Report of the Canadian Hypertension Society Consensus Conference: 2. Nonpharmacologic management and prevention of hypertensive disorders in pregnancy

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Abstract

Objective: To provide Canadian physicians with comprehensive, evidence-based guidelines for the nonpharmacologic management and prevention of gestational hypertension and pre-existing hypertension during pregnancy.

Options: Lifestyle modifications, dietary or nutrient interventions, plasma volume expansion and use of prostaglandin precursors or inhibitors.

Outcomes: In gestational hypertension, prevention of complications and death related to either its occurrence (primary or secondary prevention) or its severity (tertiary prevention). In pre-existing hypertension, prevention of superimposed gestational hypertension and intrauterine growth retardation.

Evidence: Articles retrieved from the pregnancy and childbirth module of the Cochrane Database of Systematic Reviews; pertinent articles published from 1966 to 1996, retrieved through a MEDLINE search; and review of original randomized trials from 1942 to 1996. If evidence was unavailable, consensus was reached by the members of the consensus panel set up by the Canadian Hypertension Society.

Values: High priority was given to prevention of adverse maternal and neonatal outcomes in pregnancies with established hypertension and in those at high risk of gestational hypertension through the provision of effective nonpharmacologic management.

Benefits, harms and costs: Reduction in rate of long-term hospital admissions among women with gestational hypertension, with establishment of safe home-care blood pressure monitoring and appropriate rest. Targeting prophylactic interventions in selected high-risk groups may avoid ineffective use in the general population. Cost was not considered.

Recommendation: Nonpharmacologic management should be considered for pregnant women with a systolic blood pressure of 140–150 mm Hg or a diastolic pressure of 90–99 mm Hg, or both, measured in a clinical setting. A short-term hospital stay may be required for diagnosis and for ruling out severe gestational hypertension (preeclampsia). In the latter case, the only effective treatment is delivery. Palliative management, dependent on blood pressure, gestational age and presence of associated maternal and fetal risk factors, includes close supervision, limitation of activities and some bed rest. A normal diet without salt restriction is advised. Promising preventive interventions that may reduce the incidence of gestational hypertension, especially with proteinuria, include calcium supplementation (2 g/d), fish oil supplementation and low-dose acetylsalicylic acid therapy, particularly in women at high risk for early-onset gestational hypertension. Pre-existing hypertension should be managed the same way as before pregnancy. However, additional concerns are the effects on fetal well-being and the worsening of hypertension during the second half of pregnancy. There is, as yet, no treatment that will prevent exacerbation of the condition.

Validation: The guidelines share the principles in consensus reports from the US and Australia on the nonpharmacologic management of hypertension in pregnancy.

Sponsors: Preparation of the guidelines was funded by the Canadian Hypertension So-

ciety. The guidelines are endorsed by the Canadian Hypertension Society, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens-gynécologues du Québec.

Résumé

Objectif : Fournir aux médecins du Canada des lignes directrices détaillées fondées sur des données probantes au sujet du traitement et prévention non pharmacologique de l'hypertension gravidique et de l'hypertension antérieure à la grossesse.

Option : Modification du style de vie, interventions alimentaires ou nutritives, expansion du volume plasmatique et utilisation de précurseurs ou d'inhibiteurs de la prostaglandine.

Résultats : Dans les cas d'hypertension gravidique, prévention des complications et des décès liés à son apparition (prévention primaire ou secondaire) ou à sa gravité (prévention tertiaire). Dans les cas d'hypertension antérieure, prévention de l'hypertension gravidique surajoutée et du retard de croissance intrautérin.

Preuves : Articles extraits du module sur la grossesse et l'accouchement de la base de données Cochrane sur les examens systématiques; articles pertinents publiés de 1966 à 1996 extraits à la suite d'une recherche dans MEDLINE; revue d'études randomisées originales remontant de 1942 à 1966. Lorsqu'il n'y avait pas de preuve, les membres du groupe consensuel établi par la Société canadienne d'hypertension artérielle ont dégagé un consensus.

Valeurs : On a accordé une grande priorité à la prévention, par la prestation de soins non pharmacologiques efficaces, des résultats indésirables pour la mère et le nouveau-né dans les cas de grossesses présentant une hypertension antérieure et dans ceux qui présentaient un risque élevé d'hypertension gravidique.

Avantages, préjudices et coûts : Réduction des hospitalisations de longue durée chez les femmes atteintes d'hypertension gravique, avec établissement d'une surveillance à domicile sécuritaire de la tension artérielle et repos approprié. Le ciblage d'interventions prophylactiques dans certains groupes à risque élevé peut éviter une utilisation inefficace dans la population générale. Il n'a pas été tenu compte du coût.

Recommandation : Il faudrait envisager un traitement non pharmacologique chez les femmes enceintes qui ont une tension artérielle systolique de 140 à 150 mm Hg, une tension diastolique de 90 à 99 mm Hg, ou les deux, mesurée en contexte clinique. Un court séjour à l'hôpital peut s'imposer pour que l'on puisse poser un diagnostic et exclure l'hypertension gravidique grave (prééclampsie). Dans ce dernier cas, l'accouchement est le seul traitement efficace. Le traitement palliatif qui est fonction de la tension artérielle, de l'âge de la grossesse et de la présence de facteurs de risque connexes chez la mère et le foetus, comprend la surveillance rapprochée, la limitation des activités et un peu de repos au lit. Une alimentation normale sans restriction saline est recommandée. Les interventions préventives prometteuses qui peuvent réduire l'incidence de l'hypertension gravidique, surtout lorsqu'elle est accompagnée de protéinurie, comprennent l'absorption de suppléments de calcium (2 g/j) et d'huile de poisson, ainsi qu'une thérapie à l'acide acétylsalicylique à faible dose, particulièrement chez les femmes à risque élevé d'hypertension gravidique et d'apparition hâtive. L'hypertension antérieure doit être traitée de la même façon qu'avant la grossesse. Il y a toutefois d'autres préoccupations comme les effets sur le bien-être du foetus et l'aggravation de l'hypertension au cours de la deuxième moitié de la grossesse. Il n'y a encore aucun traitement qui empêchera cet état de s'aggraver.

Validation : Les lignes directrices sont fondées sur les principes des rapports consensuels provenant des États-Unis et de l'Australie et portant sur le traitement non pharmacologique de l'hypertension au cours de la grossesse.

Commanditaires : La préparation des lignes directrices a été subventionnée par la Société canadienne d'hypertension artérielle. La Société canadienne d'hypertension artérielle, la Société des obstétriciens et gynécologues du Canada et l'Association des obstétriciens gynécologues du Québec ont approuvé les lignes directrices.

Hypertension in pregnancy affects both the mother and the fetus, and physicians should take the interests of both into account, if possible, by ensuring a safe pregnancy and delivery without sequelae.[1,2] For the mother, this means avoidance of morbidity and mortality related to sudden increase of blood pressure, eclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), cerebral hemorrhage, cardiopulmonary failure, acute renal or liver damage, abruptio placentae, and long-term target organ sequelae such as secondary persistent hypertension, neurologic morbidity or renal impairment. For the fetus, it means the prevention of intrauterine hypoxia, leading to either fetal death or intrauterine growth retardation, and the prevention of premature birth, with its associated risk of neonatal death (especially in the presence of maternal proteinuria)[3] and long-term morbidity among survivors.

The definitions and classification of hypertensive disorders in pregnancy of the Canadian Hypertension Society (CHS) appeared in part 1 of this series.[4] In this article, we discuss the available evidence for the nonpharmacologic management of gestational hypertension (pre-eclampsia), occurring during the last half of pregnancy and in which blood pressure returns to normal by 6 weeks' post partum, and of pre-existing (chronic or essential) hypertension. Although the CHS has proposed standard definitions, we report here the original terminology, because different terms were used to describe hypertensive disorders in the various publications reviewed.

We will address indications for nonpharmacologic management and present intervention options with specific recommendations according to the type and severity of the hypertensive disorder. Management of secondary arterial hypertension, as well as chronic (pre-existing) hypertension with superimposed gestational hypertension (pre-eclampsia) will not be discussed in this article because these high-risk conditions usually require pharmacologic therapy and specialized intensive intervention (these issues will be addressed in part 3 of the series, to appear in the Nov. 1 issue of *CMAJ*).

Methods

The details of the consensus process are provided in part 1.[4] In brief, the CHS decided in 1994 to develop a Canadian consensus on the diagnosis and management of hypertensive disorders in pregnancy. The president of the society (S.W.R.) and cochair (R.F.B.) were charged to create consensus panels to address the 3 parts of the project: definitions and classification, nonpharmacologic management, and pharmacologic treatment. Canadian physicians, obstetricians, internists and basic scientists with interest and expertise in the field were invited to participate. Geo-graphic representation, as well as representation from the Society of Obstetricians and Gynaecologists of Canada, was realized. The consensus project, sponsored by the CHS, involved several meetings and teleconferences and a general consensus conference held in Montreal in 1995.

The panel addressing nonpharmacologic management reviewed available evidence from various sources: *Effective Care in Obstetrics*,[5] a 2-volume textbook of evidence-based data related to obstetrics; the Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews;[6] and original randomized controlled trials and other articles published from 1942 to 1996, retrieved through a MED-LINE search using the terms "pregnancy hypertension" with "hospitalization," "bed rest," "exercise," "diet," "nutrients," "prostaglandins" and "prophylaxis." The levels of evidence used for rating had been used at an earlier CHS consensus conference on the diagnosis and management of hypertension in nonpregnant individuals.[7] The recommendations were graded according to the level of evidence supporting them (see Appendix 1 in part 1). The recommendations were carried forward if approved by all the members of this panel. Recommendations from international agencies[1,2] and societies[8] were also reviewed. Members of the panel revised the draft report several times, and the final version was endorsed by the CHS, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens gynécologues du Québec.

Indications for intervention

Nonpharmacologic management may be used in:
- the general population, to avoid gestational hypertension (primary prevention);
- women at high risk of hypertension in pregnancy, to avoid gestational hypertension, perinatal death and intrauterine growth retardation (secondary prevention); and
- women with pre-existing hypertension or gestational hypertension, to avoid exacerbation of pre-existing hypertension, superimposed gestational hypertension with proteinuria, perinatal death and intrauterine growth retardation (tertiary prevention). The indications of nonpharmacologic management in this group depend mainly on blood pressure measurements, the specific hypertensive disorder, its degree of severity, and other maternal and fetal risk factors.

Nonpharmacologic management is indicated in women with a systolic blood pressure of 140 mm Hg or greater or a diastolic pressure of 90 mm Hg or greater, or both, when measured in a clinic setting or a physician's office.[4,8] Readings lower than these are not considered indicative of hypertension in pregnancy.[3,4]

Some have suggested that the threshold of intervention

should be only a diastolic pressure of 90–99 mm Hg.[9,10] Others have recommended that nonpharmacologic management not be used alone if the systolic pressure is 150–170 mm Hg or the diastolic pressure is 100–105 mm Hg.[1,2,8,11,12] The patient's position at the time of measurement was often not specified in the articles reviewed; in one group, the threshold reported was 150/100 mm Hg for patients in a seated position and 140/90 mm Hg for those lying on their left side.[11] Similarly, intervals between readings to confirm an elevated blood pressure either have varied from 15 minutes to 6 hours[4,8,13] or have not been specified.[10,14]

In previous reports, eligibility for intervention was indicated by an increase of 30 mm Hg or more in the systolic pressure or an increase of 15 mm or more in the diastolic pressure from earlier values (measured before 13 weeks' gestation[11] or before 20 weeks' gestation[1]). However, these incremental increases have a poor predictive value, particularly for gestational hypertension.[15]

For women with a blood pressure of 140/90 mm Hg or greater measured at a clinic, self-monitoring of blood pressure has been suggested at home using various mechanical aneroid or electronic sphygmomanometers.[16] However, blood pressure readings at home have been found to be inconsistent, being lower (in 52% of cases) or no different (in 28% of cases) than clinic measurements.[17] As yet, there is no reference blood pressure reading that has been proposed for home self-monitoring. This applies also to automated 24-hour ambulatory blood pressure monitoring. Some reference standards for normal pregnancy have been proposed.[18] Only one group has presented preliminary threshold values and their predictive performance in hypertensive pregnancies.[19,20] More research is needed before widespread use of this new technology can occur in hypertensive pregnancies.

The only treatment of gestational hypertension is delivery. However, the definitive differential diagnosis of the cause of elevated blood pressure after 20 weeks' gestation can be made only after 6 weeks postpartum if the existence of essential hypertension before pregnancy is unknown to both patient and physician. Thus, one must always consider gestational hypertension first unless it is excluded by personal history or elevated blood pressure before 20 weeks' gestation.

In cases of pregnancies with mild to moderate pre-existing essential hypertension, 90% are associated with good maternal and neonatal outcomes.[21,22] These women are candidates for nonpharmacologic management. However, a subcategory of the remaining 10% of women with pre-existing mild to moderate hypertension, considered high risk, are associated with a poorer prognosis and may require antihypertensive therapy; in such cases, the blood pressure readings may be lower than 140/90 mm Hg, but

there may be target organ damage or other risk factors such as maternal age of 40 years or higher, a history of hypertension of 15 years or longer, or a history of previous perinatal death or intrauterine growth retardation.[22,23] A severe hypertensive state precludes nonpharmacologic management.[1,2,8,12]

Other associated risk factors may influence management options. Among maternal factors, gestational age is of primary importance and is directly related to perinatal mortality and morbidity. Studies of nonpharmacologic management have included hypertensive pregnancies as early as 24[14] to 28[10,11,13] weeks' gestation, with the objective of prolonging the pregnancy as close to term as possible. Maternal medical conditions such as diabetes mellitus, antepartum hemorrhage, lupus and other chronic diseases (e.g., ileitis, autoimmune disorders, anemia and recurrent infections) that are associated with poor perinatal outcomes may be contraindications to conservative management. Factors affecting the fetus, such as premature rupture of membranes, intrauterine growth retardation, multifetal pregnancy or even an unstable fetal condition, would indicate use of more definitive management.

Finally, patient compliance with the proposed intervention should be ascertained and continually monitored.[11] Some women may not comply, for various reasons: socioeconomic determinants, other children, the need to work, household demands (including health-related problems of family members) and increased stress.[24]

Nonspecific assessment should include a thorough personal history and physical examination of the mother. This may be facilitated by a short-term hospital stay with hematologic and biochemical assessments. Fetal well-being is best ascertained by the counting of fetal movements, fetal heart rate monitoring, nonstress testing, ultrasound screening for fetal growth, biophysical profile and amniotic fluid volume, and, when required, Doppler testing of uterine and umbilical arteries.

Recommendation

Nonpharmacologic management alone is recommended for women with a systolic blood pressure of 140–150 mm Hg or a diastolic pressure of 90–99 mm Hg, or both, in the absence of maternal and fetal risk factors (grade D recommendation).

Management options

Lifestyle modifications

Bed rest

Bed rest is the commonest prescribed treatment for a variety of pregnancy complications, including hyperten-

sion. However, there is a lack of consensus about the definition of "bed rest," and when and how long each day it should be prescribed. Bed rest is advised for about 18% of pregnant women and 38% of those at high risk.[24] However, there is no evidence from well-designed controlled trials that supports its effectiveness.[25] Moreover, an observational study based on a survey showed that one-third of pregnant women at high risk did not comply with the recommended bed rest and that pregnancy outcomes were similar whether they complied or not.[24]

The results of a meta-analysis of studies comparing the effects of hospital admission including bed rest with outpatient care and normal activity at home in the management of nonproteinuric hypertension in pregnancy are shown in Table 1. The outcomes assessed were the prevalence of diastolic blood pressure above 109 mm Hg and the development of proteinuria. Instances of eclampsia were ascertained in 3 randomized controlled trials (RCTs) involving 408 women.[10,25,26] There was no evidence that hospital admission and bed rest for women over 28 weeks' gestation was of value for the outcomes assessed. Further controlled studies with larger samples are necessary.

In another meta-analysis, the effect of hospital admission with or without bed rest in the management of hypertension in pregnancy with proteinuria (from 28 weeks' gestation) was tested in 2 RCTs involving a total of 145 women.[27,29] No significant differences were found in any of the outcomes measured (Table 1).

Recommendation

A policy of hospital admission and strict bed rest is not advised for gestational hypertension with or without proteinuria (grade B recommendation).

Location of care

One RCT compared management in a hospital day-care unit with that in an obstetrician's office (control group) among 54 women with nonproteinuric hypertension from 26 weeks' gestation.[13] Women in the control group were 8.8 times more likely to be admitted and 11.4 times more likely to have proteinuria than those in the experimental group (Table 1). However, there was no difference in mean birth weight, Apgar scores or rates of admission to the neonatal intensive care unit. In a descriptive retrospective study, Rosenberg and Twaddle[12] pointed out that the proportion of patients eligible for management in a day-care unit may be as low as 30%–38% of all women with gestational hypertension because of the lability of blood pressure measurements and the unpredictable occurrence of proteinuria.

Home-care programs were compared with hospital care for the management of nonproteinuric hypertension in 2 RCTs, with no evident harmful effects (Table 1).[26] Three cohort studies — involving women with mild nonproteinuric gestational hypertension,[14] mild pre-eclampsia with protein excretion of less than 0.6 g in 24 hours[11] or chronic hypertension with a diastolic blood pressure of 90–109 mm Hg[9] — reported similar perinatal outcomes when compared with historical controls. Home-care programs included bed rest of various durations (4 hours[9] to 15 hours[14] each day), and weekly prenatal visits with daily clinical and biochemical assessments. Of note, Helewa and associates[11] reported that only 24% of the women with pre-eclampsia met the eligibility criteria for the home-care program; of those, 44% were readmitted because of a worsening of their condition.

Table 1: Meta-analyses of randomized controlled trials (RCTs) of lifestyle modifications (hospital admission, strict bed rest, care in hospital day-care unit, outpatient care or aerobic exercise) in the management or prevention of gestational hypertension

Interventions	Outcomes measured	Total sample size	No. of RCTs	OR (and 95% CI)*
Admission to hospital v. home care for women with nonproteinuric hypertension[26]	Diastolic pressure > 109 mm Hg	353	2	0.74 (0.45–1.21)
	Proteinuria	353	2	0.70 (0.38–1.26)
	Eclampsia	408	3	6.70 (0.13–...)†
Admission to hospital with strict bed rest or with ambulation for women with proteinuric hypertension[27]	Diastolic pressure > 109 mm Hg	105	1	1.83 (0.72–4.33)
	Increased severity of proteinuria	105	1	0.49 (0.20–1.17)
	Fulminating pre-eclampsia	145	2	1.96 (0.97–3.94)
	Eclampsia	145	2	0.13 (0.001–6.69)
Care in physician's office v. care in hospital day-care unit for women with nonproteinuric hypertension[13]	Admission to hospital	54	1	8.80 (3.00–25.80)‡
	Proteinuria	54	1	11.40 (1.80–71.40)‡
	Induction of labour	54	1	4.90 (1.60–13.80)‡
Aerobic exercise v. no exercise[28]	Pre-eclampsia	82	2	1.21 (0.36–4.07)

*OR = odds ratio, CI = confidence interval.
†Infinity denoted as ...
‡Statistically significant.

Exercise in pregnancy

There are no primary data on the effects of regular aerobic exercise during pregnancy on hypertension. Secondary analysis of 2 RCTs involving a total of 82 women showed that exercise did not lower the risk of pre-eclampsia significantly, nor did it lower the proportion of low-birth-weight infants (Table 1).[28]

Stress control

Small studies of platelet activation in women with pre-eclampsia, in comparison with women with normal pregnancies, have shown increased plasma catecholamine levels.[30] Increased levels in plasma and urine have also been found in normotensive pregnant working women under stress.[31] However, the relation between increased life stress and deterioration of hypertensive complications of pregnancy has not been supported by evidence from small comparative trials.[31] In the largest trial, involving 345 pregnant women, a total life stress score was obtained from a questionnaire examining education, employment, social network, traumatic experiences, housing conditions and stress of work. The prevalence of high stress scores did not differ significantly among the 3 groups examined: women with pre-existing hypertension, women with gestational hypertension and pregnant women who were normotensive.[32]

Dietary interventions

Dietary advice and supplementation

Only 1 trial was identified that assessed the effect of advising pregnant women to increase their energy and protein intakes to above pregnancy requirements[33] (Table 2). However, this study excluded a number of participants after allocation, and the blinding of the observers measuring dietary intakes was not addressed.

A large trial was carried out involving underweight Chilean pregnant women to assess the effect of providing isoenergetic protein supplements on gestational weight gain and on various outcomes of pregnancy, including pre-eclampsia.[46] The incidence of pre-eclampsia was close to 6% in both arms of the trial, with an apparent increased frequency of low birth weight in the experimental arm (odds ratio 1.61; 95% CI 1.21–2.15)[34] (Table 2).

Energy and protein supplementation has been much debated for almost every possible outcome of pregnancy since the early 1940s. Only 7 of the 12 trials carried out have been retained by the Cochrane database[35] because the others suffered from methodological flaws. The main target effect was on birth weight, but 3 of the trials[47–49] addressed pre-eclampsia specifically. In these 3 trials supplementation was associated with modest increases in maternal weight and birth weight, but the prevalence of pre-eclampsia was unaffected.[35]

Recommendation

Increased energy and protein intake are not beneficial in the prevention of gestational hypertension (grade B recommendation).

Diet restriction

Although weight reduction may be helpful in reducing blood pressure in nonpregnant women, it is not recommended during pregnancy, even in obese women.[50] In a small comparative study, a 1200-kcal (5000-kJ) diet was given to 51 primigravida with high weight gain. Compared with a matched control group, body fat in the restricted group was reduced, but neonatal weight was also significantly reduced.[50] Weight reduction in pregnancy can also be associated with lower subsequent growth in infants of dieting obese mothers.[51]

Initial noncontrolled trials in the 1960s suggested that dietary restriction (1500 kcal/d [6500 kJ/d]) in obese pregnant women reduced the prevalence of gestational hypertension.[52] However, subsequent small randomized studies with untreated control groups, involving a total of 284 women, have shown that limiting weight gain does not reduce the occurrence of gestational hypertension[36,50,53,54] (Table 2).

Recommendation

Weight reduction is not recommended in the prevention of gestational hypertension (grade C recommendation).

Sodium restriction

Pregnant women with proteinuric hypertension have a lower plasma volume than normotensive pregnant women, and the severity of the hypertension correlates with the degree of plasma volume contraction.[55] In a small uncontrolled trial involving women with proteinuric gestational hypertension,[56] salt restriction (less than 5 g/d) resulted in a modest reduction of the mean blood pressure (from 117 [standard deviation (SD) 3] mm Hg to 109 [SD 4] mm Hg; $p < 0.01$) but accelerated volume depletion.

A small trial of the effect of low versus high salt intake during pregnancy on the occurrence of hypertension with proteinuria provided inconclusive results.[57] As yet, it is impossible to make any recommendation based on available evidence in relation to salt intake and the prevention of gestational hypertension[37] (Table 2).

Recommendation

Sodium restriction is not recommended in pregnancy complicated by gestational hypertension with or without proteinuria (grade C recommendation).

Alcohol restriction

Alcohol intake is related to hypertension in nonpregnant subjects, but it is not associated with an increased risk for proteinuric gestational hypertension or eclampsia.[58] Although drinking during pregnancy is not advised, there is no conclusive evidence of adverse effects on pregnancy outcomes, including fetal growth, at levels of consumption below 120 g of alcohol per week.[59–61]

Nutrient supplementation

Magnesium: Prophylactic oral magnesium supplementation was not found to be beneficial in the prevention of gestational hypertension with or without proteinuria in 2 recent trials involving a total of 942 women.[38,39] Only 1 RCT was identified that tested its effectiveness in the treatment of established gestational hypertension in 58 women; there was insufficient evidence for any reliable recommendation about its effects[40] (Table 2).

Recommendation

Magnesium supplementation during pregnancy, either to prevent or to treat gestational hypertension, is not justified (grade B recommendation).

Calcium supplementation: Epidemiologic studies have suggested an inverse relation between dietary calcium intake and the development of gestational hypertension.[62] Intraerythrocyte calcium levels and intracellular calcium ion concentrations are reported to be increased in women with pre-eclampsia.[63,64] Pre-eclampsia is also a hypocalciuric state.[65] A hypothetical mechanism of action is that calcium supplementation reduces serum parathyroid hormone levels, which in turn reduces the intracellular calcium concentration in vascular smooth muscle cells, diminishing their responsiveness to pressure stimuli.[66]

Table 2: Meta-analyses of RCTs of dietary and nutrient interventions in the management or prevention of gestational hypertension

Interventions	Outcome	Total sample size	No. of RCTs	OR (and 95% CI)
Dietary advice v. no advice[33]	Preeclampsia	136	1	0.86 (0.33–2.22)
Isoenergetic balanced protein supplementation v. no supplementation[34]	Pre-eclampsia	782	1	1.00 (0.55–1.88)
Balanced protein and energy supplementation v. no supplementation[35]	Pre-eclampsia	516	3	1.25 (0.72–2.17)
Restriction of energy intake v. no restriction in overweight women[36]	Pre-eclampsia	284	2	1.15 (0.55–2.40)
Low v. high salt intake[37]	Hypertension	36	1	1.78 (0.28–11.52)
	Proteinuria	36	1	1.12 (0.07–18.75)
Prophylactic magnesium supplementation v. placebo[38,39]	Pre-eclampsia	942	2	0.94 (0.61–1.44)
Magnesium supplementation in women with established hypertension[40]	Use of antihypertensive drugs	58	1	1.54 (0.55–4.28)
Prophylactic calcium supplementation v. placebo[41]	Hypertension	1729	6	0.44 (0.33–0.59)*
	Proteinuric pre-eclampsia	1729	6	0.34 (0.22–0.54)*
Calcium supplementation v. placebo in women with established pre-eclampsia[42]	Severe pre-eclampsia	75	1	1.05 (0.43–2.59)
Zinc supplementation v. no supplementation[43]	Hypertension	656	2	0.76 (0.37–1.60)
Iron supplementation v. no supplementation[44]	Proteinuric hypertension	203	3	0.74 (0.25–2.20)
Folate supplementation v. no supplementation[45]	Proteinuric hypertension	936	3	1.28 (0.86–1.90)

*Statistically significant.

A large prospective RCT of elemental calcium (2 g/d) versus placebo in nulliparous women, started after 20 weeks' gestation, showed a significant reduction in the prevalance of pre-eclampsia (9.8% in the calcium group v. 14.8% in the control group; odds ratio 0.63, 95% CI 0.44–0.90).[67] Several other smaller RCTs, mostly from Latin America, have also demonstrated a trend toward a protective effect of calcium supplementation against pre-eclampsia.[68–72] A meta-analysis showed an odds ratio of 0.44 (95% CI 0.33–0.59) in the prevention of gestational hypertension with calcium supplementation[41] (Table 2). There is also promising evidence that calcium supplementation is associated with a reduction in the incidence of proteinuric hypertension during pregnancy (odds ratio 0.34, 95% CI 0.22–0.54) and in preterm delivery (odds ratio 0.66, 95% CI 0.45–0.97).[41] A recent meta-analysis confirmed these observations and showed that a calcium intake of 1.5–2.0 g/d was associated with significant reductions in systolic and diastolic blood pressure;[73] however, trials included in this meta-analysis were heterogenous. Most recent studies of the prevention of pre-eclampsia with calcium and vitamin D supplementation, in an antenatal care protocol[74] and in the care of pregnant women with a sensitivity to angiotensin II,[75] have supported this preventive effect. Calcium supplementation of 2 g/d has no documented maternal or fetal side effects. However, whether women with prior renal disease and chronic urinary tract infections may be at increased risk of urinary calcium crystal formation is debatable.[67]

A recent study assessed the effect of elemental calcium supplementation of 2 g/d at 24–36 weeks' gestation in 75 women who had mild gestational hypertension (blood pressure 140–159/90 mm Hg) with proteinuria (protein excretion > 0.3 < 5.0 g/d).[42] No significant difference in preventing further development of severe gestational hypertension was observed (Table 2).

Recommendation

Calcium supplementation of 2 g/d is associated with a reduction of blood pressure in gestational hypertension, with or without proteinuria, in both low- and high-risk women (grade B recommendation). There is no apparent effect on the prevention of more severe gestational hypertension in women with established gestational hypertension (grade B recommendation).

Zinc supplementation: The effect of routine zinc supplementation during pregnancy on the incidence of gestational hypertension was tested in 2 RCTs[43,76,77] (Table 2). Zinc supplementation was found to have either a protective effect (in a sample of Mexican women)[76] or a deleterious effect (in a sample of women from Zimbabwe).[77] With so few trials, results are inconclusive.[43]

Iron supplementation: Numerous trials involving various populations of pregnant women with normal hemoglobin levels have evaluated the effects of iron supplementation on several outcomes. A meta-analysis of 3 trials[44,78–80] showed no effect on the occurrence of proteinuric gestational hypertension (Table 2), although they did show that iron supplementation was effective in preventing anemia during pregnancy.[44]

Folate supplementation: Three RCTs of the effect of folate supplementation on the prevalence of gestational hypertension with proteinuria were carried out in different populations, including Nigerian and Indian women.[81–83] All of the trials provided inconclusive results and suffered from methodological defects.[45] However, this does not alter the recommendation that folic acid should be administered before and during the start of pregnancy to prevent neural tube defects.

Recommendation

Zinc, iron and folate supplementation during pregnancy are not effective in the prevention of gestational hypertension (grade B recommendation). However, iron and folate supplementation should be prescribed for other established beneficial effects on pregnancy.

Nonpharmacologic therapy

Plasma volume expansion

A meta-analysis of the effect of plasma volume expansion in the treatment of hypertension in pregnancy is summarized in Table 3. Two small trials involving a total of 42 women reported no beneficial effect.[87,88] There is insufficient evidence at present to assess its potential in the treatment of hypertension in pregnancy.[84]

Prostaglandin precursors

It has been suggested that dietary supplementation with prostaglandin (PG) precursors may increase PGE levels and thus result in lower vascular sensitivity to angiotensin II in pregnancy. A small placebo-controlled trial of evening primrose oil (linoleic and gamma linoleic acid) in women with established gestational hypertension showed no effect on perinatal outcomes.[89]

The routine use of prophylactic supplementation with fish oil containing eicosapentaenoic acid and docosahexaenoic acid, which act as PG precursors, was first reported in 1942 in a large population-based trial.[90] This trial had some methodological limitations. Two smaller trials have been recently published.[91,92] Both showed that fish oil supplementation did not significantly decrease the prevalence of gestational hypertension but that it did sig-

nificantly reduce the incidence of proteinuric gestational hypertension and preterm delivery[85] (Table 3). Trials with larger samples of Canadian women are required to assess reliably the potential benefits or adverse effects of fish oil supplementation during pregnancy.

Recommendation

Fish oil supplementation potentially prevents proteinuric gestational hypertension (grade B recommendation).

Low-dose acetylsalicylic acid therapy

Initial interest in the use of low-dose acetylsalicylic acid (ASA) therapy in the prevention of gestational hypertension arose because of the finding of an in vitro placental imbalance in the production of vasoactive prostaglandins (thromboxane A_2 [TXA_2] and prostacyclin [PGI_2]), which leads to platelet activation and arteriolar vasoconstriction.[93] PGI_2, produced in the vascular endothelium, inhibits platelet aggregation and is an active vasodilator. TXA_2, synthesized predominantly by platelets, induces platelet aggregation and vasoconstriction. PGI_2 and TXA_2 are derived from arachidonic acid by the enzyme cyclooxygenase. Increased synthesis of TXA_2 combined with decreased synthesis of PGI_2 may lead to the altered vascular sensitivity to angiotensin II found in women with pre-eclampsia.[94] In addition, it may also mediate the reduction in uteroplacental perfusion, abnormal platelet behaviour and formation of placental thrombi and infarcts.

ASA acetylates cyclo-oxygenase and reduces the formation of both TXA_2 and PGI2. However, at low doses (60–80 mg/d) it selectively suppresses the synthesis of platelet TXA_2.[95] Initially, small prospective controlled trials suggested that low-dose ASA therapy, begun at 12 to 32 weeks' gestation and continued to term, reduced the incidence of gestational hypertension.[96,97] A meta-analysis of these RCTs suggested the effectiveness of ASA therapy in reducing gestational hypertension with a risk reduction of 65%.[98]

Recent larger trials, however, have failed to demonstrate the protective effect of ASA therapy.[86,99,100] The Network of Maternal–Fetal Medicine Units (National Institute of Health and Child Development) noted a decreased incidence of gestational hypertension among nulliparous women, but no decrease in perinatal mortality.[99] The Italian Study of Aspirin in Pregnancy found no decrease in the frequency of gestational hypertension nor of intrauterine growth retardation.[100] The largest trial, CLASP, also failed to show a significant decrease in the incidence of gestational hypertension but noted a significant trend toward a progressive decrease in the incidence of proteinuric gestational hypertension the more preterm the delivery.[86] Meta-analysis of all trials showed a 25% odds reduction in proteinuric gestational hypertension, but no significant decrease in perinatal mortality.[86] However, the results of this meta-analysis should be treated with the usual caution, because many unpublished studies showing negative results were not included.[101]

Three categories of risk for gestational hypertension can be assessed according to the initial screening test: a low risk in the general population (less than 7%), a moderate risk (7%–14%) and a high risk (15% or greater) when angiotension II sensitivity test or Doppler were used. The respective odds ratios (and 95% CIs) are 0.68 (0.52–0.89), 0.84 (0.71–0.99) and 0.26 (0.15–0.45).[102]

Low-dose ASA therapy was associated with an increase in placental hemorrhage (0.7%) in one trial in which the proportion in the control group was lower than that in the general population (0.1% v. 1.0%).[99] This was not reported in any other trial.[86,98,100,103] No problem with bleeding at the time of epidural anesthesia was reported.[86,104] Low-dose ASA therapy also seemed safe for the fetus and neonate, with no increased likelihood of bleeding.[103,104]

Recommendations

Data do not support the routine prophylactic use of low-dose ASA therapy in pregnant women with no identifiable risk factors for gestational hypertension (grade B recommendation).

Table 3: Meta-analyses of RCTs of nonpharmacologic therapy (plasma volume expansion, fish oil supplementation or low-dose ASA therapy) in the treatment or prevention of gestational hypertension and associated outcomes*

Interventions	Outcome	Total sample size	No. of RCTs	OR (and 95% CI)
Plasma volume expansion v. no expansion[84]	Cesarean section	42	2	2.04 (0.59–7.02)
	Perinatal death	32	1	5.70 (0.32–...)
Fish oil supplementation v. placebo[85]	Hypertension	5 135	2	0.95 (0.83–1.09)
	Proteinuric pre-eclampsia	5 135	2	0.68 (0.53–0.88)†
	Preterm birth	5 550	2	0.79 (0.69–0.90)†
Prophylactic low-dose ASA therapy v. placebo[86]	Proteinuric pre-eclampsia	15 133	17	0.75 (0.67–0.84)†
	Perinatal death	15 477	18	0.97 (0.79–1.19)

*ASA = acetylsalicylic acid.
†Statistically significant.

Low-dose ASA therapy is effective in decreasing the incidence of preterm delivery and early-onset proteinuric gestational hypertension in women at risk of gestational hypertension with proteinuria (grade A recommendation).

Low-dose ASA therapy is not effective in preventing intrauterine growth retardation and neonatal mortality in women at risk of gestational hypertension with proteinuria (grade B recommendation).

Low-dose ASA therapy is not effective in preventing intrauterine growth retardation and perinatal mortality in women with established gestational hypertension with proteinuria (grade B recommendation).

Management of women with pre-existing hypertension

Pre-existing hypertension, so-called low-risk essential hypertension,[21,23] has been far less studied during pregnancy and is usually managed the same way as in the nonpregnant state. However, additional concerns are effects on fetal well-being (mainly intrauterine growth retardation) and the worsening of hypertension during the second half of pregnancy, particularly as a result of superimposed gestational hypertension with proteinuria.[23]

The management of hypertension before pregnancy consists of comprehensive evaluation to exclude any target organ involvement as well as weight reduction in obese women. During pregnancy, blood pressure monitoring at home is advised together with more frequent prenatal visits for the early detection of worsening of the hypertensive state or of adverse effects on fetal health.[1,8] Failure of nonpharmacologic intervention to manage worsening hypertension, especially in the presence of maternal risk factors,[21] requires consideration of pharmacologic treatment.

Of the interventions reported to be potentially beneficial in the management of gestational hypertension, no RCT has tested their effectiveness in the management of pre-existing hypertension. A retrospective study with a historical control group reported no difference in outcomes when bed rest and limited activities were prescribed at home or in hospital.[32] A normal diet is usually advised. Sodium restriction is not advised; however, if a woman is known to be salt-sensitive, it is reasonable to continue sodium restriction during pregnancy to optimize maternal blood pressure control, but its effect on fetal and neonatal outcome is as yet unknown. Furthermore, although epidemiologic studies have suggested that an abnormal calcium metabolism may contribute to the development of hypertension in the nonpregnant state, observational studies failed to demonstrate any difference in circulating calcium levels between pregnant women without hypertension and those with pre-existing hyper-

tension.[105] Dietary calcium or fish oil supplementation was not tested for that condition. Finally, a subgroup analysis of women with pre-existing hypertension and no risk factors,[21] taking part in the large low-dose ASA trials, failed to show a reduction in the incidence of superimposed gestational hypertension or of perinatal mortality.[86,96,102]

Recommendations from the US and Australia

Consensus reports from the US[1] and Australia[8] emphasized that the only definitive treatment of pregnancy-induced hypertension is delivery but that management options should take into account the gestational age and the potential benefit for the fetus to prolong its intrauterine life. Close supervision was recommended, with regular daily clinical and laboratory assessments. In Australia, bed rest was advised, preferably in hospital, although its effectiveness has not been proven. Both reports argued against the potential benefit of strict bed rest but recommended the limitation of activities. In the US, outpatient surveillance with home blood pressure monitoring was advised after initial hospital admission.[1] Neither report recommended diet modification or salt restriction, and both recommended that alcohol and tobacco be avoided.

The prevention of gestational hypertension with low-dose ASA therapy was poorly addressed in the consensus reports because the results of the CLASP trial had not been available. The US report raised the issue of oral calcium supplementation but stated that insufficient data precluded recommending its use;[1] it also alluded to the potential effect of calcium supplementation on lowering blood pressure in the nonpregnant state. Neither report offered advice on preventive nonpharmacologic treatment to avoid the worsening of pre-existing hypertension or superimposed gestational hypertension.

Consensus statement

There are still several gaps in the knowledge of the nonpharmacologic management and prevention of hypertension in pregnancy. Although there is no evidence that systolic or diastolic blood pressure is related to pregnancy outcome, current opinion is that nonpharmacologic treatment should be considered for pregnant women with a systolic blood pressure 140–150 mm Hg and a diastolic pressure of 90–99 mm Hg in a clinical setting. Home blood pressure monitoring needs further investigation before reference levels can be used in clinical practice.

Nonpharmacologic management of gestational hypertension may involve a short-term hospital stay to ascertain the diagnosis and exclude severe gestational hypertension. The only curative treatment is delivery. Palliative treat-

ment, dependent on blood pressure readings, gestational age and the presence of associated maternal and fetal risk factors, includes close supervision on an outpatient basis and limitation of activities with some bed rest. A normal diet without salt restriction is advised. Available evidence from RCTs does not justify strict bed rest in hospital, plasma volume expansion, calcium supplementation or low-dose ASA therapy. There is insufficient data to recommend care in a hospital day-care unit or the use of magnesium supplementation for women with established gestational hypertension.

There are promising preventive interventions that may reduce the incidence of gestational hypertension, especially with proteinuria. These include calcium supplementation (2 g/d), low-dose ASA therapy, particularly in women at high risk for early-onset gestational hypertension, and fish oil supplementation. Large, well-designed RCTs are required to substantiate the effectiveness of these interventions in Canada. Other management options, found to be ineffective, are not recommended: these include increased energy and protein intake, weight reduction in obese pregnant women, and magnesium, zinc, iron and folate supplementation. However, iron and folate supplementation should be prescribed for other established beneficial effects on pregnancy. There is insufficient data to recommend regular aerobic exercise or the avoidance of daily life stressors in the prevention of hypertension during pregnancy.

Mild to moderate pre-existing (chronic, essential) hypertension without any risk factors should be managed the same way as in the nonpregnant state. However, additional concerns are effects on fetal well-being (mainly intrauterine growth retardation) and worsening of hypertension, particularly as a result of superimposed gestational hypertension with proteinuria. As yet, there is no established intervention that may prevent these outcomes.

Validation

These recommendations need to be field tested and validated in Canada. They will be subject to change as new evidence emerges and therefore should be reviewed periodically.

The recommendations have been endorsed by the CHS, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens-gynécologues du Québec.

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