementation in the third trimester was reported to decrease "gestational hypertension," but this was not defined.[198]

Garlic may decrease lipid peroxidation and platelet aggregation. In a small trial of 100 women at increased risk of preeclampsia based on a positive roll-over test, no impact of garlic was seen on preeclampsia; garlic supplementation was association with more reports of odour than was placebo.[199]

We did not identify trials of zinc, pyridoxine, iron (with/without folic acid), zinc, multivitamins with/without micronutrients, vitamin A, iodine, or copper for preeclampsia prevention in women at increased risk.

Prostaglandin Precursors

Prostaglandin precursors did not decrease the risk of preeclampsia in mixed populations of women at low and high risk (RR 0.87; 95% CI 0.59–1.28) (5 trials, 1683 women).[168] Birth before 34 weeks was marginally decreased (RR 0.69; 95% CI 0.49–0.99).

Vitamins C and E

Vitamins C (1000 mg/d) and E (400 IU/d) decreased the risk of preeclampsia in one[200] of two small pilot RCTs (2 trials, 483 women).[200,201] Another small RCT found a decreased risk of preeclampsia with administration of multiple antioxidants (including vitamins C and E) in women who had a low superoxide dismutase levels (1 trial, 60 women).[202] However, in an adequately powered RCT in women at high risk (VIP Trial[203]), vitamins C and E did not decrease the incidence of preeclampsia; rather, vitamins C and E were more frequently associated with birthweight < 2.5 kg.[203] The (high risk arm of the) INTAPP trial of vitamins C and E before 18 weeks in women at increased risk of preeclampsia was stopped early but data are pending.[174]

PROGNOSIS (MATERNAL AND FETAL) IN PREECLAMPSIA

Recommendations

1. Serial surveillance of maternal well-being is recommended, both antenatally and post partum. (II-3B)
2. The frequency of maternal surveillance should be at least once per week antenatally, and at least once in the first three days post partum. (III-C)
3. Serial surveillance of fetal well-being is recommended. (II-2B)
4. Antenatal fetal surveillance should include umbilical artery Doppler velocimetry. (I-A)
5. Women who develop gestational hypertension with neither proteinuria nor adverse conditions before 34 weeks should be followed closely for maternal and perinatal complications. (II-2B)

Comments

Women with preeclampsia should undergo serial maternal and fetal surveillance of well-being. However, the nature of surveillance (and its frequency), particularly among women undergoing expectant management of preeclampsia, has not been defined. Table 3 presents a list of suggested investigations, based on detection of end-organ dysfunction. A comprehensive program of maternal and fetal evaluation (that included all of the tests recommended in Table 3) decreased adverse maternal outcomes from 5.1% to 1.2% in one tertiary perinatal centre.[204] Maternal surveillance should continue post partum because of the risk of postpartum deterioration, particularly when there are end-organ complications of preeclampsia.[205]

Maternal surveillance

In a 1999 survey, at least 80% of Canadian obstetric care providers reported using complete blood count, coagulation tests, serum creatinine, serum uric acid, aspartate and alanine aminotransferases, lactate dehydrogenase, urinary dipstick proteinuria, and 24-hour urinary protein.[206] These were performed at least once each week (and rarely daily).

Among women with proteinuria, higher (vs. lower) levels of proteinuria have not been consistently associated with higher maternal or perinatal mortality or morbidity,[17,70,207–209]and have not predicted short-term maternal renal failure or ongoing proteinuria.[208–211] However, given the central role of proteinuria in preeclampsia, we are unwilling to recommend against use of protein quantification (by any method) until further data are available.

Fetal surveillance

In general, a program of antepartum fetal assessment reduces perinatal morbidity and/or mortality in women with HDP.[212] In general, few trials have compared these techniques, and no one technique appears to be superior. For gestational hypertension or preeclampsia specifically, use of umbilical artery Doppler velocimetry appears to decrease perinatal mortality (OR 0.71; 95% CI 0.50–1.01) (11 trials, nearly 7000 women). [213,214] Weekly Doppler

interrogation of the umbilical artery is suggested as reasonable clinical practice.

In the 1999 survey by Caetano et al. (see *Maternal surveillance*), at least 80% of Canadian obstetricians reported using kick count, non-stress test/cardiotocography, and biophysical profile.[206] Compared with maternal surveillance, there is less consistency regarding frequency of fetal testing: daily kick counts daily (83%); at least weekly NST (65%), BPP (88%), or umbilical artery Doppler velocimetry (56%); and less than once weekly ultrasonographically estimated fetal weight.

Gestational Hypertension

Approximately 35% of women with gestational hypertension with onset at < 34 weeks develop preeclampsia,[21–26] and the associated risks of serious maternal (2%) and perinatal complications (16%) are high.[24] These women should receive heightened maternal and fetal surveillance, the nature and frequency of which has not been established.

Treatment of the Hypertensive Disorders of Pregnancy

ANTENATAL TREATMENT

Dietary Changes

Recommendations

1. New dietary salt restriction is not recommended. (II-2D).
2. There is insufficient evidence to make a recommendation about the usefulness of the following: ongoing salt restriction among women with pre-existing hypertension, (III-I) heart-healthy diet, (III-I) and calorie restriction for obese women. (III-I)

Comments

We were unable to identify trials examining the impact of the following on outcomes in any of the HDP: new salt restriction, ongoing salt restriction among women with pre-existing hypertension, heart-healthy diet, or calorie restriction among women who are overweight. An observational study did find that for preeclampsia, a low-salt diet did not decrease BP but did accelerate volume depletion, which may be harmful.[215]

Lifestyle Changes

Recommendations

1. There is insufficient evidence to make a recommendation about the usefulness of: exercise, workload reduction, or stress reduction. (all III-I)
2. For women with gestational hypertension (without preeclampsia), some bed rest in hospital (compared with unrestricted activity at home) may be useful. (I-B)
3. For women with preeclampsia who are hospitalized, strict bed rest is **not** recommended. (I-D)
4. For all other women with HDP, the evidence is insufficient to make a recommendation about the usefulness of bed rest, which may nevertheless, be advised based on practical considerations. (III-C)

Comments

We were unable to identify studies of the impact of exercise on outcomes in any HDP. However, preeclampsia is listed as a contraindication to vigorous exercise in the SOGC 2003 Clinical Practice Guidelines on exercise in pregnancy.[216]

It is common practice to recommend workload reduction or cessation when either non-severe gestational hypertension or preeclampsia is diagnosed and outpatient care is continued. There are no RCT data to support this practice, although it may be practical from the perspectives of both patient (e.g., facilitating maternal and fetal monitoring) and employer (e.g., transition planning). Outside pregnancy, stress management may be useful if stress appears to be associated with hypertension.

Since its introduction in 1952,[217] bed rest has become standard therapy for women with an HDP, as either primary or adjunctive therapy.[218] How bed rest is defined has varied widely, and compliance with recommendations has been questioned.[197] However, bed rest should be determined to be clearly beneficial before it can be recommended, in hospital or at home, because it may have harmful physical, psychosocial, and financial effects.[219,220] There is limited RCT evidence to consider.

For preeclampsia (defined as gestational hypertension with proteinuria), strict (vs. some) bed rest in hospital is not associated with differences in maternal or perinatal outcomes (2 trials, 145 women) (Crowther 1986, cited in Meher[218]).[221] For gestational hypertension (without preeclampsia), some bed rest in hospital (vs. routine activity at home) decreases severe hypertension (RR 0.58; 95% CI 0.38–0.89) and preterm birth (RR 0.53; 95% CI 0.29–0.99) (2 trials, 304 women), although women prefer unrestricted activity at home[222–224]; whether the beneficial effect is from the bed rest or the hospitalization is not clear.

Place of Care

Recommendations

1. In-patient care should be provided for women with severe hypertension or severe preeclampsia. (II-2B)
2. A component of care through hospital day units (I-B) or home care (II-2B) can be considered for women with non-severe preeclampsia or non-severe (pre-existing or gestational) hypertension.

Comments

Out-of-hospital care for preeclampsia assumes that a full assessment (usually in hospital) of maternal and fetal

well-being has been made, and that women do not have severe disease (see *Classification of HDP*). The outpatient literature has excluded women with severe hypertension or severe preeclampsia. The options for outpatient care include obstetrical day units and home care (usually through formal antepartum home care programs). Eligibility will depend on the distance of the woman's primary residence from the hospital, ability to provide adequate surveillance, patient compliance, lability of BP, and lack of progression of preeclampsia or comorbid conditions.

Hospital Day Units

Eligibility for admission to day units has varied from 30% to 60%.[225,226] Trials have focussed on gestational hypertension, and compared care in hospital day units with inpatient care (2 trials, 449 women).[226,227] Maternal and perinatal outcomes and costs were similar, although days in hospital were reduced by care in day units. Women preferred out-of-hospital care in trials[226] as in previous observational studies.[228]

Home Care

Eligibility for formal home care programs is no greater than 25%,[42] although eligibility criteria have varied widely. As a basis for home care, it has been shown that women can accurately measure BP at home using an automated device,[229] and that BP at home is not consistently different from that in hospital, although values for individual women vary widely, particularly for those on antihypertensive therapy.[230]

In observational studies, the definition of home care has varied in terms of prescriptions for bed rest; proportion of self-assessments versus those done by a nurse/midwife; and communication in person, by telephone, or by telephonic electronic transfer.[231,232] However, all involved some component of daily contact and a (usually) weekly hospital or office outpatient visit.[42,231,232]

No RCTs have compared a formal antepartum home care program with either hospital day care or inpatient care. However, for gestational hypertension (without preeclampsia), routine activity at home (vs. some bed rest in hospital) is associated with more severe hypertension (RR 1.72; 95% CI 1.12–2.63) and preterm birth (RR 1.89; 95% CI 1.01–3.45) (2 trials, 304 women), but women prefer routine activity at home.[222,223] It is unclear whether the beneficial effect of bed rest in hospital is from the bed rest or the hospitalization. Formal antepartum home care programs include some component of bed rest.

In observational studies of antepartum home care (vs. inpatient care), hospital admission (25%)[232] and re-admission rates (44%)[42] were quite high. However, home care resulted in similar maternal and perinatal outcomes among women with mild preeclampsia (321 women)[42] or gestational hypertension (592 women),[233] and with reduced costs.[232] Women were satisfied with home care.[234]

Antihypertensive Therapy

The following recommendations apply to women with either pre-existing or gestational hypertension.

For Severe Hypertension (BP of > 160 mmHg Systolic or ≥ 110 mmHg Diastolic)

Recommendations

1. BP should be lowered to <160 mmHg systolic and <110 mmHg diastolic. (II-2B)
2. Initial antihypertensive therapy should be with labetalol, (I-A) nifedipine capsules, (I-A) nifedipine PA tablets, (I-B) or hydralazine. (I-A)
3. $MgSO_4$ is not recommended as an antihypertensive agent. (I-E)
4. Continuous FHR monitoring is advised until BP is stable. (III-I)
5. Nifedipine and $MgSO_4$ can be used contemporaneously. (II-2B)

Comments

Severe elevations of BP (i.e., ≥ 160/110 mmHg) should be confirmed after 15min. There is general consensus that severe hypertension should be treated in pregnancy to decrease maternal morbidity and mortality.[40] Most women with severe hypertension in pregnancy will have preeclampsia, and most of those will have had normal BP in the recent past. These hypertensive events are considered urgencies, given such potentially large and acute increases in BP, even in the absence of symptoms.

Obstetricians most frequently prescribe parenteral hydralazine or labetalol for treatment of severe hypertension (Table 6) according to a 1999 survey of Canadian practitioners.[235] By meta-analysis of the relevant (21 trials, 1085 women), parenteral hydralazine, compared with other short-acting antihypertensives, may be associated with more adverse effects, including maternal hypotension, CS, and adverse FHR effects.[236] Observational literature illustrates that hypotension may result with any short-acting antihypertensive agent administered to women with preeclampsia, because they are intravascularly volume depleted. Therefore, it may be prudent to continuously monitor FHR until BP has stabilized. The same meta-analysis shows that labetalol may be associated with more neonatal bradycardia (which required intervention in one of six affected babies[237]).[236] Labetalol was administered

Table 6. Doses of most commonly used agents used for treatment of a BP of ≥ 160/110 mmHg hypertension

Agent	Dosage	Comments
Labetalol	Start with 20 mg IV; repeat 20–80 mg IV q 30min, or 1–2 mg/min, max 300 mg (then switch to oral)	Best avoided in women with asthma or heart failure. Neonatology should be informed, as parenteral labetalol may cause neonatal bradycardia
Nifedipine	5–10 mg capsule to be bitten and swallowed, or just swallowed, every 30 min	There are three types of nifedipine preparations (i.e., capsules, intermediate-release tablets [PA], and slow-release tablets [SL]) with which all staff must be familiar
	10 mg PA tablet every 45 min to a maximum of 80 mg/d	
Hydralazine	Start with 5 mg IV; repeat 5–10 mg IV every 30 min, or 0.5–10mg/hr IV, to a maximum of 20mg IV (or 30 mg IM)	May increase the risk of maternal hypotension

parenterally in these studies; however, it has been given orally for hypertensive urgencies, with good effect.[238]

Forty percent of Canadian obstetricians describe frequent use of $MgSO_4$ for treatment of severe hypertension.[235] The limited (and observational) literature describes no decreases[239] or transient decreases in BP[240–243] 30 minutes after 2 to 5 g of IV $MgSO_4$ (with or without ongoing infusion), usually in patients with preeclampsia. Therefore, although a sustained lowering of BP cannot be anticipated following an $MgSO_4$ bolus, the potential for a transient lowering of BP 30 minutes after administration should be considered when antihypertensives are co-administered.

The nifedipine preparations that are appropriate for treatment of severe hypertension are the capsule and the PA tablet.[244] Most authors of randomized trials did not specify whether nifedipine capsules were bitten (prior to swallowing), which may have a greater effect on BP. Although the 5 mg (vs. 10 mg) capsule may reduce the risk of a precipitous fall in BP, there are no published studies comparing the 5 mg and 10 mg doses. The risk of neuromuscular blockade with contemporaneous use of nifedipine and $MgSO_4$ is < 1%, based on a single-centre, controlled study, and a complete data synthesis from the literature[245]; blockade is reversed with 10g of IV calcium gluconate.

Nitrogylcerin is primarily venodilatory. Theoretically, it may not be a good choice of antihypertensive in women with preeclampsia. However, no adverse clinical effects have been demonstrated in small studies.[246,247] For refractory hypertension in an intensive care setting, consideration can be given to using sodium nitroprusside or diazoxide.[248]

For Non-Severe Hypertension (BP of 140–159/90–109 mmHg)

Recommendations

1. For women without comorbid conditions, antihypertensive drug therapy should be used to keep sBP at 130–155 mmHg and dBP at 80–105 mmHg. (III-C)
2. For women with comorbid conditions, antihypertensive drug therapy should be used to keep sBP at 130–139 mmHg and dBP at 80–89 mmHg. (III-C)
3. Initial therapy can be with one of a variety of antihypertensive agents available in Canada: methyldopa, (I-A) labetalol, (I-A) other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol), (I-B) and calcium channel blockers (nifedipine). (I-A)
4. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should not be used. (II-2E)
5. Atenolol and prazosin are not recommended. (I-D)

Comments

Management of a patient/woman with a BP of 140–159/90–109 is much debated. Any antihypertensive therapy will, compared with placebo or no therapy, decrease the risk of transient, severe hypertension (RR 0.50; 95% CI 0.41–0.61; 19 trials, 2409 women; NNT 9–17), without a clear difference in other maternal or perinatal outcomes, such as stroke, perinatal death, or preterm delivery (28 trials, 3200 women).[249] The results of a small pilot RCT[25,179] and a meta-regression of RCTs indicate that antihypertensive therapy may be harmful. The meta-regression of RCTs found a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of SGA infants or lower birthweight.[250,251]There are no reliable data on long-term developmental outcomes.[252,253] A large definitive trial is needed.

Women without comorbid conditions should have antihypertensive therapy to lower dBP to 80–105 mmHg. Choosing an upper limit of 105 mmHg for dBP acknowledges intra-patient variability in BP, the inaccuracies of BP measurement, the desire to avoid severe diastolic hypertension (dBP ≥ 110 mmHg), and the recognition that outside pregnancy, non-severe hypertension is not an indication for immediate treatment.[254] Choosing a lower limit of 80 mmHg for the dBP goal is consistent with non-pregnancy recommendations that do not recommend

Table 7. Doses of most commonly used agents used for treatment of a BP of 140-159/90-105 mmHg

Agent	Dosage	Comments
Methyldopa	250–500mg po bid-qid (max 2g/d)	There is no evidence to support a loading dose of methyldopa.
Labetalol	100–400mg po bid-tid (max 1200 mg/d)	Some experts recommend a starting dose of 200 mg po bid.
Nifedipine	PA tablets (10–20 mg po bid-tid, max 180 mg/d) or XL preparation (20–60 mg po OD, max 120 mg/d)	Caution should be exercised in ensuring that the correct form of nifedipine has been prescribed.

lowering beyond this number in the absence of a comorbid condition (e.g., type I diabetes mellitus). This goal also reflects concern that a dBP < 80 mmHg may limit uteroplacental perfusion.[250,251]

In contrast, **women with comorbid conditions** (Table 2) should probably have their sBP lowered to 130–139 mmHg and their dBP lowered to 80–90 mmHg. Given that antihypertensive therapy in pregnancy aims to optimize pregnancy outcome (rather than affect long-term cardiovascular risk), other cardiovascular risk markers that are considered compelling indications outside pregnancy are not considered as such in pregnancy. These are cigarette smoking, abnormal (pre-pregnancy) lipid profile, strong family history of premature cardiovascular disease, truncal obesity, or sedentary lifestyle. Choosing a higher BP goal than the non-pregnancy recommendation of BP < 130/80 mmHg represents a compromise between maternal protection and maintenance of placental perfusion.

For women with preeclampsia, data are insufficient to prompt different recommendations for management of a BP of 140–159/90–109 mmHg. Antihypertensive therapy does not decrease maternal morbidity in preeclampsia or eclampsia, and eclampsia is not simply a hypertensive encephalopathy. However, there may be circumstances (e.g., severe headache) in which it seems prudent to normalize BP, and others (e.g., absent end-diastolic flow)in which it does not.

The Canadian Hypertension Education Program recommendations[254] provide the clinician/caregiver with initial guidance with respect to treatment of secondary causes of hypertension in pregnancy.

When a decision is made to use antihypertensive therapy, there is little to guide the choice of agent. In RCTs, a wide variety of antihypertensive agents have been compared with placebo or no therapy: methyldopa, labetalol, other pure beta-blockers (acebutolol, mepindolol, metoprolol, pindolol, and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine, and verapamil), hydralazine, prazosin, or ketanserin (28 trials, 3200 women)[249]; ketanserin, isradipine, nicardipine, and mepindolol are not used in Canada. In comparative trials (usually of beta-blockers compared with methyldopa), beta-blockers (i.e., labetalol, pindolol, metoprolol, or oxprenolol) may be more effective antihypertensives than methyldopa (RR 0.75; 95% CI 0.58–0.94) (10 trials, 539 women), but no other differences in maternal or perinatal outcomes have been demonstrated (19 trials, 1282 women).[177,249,255] Very limited data have not revealed adverse effects of (any) antihypertensive agent on health or neurodevelopment assessed at one year (nifedipine, 110 children),[253] 18 months (atenolol, 190 children),[256] or 7.5 years (methyldopa, 242 children)[252] in placebo-controlled trials.

Labetalol and methyldopa are the oral agents used most frequently in Canada[235] (Table 7). ACE inhibitors and ARBs are fetotoxic,[257] especially to the fetal kidney; however, an ACE inhibitor or ARB that was prescribed pre-pregnancy for renoprotection should be restarted post partum, even during breastfeeding.[258] Thiazide diuretics can be considered for use; despite concerns that thiazides may inhibit the normal plasma volume expansion of pregnancy, thiazides used after the first trimester for preeclampsia prevention have not increased adverse maternal or perinatal outcomes but have not prevented preeclampsia or severe hypertension (5 trials, 1836 women)[172]; there are no follow-up studies on children exposed to thiazides in utero. Specific mention should be made of a few agents. It is not clear why atenolol (in contrast to other beta-blockers, even cardioselective) may be associated with adverse effects on fetal growth[259–263]; until further data are available on the risks of atenolol in pregnancy, other agents are preferable. More stillbirths were reported in the prazosin arm of one trial.[264] Hydralazine is not recommended because of maternal side effects when used alone.[265] Oral antihypertensives do not appear to change FHR or pattern, but the quality of the data is poor[266]; as a conservative approach, changes in FHR or pattern while a woman is taking antihypertensive therapy are best attributed to evolution of the underlying HDP, and not to the antihypertensive agent.

Corticosteroids for Acceleration of Fetal Pulmonary Maturity

Recommendations

1. Antenatal corticosteroid therapy should be considered for all women who present with preeclampsia before 34 weeks' gestation. (I-A)
2. Antenatal corticosteroid therapy may be considered for women who present at < 34 weeks' with gestational hypertension (despite the absence of proteinuria or 'adverse conditions') if delivery is contemplated within the next 7 days. (III-I)

Comments

When administered prior to 34 weeks,' antenatal corticosteroids (i.e., betamethasone 12mg IM every 24 hours for two doses) accelerate fetal pulmonary maturity and decrease neonatal mortality and morbidity.[267]

If expectantly managed, women with preeclampsia will be delivered within two weeks of administration of corticosteroids at >34 weeks' gestation, but the duration of pregnancy prolongation varies from hours to weeks; therefore all women with preeclampsia should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity.

One third of women with gestational hypertension without proteinuria or adverse conditions at < 34 weeks' will develop preeclampsia; however, the mean time to delivery is about five weeks, and delivery is unlikely within seven days of administration.[24] Whether or not these women should receive antenatal corticosteroids at onset of gestational hypertension is unclear.

Antenatal corticosteroids may cause significant, transient changes in FHR and variability up to four days after administration, as measured by either computerized or visual analysis of the CTG.[214,268,269]

Mode of Delivery

Recommendations

1. For women with any HDP, vaginal delivery should be considered unless a Caesarean section is required for the usual obstetric indications. (II-2B)
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery. (I-A)
3. Antihypertensive treatment should be continued throughout labour and delivery to maintain sBP at < 160 mmHg and dBP at < 110 mmHg. (II-2B)
4. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopenia or coagulopathy. (I-A)
5. Ergometrine should not be given in any form. (II-3D)

Comments

All women with HDP should be considered for induction of labour.

For induction of labour, cervical ripening is recommended to increase the chance of successful vaginal delivery; these data are derived from normotensive pregnancies.[270] Induction of labour in women with severe preeclampsia takes more time[271] and is less successful than in women with normotensive pregnancies.[272] However, success is 60% at > 32 weeks.[273,274] A success rate of 30% can be achieved even when birthweight is < 1500 g.[275,276] The success rate is low (10%) at < 26 weeks[273] An unfavourable cervix does not preclude successful induction.[276] Neither IUGR nor oligohydramnios are contraindications to induction of labour.[275] When there is increased resistance to diastolic flow in the umbilical artery, the vaginal delivery rate is significantly lower but still greater than 50%.[277,278] Most babies with absent or reversed end-diastolic flow by Doppler velocimetry of the umbilical artery are delivered by CS.[279]

With induction of labour, in observational studies, maternal and fetal outcomes are similar or improved in severe preeclampsia.[273–275,280] There are also future considerations relevant to CS, such as the risk of uterine rupture with subsequent pregnancies or morbidity associated with repeat Caesarean sections.[281]

Epidural analgesia lowers BP and possibly cerebral blood flow index.[282] Women with preeclampsia are at risk of thrombocytopenia and coagulopathy (antepartum or de novo, post partum), and all standard measures (such as active management of the third stage with oxytocin[283]) should be taken to avoid postpartum hemorrhage.

Anaesthesia, Including Fluid Administration

Recommendations

1. The anaesthesiologist should be informed when a woman with preeclampsia is admitted to delivery suite. (II-3B)
2. A platelet count should be performed in all women with HDP on admission to the delivery suite, but tests of platelet function are not recommended. (III-C)
3. Regional analgesia and/or anaesthesia are appropriate in women with a platelet count > 75×10^9/L, unless there is a coagulopathy, falling platelet concentration, or co-administration of an antiplatelet agent (e.g., ASA) or anticoagulant (e.g., heparin). (III-B)
4. Regional anaesthesia is an appropriate choice for women who are taking low-dose ASA in the absence of coagulopathy and in the presence of an adequate platelet count. (I-A)

5. Regional anaesthesia is an appropriate choice for women on low-molecular weight heparin (LMWH) 12 hours after a prophylactic dose, or 24 hours after a therapeutic dose. (III-B)
6. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of pain. (I-A)
7. A fixed intravenous fluid bolus should not be administered prior to regional analgesia and / or anaesthesia. (I-D)
8. Small doses of phenylephrine or ephedrine may be used to prevent or treat hypotension during regional anaesthesia. (I-A)
9. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean section: epidural, spinal, combined spinal-epidural, and general anaesthesia. (I-A)
10. Intravenous and oral fluid intake should be minimized in women with preeclampsia, to avoid pulmonary edema. (II-1B)
11. Fluid administration should not be routinely administered to treat oliguria (< 15 mL/hr). (III-D)
12. For persistent oliguria, neither dopamine nor furosemide is recommended. (I-D)
13. Central venous access is not routinely recommended, and if a central venous catheter is inserted, it should be used to monitor trends and not absolute values. (II-2D)
14. Pulmonary artery catheterization is not recommended unless there is a specific associated indication, (III-D) and then only in a high dependency unit setting. (III-B)

Comments

There should be early consultation with an anaesthesiologist, ideally antepartum, but certainly on admission to the labour ward of a woman with preeclampsia. The importance of communication between caregivers has been repeatedly highlighted by the Confidential Enquiries into Maternal Deaths in the UK.[284] The anaesthesiologist can assess the patient for coagulation, airway, previous anaesthetic problems, severity of hypertension, level of consciousness, and medication used, such as $MgSO_4$, which interacts with non-depolarizing muscle relaxants. The anaesthesiologist can also facilitate effective management of preeclampsia complications (e.g., pulmonary edema), initiate early epidural analgesia, and insert an indwelling arterial catheter in women who need serial blood sampling and/or parenteral antihypertensive medication (and close BP monitoring). Women who are obtunded and/or have evidence of increased intracranial pressure can be administered an appropriate anaesthetic to prevent both an increase in BP with induction and an increase in intracranial pressure.

All women with a HDP should have a platelet count. Tests of platelet function, such as bleeding time, thromboelastrography, or platelet function analyzer 100, are not indicated, as there is no evidence that an abnormal result increases bleeding risk.[285] Both the absolute number of, and trend in, platelet counts are important. Bleeding into the epidural space following neuraxial anaesthesia has not been associated with platelet counts above $75x10^9$/L, as long as there is no platelet dysfunction or associated coagulopathy.[286] Among anaesthesiologists, practice varies widely within the range of $50–100x10^9$/L platelets.[287,288] The same comments made about epidural catheter insertion apply to platelet counts necessary for catheter removal. Women on low-dose ASA are eligible for neuraxial anaesthesia.[187]

In addition to platelet count, it may be prudent to include tests of coagulation, particularly if there is other end-organ system involvement or platelets are abnormal in number. Regardless, some anaesthesiologists will require specific tests of coagulation (INR, aPTT and fibrinogen) prior to regional analgesia/anaesthesia.[287,289]

The American Society of Regional Anesthesia guidelines specify that women are not eligible for regional anaesthesia until at least 10 to 12 hours after a prophylactic dose or 24 hours after a therapeutic dose of LMWH, based on reports of epidural hematoma in non-pregnancy populations.[290] However, some anaesthesiologists prefer to wait 24 hours after any dose of LMWH because of the unknown risk of an epidural hematoma.

Early placement of an epidural catheter is advantageous. First, it maintains the option of regional anaesthesia should the maternal condition subsequently change (e.g., thrombocytopenia develops) or the fetal condition change quickly, such that general anaesthesia would otherwise be required. However, should delivery be required in less than 5 to 10 minutes, general anaesthesia will still be required, even if there is an epidural catheter in place. Second, epidural analgesia ablates the labour pain-induced increase in cardiac output and BP mediated by the sympathetic nervous system, which is activated particularly in women with preeclampsia.[291–293] Epidural analgesia does not harm the fetus; in fact, Doppler velocimetry of the umbilical artery may improve.[291,294,295] Epidural analgesia does not increase the risk of CS in women with severe preeclampsia.[296] Combined spinal-epidural anaesthesia is acceptable.[297]

If there is a contraindication to regional analgesia and/or anaesthesia, then intravenous opioid analgesia is a reasonable alternative. However, there is a higher risk of neonatal

depression, and neonates more frequently need naloxone (one small RCT).[298]

For CS in the absence of an epidural catheter, spinal anaesthesia is preferred to epidural anaesthesia because its effect is more rapid and effective, and it requires use of a smaller needle.[288] Spinal is preferred to general anaesthesia because it avoids the risks of the hypertensive response to intubation; however, spinal anaesthesia may take more time to achieve, and it may be associated with lower cord pH and higher cord base deficit, the clinical implications of which are not known.[299] No differences in uteroplacental hemodynamics have been demonstrated during spinal anaesthesia.[300]

General anaesthesia in women with a hypertensive disorder is more likely to be associated with difficult (or failed) intubation[301,302] and to be associated with a hypertensive response to intubation.[303,304] This hypertensive response can be attenuated by antihypertensive (such as parenteral labetalol or oral nifedipine), nitroglycerin, or parenteral opioids.[304–308]

Prior to neuroaxial analgesia/anaesthesia, preloading with a fixed volume of crystalloid (i.e., 500–1000 mL) is neither necessary nor effective in preventing a fall in BP in normal women prior to CS (meta-analysis of RCTs)[309]; no studies are available for hypertensive pregnant women. Exceptions to this statement could include dehydration and/or FHR abnormalities. Pre-loading may also increase the risk of pulmonary edema, which is the major cause of death in women with preeclampsia.[2] If pre-loading is performed, then it may be prudent to use colloid, although concerns have been raised about the potential to cause coagulopathy.[310]

Oliguria (< 15 mL urine/hr) is common in preeclampsia, particularly post partum. In the absence of pre-existing renal disease or a rising creatinine, oliguria should be tolerated, at least over hours. First, oliguria is non-specific and has many causes, including oxytocin administration and high levels of ADH following surgery. Second, pulmonary edema from fluid administration is a leading cause of death in women with preeclampsia,[2] and more fluid administration is associated with more pulmonary edema.[311,312] Fluid balance should be closely monitored, and furosemide should not be administered unless there is pulmonary edema. No conclusions can be drawn about the benefits of furosemide or dopamine for oliguria, and they are not recommended.[313,314]

If hypotension does develop following regional analgesia/anaesthesia, vasopressors should be administered as an infusion or small boluses of ephedrine (5–10 mg/bolus) or phenylephrine (50–100 μg/bolus).[315] Small doses are recommended to avoid an exaggerated response in hypertensive pregnant women.

Central venous access is recommended only in women who are hemodynamically unstable, with, for example, hemorrhage or acute renal failure. Women can be effectively monitored by vital signs and oxygen saturation. There is no correlation between CVP and pulmonary capillary wedge pressure, so absolute values of CVP are less important than the trend. CVP should be used for monitoring response to therapy, rather than for diagnostics. Pulmonary artery catheterization is not recommended unless there is a specific associated indication, and then it should be done in the ICU.

Aspects of Care Specific to Women With Pre-Existing Hypertension

Recommendations

1. Pre-conceptual counselling for women with pre-existing hypertension is recommended. (III-I)
2. Discontinue ACE inhibitors and ARBs pre-pregnancy (or as soon as pregnancy is diagnosed). (II-2D)
3. If antihypertensive agent(s) are to be discontinued or changed to allow treatment to continue during pregnancy, then consider changing the agent(s) pre-pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid-conditions, she is likely to conceive easily (within 12 months). (III-I)
4. Consider discontinuing atenolol when pregnancy is diagnosed. (I-D)
5. A variety of antihypertensive drugs may be used in the first trimester of pregnancy (e.g., methyldopa, labetalol, and nifedipine). (II-2B)

Comments

One percent of women under 30 years of age are hypertensive. Pre-conceptual counselling is ideal, but as 50% of pregnancies are unplanned, inadvertent exposure to antihypertensives will occur. The adequacy of contraception and the potential for teratogenicity of drugs must be considered when prescribing antihypertensives to women of child-bearing age. All such women should be reminded to take at least 0.8 mg/day of folic acid prior to pregnancy.

The potential teratogenicity of antihypertensives must be assessed relative to the baseline risk of major malformations: 1% to 5% of pregnancies. None of the antihypertensive agents has been proven not to be teratogenic, but the quality of the information is only fair for most agents.[316] (Information can be obtained rapidly from the DART database.[317]) The most commonly used antihypertensive agents are methyldopa and labetalol. A teratogenic effect of ACE inhibitors has been reported, but the confounding effects of factors related to major

malformations (such as pre-gestational diabetes) have not been established.[318] ARBs are considered to have the same potential for teratogenicity and are described in fewer published studies.[319] The potential for atenolol to have adverse effects on fetal growth has been associated in particular with use from early pregnancy.[259–263]

There is little information to guide clinicians/caregivers in determining whether ACE inhibitors, ARBs, atenolol, or a less commonly used antihypertensive should be replaced pre-pregnancy or when pregnancy is diagnosed, and if so, with what. There are a number of issues to consider:

- **What is the indication for the drug?**
  In an otherwise healthy woman with non-severe hypertension, then it is not critical to normalize BP over months. BP falls in pregnancy anyway, reaching a nadir at about 20 weeks, and then rising towards pre-pregnancy levels by term. It is possible, therefore, that antihypertensive agents may not be needed, or that a lower dosage may be needed towards the end of pregnancy.
- **Is there an alternative agent available?**
  If ACE inhibitors are being given for renoprotection, no alternative is available. Data are too limited to recommend diltiazem to decrease proteinuria and preserve renal structure and function in pregnant women with chronic renal disease in pregnancy.[320]
- **How long will conception take?**
  It is normal for conception to take up to 12 months, but women over the age of 30 years have a higher incidence of subfertility. If an ACE inhibitor is discontinued pre-pregnancy in a woman with renal disease, yet conception does not occur after 12 months and proteinuria is rising despite excellent BP control (i.e., < 130/80 mmHg), then it may be prudent to reinstate ACE inhibition, perform monthly pregnancy tests, and proceed with investigations of subfertility. The level of proteinuria is a prognostic factor for long-term renal survival.

Women with pre-existing hypertension may have other comorbidities and/or cardiovascular risk factors that are being treated.

Published case reports suggest that lovastatin, the statin for which the most information with respect to use and effects in pregnancy is available, is unlikely to represent a reproductive risk.[321] However, as the objective of statin therapy is to decrease long-term cardiovascular risk, the potential risks of statin therapy (over the nine months of pregnancy) may outweigh the potential benefits of statin therapy (realized over years of therapy including the nine months of pregnancy). Statin therapy should be discontinued pre-pregnancy or as soon as pregnancy is diagnosed.

Aspirin is recommended for global cardiovascular risk protection in non-dyslipidemic individuals with hypertension in the presence of three or more major cardiovascular risk markers, including but not limited to diabetes mellitus, smoking, family history of premature cardiovascular disease, microalbuminuria or proteinuria, total cholesterol to high-density lipoprotein ratio = 6, and left ventricular hypertrophy.[69] Low-dose aspirin can be continued throughout pregnancy (see *Preventing Preeclampsia and its Complications*).

See information on management of renal disease in pregnancy, see the update by Davison.[322]

Aspects of Care Specific to Women With Preeclampsia

Timing of Delivery of Women With Preeclampsia

Recommendations

Management should be based on the understanding that delivery is the only cure for preeclampsia.

1. Obstetric consultation is mandatory in women with severe preeclampsia. (III-B)
2. For women at < 34 weeks' gestation, expectant management of preeclampsia (severe or non-severe) may be considered, but only in perinatal centres capable of caring for very preterm infants. (I-C)
3. For women at 34–36 weeks' gestation with non-severe preeclampsia, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management. (III-I)
4. For women at ≥ 37[0] weeks' gestation with preeclampsia (severe or non-severe), immediate delivery should be considered. (III-B)

Comments

The Confidential Enquiries into Maternal Death[284] have consistently identified the failure to appreciate risk in preeclampsia as responsible for potentially avoidable complications. Subspecialty consultation has been advised, particularly for women with severe preeclampsia.[2] Given geographical considerations, obstetrical advice could be obtained by telephone.

The phrase, "planned delivery on the best day in the best way," alludes to the fact that there are a myriad of considerations regarding timing (and mode of) delivery in women with preeclampsia.[238] When a woman should be delivered will depend on evolving adverse conditions (Table 2) and gestational age; the adverse conditions in the classification

of the HDP do not necessarily represent indications for delivery.

Expectant management of preeclampsia refers to attempted pregnancy prolongation following a period of observation, assessment, stabilization (usually of maternal BP), and, if gestational age is less than 34 weeks, administration of corticosteroids for acceleration of fetal pulmonary maturation. Following stabilization, appropriate candidates for expectant management remain undelivered while maternal and fetal well-being are closely monitored. (Details of maternal and fetal surveillance are discussed in *Prognosis in Preeclampsia*.) Expectant management is best considered when the potential perinatal benefits are substantial. The advisability of expectant management is greatly influenced by gestational age, which is the most important determinant of perinatal outcome.

Expectant management of preeclampsia at < 32–34 weeks may decrease neonatal respiratory distress syndrome, necrotizing enterocolitis, and the need for neonatal intensive care, despite poor fetal growth velocity during the period of pregnancy prolongation (two trials, N = 133 women).[323,324] The presence and/or magnitude of maternal risk have not been established in adequately powered trials, although rates are very low in uncontrolled observational studies conducted in developed countries.[325,326] Determination of when these women should be delivered must be made individually.[327]

For women with preeclampsia who are late preterm (34–36 weeks) or at term (37–42 weeks), pregnancy prolongation is not expected to have substantial perinatal survival benefits. However, near term, the fetal brain is particularly vulnerable to injury.[328] Also, delaying delivery may allow time for cervical ripening and successful vaginal delivery. However, there is no literature that evaluates pregnancy prolongation to achieve these goals. In trials comparing one antihypertensive with another near or at term, pregnancy prolongation has been associated with a CS rate of about 70%,[329–333] with little reported information about other maternal or substantive perinatal outcomes and no information on the magnitude of pregnancy prolongation.

Magnesium Sulphate ($MgSO_4$) for Eclampsia Prophylaxis or Treatment

Recommendations

1. $MgSO_4$ is recommended for first-line treatment of eclampsia. (I-A)
2. $MgSO_4$ is recommended as prophylaxis against eclampsia in women with severe preeclampsia. (I-A)
3. $MgSO_4$ may be considered for women with non-severe preeclampsia. (I-C)
4. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to $MgSO_4$ or it is ineffective. (I-E)

Comments

In women with eclampsia, $MgSO_4$ more effectively reduces recurrent seizures than does phenytoin (6 trials, 897 women) or diazepam (7 trials, 1441 women).[334,335] Of note, the protocol for women in the $MgSO_4$ arm of the largest of these trials, the Collaborative Eclampsia Trial, did not include administration of benzodiazepines for seizure termination. The initial intravenous treatment protocol was $MgSO_4$ 4g IV bolus, followed by an infusion of 1 g/hour; a recurrent seizure was treated with another 2 to 4 g IV bolus. Serum Mg levels were not measured, but women were followed clinically for adverse Mg-related effects.

In women with preeclampsia (defined in MAGPIE[336] as hypertension, ≥ 1+ proteinuria, and uncertainty about the benefit of $MgSO_4$), $MgSO_4$ (compared with placebo or no therapy in 6 trials, 11 444 women) more than halved the incidence of eclampsia (RR 0.41; 95% CI 0.29–0.58).[337] The NNT (95% CI) to prevent one seizure among women with severe preeclampsia was 50 (34–100) and for non-severe preeclampsia 100 (100–500). $MgSO_4$ also decreased the risk of abruption (RR 0.64; 95% CI 0.50–0.83; NNT of 100 [50–1000]) but increased the risk of CS (50% vs. 47%; RR 1.05; 95% CI 1.01–1.10). $MgSO_4$ was more frequently associated with side effects (24% vs. 5%; RR 5.26; 95% CI 2.59– 6.03).

In women with preeclampsia, $MgSO_4$ (compared with other agents) also reduced the incidence of eclampsia. $MgSO_4$ (compared with phenytoin in 2 trials, 2241 women)[338,339] reduced eclampsia (RR 0.05; 95% CI 0–0.84) but increased CS (RR 1.21; 95% CI 1.05–1.41).[337] $MgSO_4$ (compared with nimodipine in 1 trial, 1650 women), reduced eclampsia, but there were more respiratory problems (1.3% vs. 0.4%; RR 3.61; 95% CI 1.01–12.91) and the need for additional antihypertensive therapy (54% vs. 46%; RR 1.19; 95% CI 1.08–1.31).[340] Trials comparing $MgSO_4$ with diazepam (2 trials, 2241 women) are too small for conclusions to be drawn.[337]

Therefore, for women with preeclampsia, although the risk of eclampsia is lower with $MgSO_4$ (compared with placebo, no therapy, or other anticonvulsants), there is ongoing controversy about whether women with non-severe preeclampsia benefit overall, particularly as $MgSO_4$ is associated with more Caesarean sections and maternal adverse effects, and is very expensive (US$23 000 to prevent one seizure if $MgSO_4$ is given to all women with preeclampsia).[341] In a large American centre that changed its policy from universal prophylaxis of all women with gestational hypertension to a selective approach for only

women with severe gestational hypertension, there was more eclampsia and, in those women, more general anaesthesia and adverse neonatal outcomes, although absolute rates of these complications were very low.[342]

Plasma Volume Expansion for Preeclampsia

Recommendation

1. Plasma volume expansion is not recommended for women with preeclampsia. (I-E)

Comments

The rationale for plasma volume expansion for preeclampsia is that these women are intravascularly volume contracted and sympathetic tone is high. Colloid has been advocated over crystalloid by some authors, as in healthy women, crystalloid is gone from the intravascular space in 20 minutes,[343] and possibly sooner in the presence of the endothelial dysfunction of preeclampsia. In women with severe preeclampsia, observational studies have demonstrated that various types and amounts of crystalloid or colloid have improved maternal haemodynamics,[344,345] umbilical blood flow velocities,[346] fetal growth and perinatal mortality.[345] However, trials (of colloid solution) have demonstrated no improvement in maternal or perinatal outcomes (4 trials, 277 women).[347–351] In a more recent, large trial,[351] plasma volume expansion was associated with more Caesarean sections, (non-significant) shorter pregnancy prolongation, and a non-significant increase in pulmonary edema. There was also no significant difference in fetal middle cerebral or umbilical artery blood flow velocity, as reported by observational studies.

Therapies for HELLP Syndrome

Recommendations

1. Prophylactic transfusion of platelets is not recommended, even prior to Caesarean section, when platelet count is > $50x10^9$/L and there is no excessive bleeding or platelet dysfunction. (II-2D)

2. Consideration should be given to ordering blood products, including platelets, when platelet count is < 50×10^9/L, platelet count is falling rapidly, and/or there is coagulopathy. (III-I)

3. Platelet transfusion should be strongly considered prior to vaginal delivery when platelet count is < 20×10^9/L. (III-B)

4. Platelet transfusion is recommended prior to Caesarean section, when platelet count is < 20×10^9/L. (III-B)

5. Corticosteriods may be considered for women with a platelet count < 50×10^9/L. (III-I)

6. There is insufficient evidence to make a recommendation regarding the usefulness of plasma exchange or plasmapheresis. (III-I)

Comments

There is general agreement that perioperatively, prophylactic transfusion of platelets is not necessary above $50x10^9$/L,[352] in the absence of clinical bleeding or platelet dysfunction.[353] At platelet counts < 10–20 x 10^9/L, prophylactic transfusion of platelets may be considered as the risk of profound hemorrhage is increased even with non-operative delivery.[354] In the setting of bleeding, transfusion (of platelets and other blood products) is discussed in the SOGC guidelines on hemorrhagic shock guidelines.[355]

A D(Rho)-negative woman may develop anti-D antibodies to RBCs within units of platelets. (Four units of platelets can contain as much as 2 mL of RBCs.) In these circumstances, sensitization can be prevented by anti-D prophylaxis, in the form of one 300μg does of anti-D immune globulin; this is sufficient to prevent sensitization following transfusion of up to 30 units of platelets.[354]

Among women with HELLP (with platelets < 50 or < 100×10^9/L), corticosteroids improve maternal haematological and biochemical indices, and possibly the rate of regional anaesthesia[356] in observational studies. However, no benefit was demonstrated on important maternal and perinatal outcomes in small, but underpowered, RCTs.[357]

Women with progressive HELLP syndrome, particularly post partum, have been described in observational studies to improve with plasma therapies; these are effective for thrombotic thrombocytopenic purpura (TTP) that mimics HELLP.[358] No RCTs were identified.

Other Therapies for Treatment of Preeclampsia

Recommendations

1. Women with preeclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity. (I-A)

2. Thromboprophylaxis may be considered when bed rest is prescribed. (II-2C)

3. Low-dose aspirin is not recommended for treatment of preeclampsia. (I-E)

4. There is insufficient evidence to make recommendations about the usefulness of treatment with the following: activated protein C, (III-I) antithrombin, (I-I) heparin, (III-I) L-arginine, (I-I) long-term epidural anaesthesia, (I-I) N-acetylcysteine, (I-I) probenecid, (I-I) or sildenafil nitrate. (III-I)

Comments

There is currently no reliable way of determining which women with preeclampsia will develop adverse maternal or fetal conditions that mandate delivery. On average, women with preeclampsia remote from term who undergo expectant management of their disease, can have their pregnancies prolonged by two weeks, based on small randomized trials; they should receive antenatal corticosteroids if they present at < 34 weeks.[323,324]

Preeclampsia, many of its risk markers (obesity, age > 35 years, thrombophilia, or renal disease with nephrotic syndrome), and many aspects of its treatment (e.g., bed rest) put women at increased thromboembolic risk. Thromboprophylaxis should be considered in these women antenatally and/or postnatally, as described in the SOGC guideline (2000)[359]; although the effectiveness of treatment has not been adequately assessed in pregnancy,[360] RCTs may not be feasible.[361]

New therapies for preeclampsia are based on its pathogenesis involving vasoconstriction, inflammation, hypercoagulability, and oxidative stress. There is insufficient information to evaluate the effects of:, activated protein C[76]; antithrombin (3 trials, 185 women)[362–364]; heparin (no trials)[365]; long-term epidural anaesthesia (1 trial, 20 women)[366]; L-arginine (2 trials, 91 women)[367,368]; N-acetylcysteine (1 trial, 38 women)[369]; probenecid (1 trial, 40 women),[370] or sildenafil nitrate (based on treatment for IUGR[371]).

POSTPARTUM TREATMENT

Care in the Six Weeks Post Partum

Recommendations

1. BP should be measured during the time of peak postpartum BP, at days three to six after delivery. (III-B)
2. Antihypertensive therapy may be restarted post partum, particularly in women with severe preeclampsia and those who have delivered preterm. (II-2 I)
3. Severe postpartum hypertension should be treated with antihypertensive therapy, to keep sBP < 160 mmHg and diastolic BP < 110 mmHg. (II-2B)
4. Antihypertensive therapy may be used to treat non-severe postpartum hypertension, particularly in women with comorbidities. (III-I)
5. Antihypertensive agents acceptable for use in breastfeeding include the following: nifedipine XL, labetalol, methyldopa, captopril, and enalapril. (III-B)
6. There should be confirmation that end-organ dysfunction of preeclampsia has resolved. (III-I)
7. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be given post partum if hypertension is difficult to control or if there is oliguria, an elevated creatinine (i.e., ≥ 100 μM), or platelets < 50×10^9/L. (III-I)
8. Postpartum thromboprophylaxis may be considered in women with preeclampsia, particularly following antenatal bed rest for more than four days or after Caesarean section. (III-I)
9. LMWH should not be administered post partum until at least two hours after epidural catheter removal. (III-B)

Comments

Hypertension may develop for the first time post partum, with a peak on days 3–6 post partum due to mobilization of extracellular fluid accumulated during pregnancy. Hypertension may also represent the continuation of an antenatal hypertensive disorder, in up to 50% of women. Women at greatest risk are those with antenatal preeclampsia, particularly with preterm delivery, and among multiparous women, those with higher uric acid levels or blood urea nitrogen.[372,373] In addition to hypertension, the proteinuria and other adverse conditions of preeclampsia may also worsen post partum, usually in the first few days, and especially in the setting of severe disease.[205] Postpartum monitoring is appropriate,[374] and any end-organ dysfunction should be documented to resolve in the days to weeks after delivery.

There are no reliable data to guide whether or not antenatal antihypertensive therapy should be continued post partum, or if so, which antihypertensive agent is best.[375] What is clear is that there is potential for postpartum deterioration in up to 25% of women with preeclampsia, so close monitoring is prudent. Regardless, follow-up of BP is warranted.

There is consensus that all severe hypertension should be treated, be it antenatal or post partum. For non-severe hypertension, the three drug versus placebo/no treatment trials and three drug versus drug trials provide insufficient data to guide clinical practice.[376] Women with comorbid conditions should be treated according to the CHEP guidelines.[69] As there are a wide range of agents that are acceptable for use in breastfeeding, clinicians should choose agents with which they are familiar. On average, antihypertensive agents are needed for longer in women with preeclampsia (approximately two weeks) compared with those with gestational hypertension without proteinuria (approximately one week), although there is substantial variability between women.[37] Postpartum follow-up is important, particularly in the week following delivery.

The American Academy of Pediatrics considers the antihypertensives used most commonly in pregnancy to be "usually acceptable" for breastfeeding, in addition to

captopril and enalapril.[377,378] Recommendations are based on an estimated intake by a breastfeeding infant of < 10% of a therapeutic dose. However, there are no studies of the effects of antihypertensives on breast-fed preterm infants or those of low birthweight. Also, long-term effects of antihypertensive drug exposure (antenatally or through breast milk) have been largely unstudied. Therefore, any adverse effects observed in the infant should be thoroughly evaluated.

NSAIDs, which may exacerbate non-pregnancy hypertension, are self-administered analgesics in many obstetric units and may play a role in contributing to postpartum hypertension, elevated creatinine, or renal failure.[379]

Preeclampsia is a risk marker for postpartum thromboembolism.[219] Other risk markers are more frequent among these patients, including obesity, bed rest for more than four days prior to delivery, and Caesarean section. Postpartum thromboprophylaxis should be considered,[359] although it is of unproven benefit.[360]

The American Society of Regional Anesthesia guidelines specify that LMWH should not be administered post partum (in prophylactic or therapeutic doses) until at least two hours after epidural catheter removal.[290]

Care Beyond Six Weeks Post Partum

Recommendations

1. Women with a history of severe preeclampsia (particularly those who presented or delivered before 34 weeks' gestation) should be screened for pre-existing hypertension, (II-2B) underlying renal disease, (II-2B) and thrombophilia. (II-2C)
2. Women should be informed that intervals between pregnancies of < 2 or ≥ 10 years are both associated with recurrent preeclampsia. (II-2D)
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future pregnancy (II-2A) and for long-term health. (I-A)
4. Women with pre-existing hypertension should undergo the following investigations (if not done previously): urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting total cholesterol and high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides; and standard 12-lead electrocardiography. (III-I)
5. Women who are normotensive but who have had an HDP, may benefit from assessment of traditional cardiovascular risk markers. (II-2B)
6. All women who have had an HDP should pursue a healthy diet and lifestyle. (I-B)

Comments

Gestational hypertension usually resolves by six weeks post partum, but women with severe preeclampsia may remain hypertensive (or proteinuric) for up three to six months.[380]

The recommended investigations or interventions are aimed at either preventing preeclampsia or its complications in future pregnancy, or preventing long-term cardiovascular morbidity or mortality.

Recommendations Regarding Future Pregnancy

Thrombophilia appears to confer an increased risk of preeclampsia (and other placenta mediated pregnancy complications), but the magnitude of the association appears to be weaker than originally suggested.[381,382] Also, there is a lack of RCT evidence that permits conclusions about the relative benefits and risks of thromboprophylaxis of thrombophilic women, although it is biologically plausible that such prophylaxis may reduce the incidence of preeclampsia in subsequent pregnancies. Thrombophilia testing may, however, influence the choice of contraceptive method.

Screening for other underlying causes of preeclampsia (such as renal disease) may better inform management of the woman's health between pregnancies or in subsequent pregnancies. Abnormalities detected should prompt referral to the appropriate specialist.

In a prospective study of 79 women with severe obesity, surgical management reduced the risk of gestational hypertension in the subsequent pregnancy.[383] However, of greater relevance to pregnant women is robust epidemiological data that weight gain between pregnancies (even in non-obese women) is associated with significantly more preeclampsia and other pregnancy complications, such as CS and gestational diabetes.[193]

Recommendations Regarding Long-Term Cardiovascular Health

Women with pre-existing hypertension

Women with pre-existing hypertension should undergo the basic laboratory tests recommended by the CHEP[10,384]; most should have been performed in pregnancy (and do not need to be repeated), with the exception of fasting lipids and 12-lead EKG. Specific cardiovascular risk factors should be addressed according to existing guidelines. In addition, all women with pre-existing hypertension should comply with CHEP recommendations for dietary and lifestyle modification (Table 8).[69,384]

Women who are normotensive but who had an HDP

Most women who develop an HDP will become normotensive after delivery. However, pregnancy can be regarded as a stress test of sorts, informing women of their

Table 8. Dietary and lifestyle modifications recommended for all women

Intervention	Details
Heart healthy diet	Apply the DASH diet (which emphasizes fruits, vegetables, low-fat dairy products, reduced in saturated fat and cholesterol) in addition to dietary and soluble fibre, whole grains, and protein from plant sources
Regular physical activity	Exercise for 30–60 minutes of moderate intensity dynamic exercise (such as walking, jogging, cycling or swimming) on 4–7 days/week
Alcohol consumption	Reduce alcohol consumption to ≤ 2 drinks/day and ≤ 8/week
Weight reduction	Attain and maintain ideal body weight (i.e., BMI 18.5–24.9 kg/m^2)
Reduce waist circumference	Attain and maintain a waist circumference of < 88 cm
Salt intake	Reduce intake to < 100 mmol/d
Smoking cessation	In addition to a smoke-free environment.

future cardiovascular risk.[385] Large-scale epidemiological studies have associated gestational hypertension, and preeclampsia in particular, with an increased risk of hypertension, renal disease,[386] and cardiovascular and cerebrovascular morbidity and mortality.[387–390] Preeclampsia may also be associated with a small increased risk of subsequent thromboembolism.[387,391] An excess of microalbuminuria has also been documented, but it is unclear whether or not this represents underlying renal disease or an independent cardiovascular risk marker.[392–394] Whether these effects are genetic and/or influenced by an underlying dysmetabolic syndrome is unclear. Also, whether early testing (and intervention) for traditional cardiovascular risk factors will decrease subsequent vascular events is unproven.

As a routine for all patients, the Canadian Task Force on Preventive Health Care[395] recommends routine cardiovascular risk marker screening only for patients with hypertension and smoking. The Canadian Diabetes Association recommends blood glucose screening at age 40 years (and every 3 years thereafter),[396] and the Canadian Working Group on Hypercholesteremia recommends screening for dyslipidemia after age 50 years (or menopause) (and every 5 years thereafter),[397] assuming that there are no other cardiovascular risk markers.

The CHEP recommends dietary and lifestyle changes (Table 8) for the primary prevention of hypertension. It may be easier to engage women of child-bearing age in these changes following complicated pregnancy. If so, this would be valuable from a public health perspective, given the prevalence and importance of cardiovascular disease in women, and the central role of the woman as caregiver to children, spouse, and other family members.

Future Directions

This represents the second iteration of these guidelines. There are many aspects of diagnosis, evaluation and treatment that must be further clarified. However, some aspects of care clearly supported by the literature are $MgSO_4$ for severe preeclampsia, and antenatal corticosteroids for women with preeclampsia before 34 weeks. The following have been identified as priorities: the role of self-measurement of BP, accuracy of the ratios of urinary protein to creatinine and albumin to creatinine for diagnosis of proteinuria, multivariable models for prediction of preeclampsia, prediction of complications in women with preeclampsia, the role of bed rest in the prevention or treatment of preeclampsia, the BP goal that optimizes perinatal and maternal outcomes in women with non-severe hypertension, the use of $MgSO_4$ for non-severe preeclampsia, and postpartum follow-up and interventions related to future pregnancy and cardiovascular risk. Forthcoming iterations are planned, no less frequently than every three years.

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