



Invited Review

The management of hypertension in women planning for pregnancy

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Abstract

Introduction or background: Poorly-controlled hypertension in the first trimester significantly increases maternal and fetal morbidity and mortality. The majority of guidelines and clinical trials focus on the management and treatments for hypertension during pregnancy and breast-feeding, while limited evidence could be applied to the management for hypertension before pregnancy. In this review, we summarized the existing guidelines and treatments of pre-pregnancy treatment of hypertension.

Sources of data: PubMed.

Areas of agreement: Methyldopa and labetalol are considered the first choice, but angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) need to be withdrawn if a hypertensive woman wishes to become pregnant. In women with chronic hypertension, it is very important to make an assessment before conception to exclude secondary causes of hypertension, evaluate their hypertensive control to ensure that it is optimal, discuss the increased risks of pre-eclampsia, and provide education regarding any drug alterations before they become pregnant.

Areas of controversy: There is increasing debate regarding discouraging the use of diuretics. There is also controversy regarding the use of supplementations such as calcium, antioxidants and low-dose aspirin.

Growing points: A less restricted blood-pressure goal could be set for hypertensive women planning for pregnancy. A healthy body weight before pregnancy could lower the risk of pregnancy-related hypertensive

disorders. Recent guidelines also encourage women with chronic hypertension to keep their dietary sodium intake low, either by reducing or substituting sodium salt before pregnancy.

Timely areas for developing research: Large, worldwide, randomized trials should be conducted to see the outcomes for hypertensive women who take antioxidants/physical activity before pregnancy.

Key words: hypertension, pre-pregnancy, guidelines, lifestyle, diet, BMI, blood pressure

Introduction

The rate of hypertension continues to rise dramatically; almost 8% of women of reproductive age (22–44 year) are affected by hypertension in the USA.¹ The incidence of hypertension prior to pregnancy among 15 54-year-old women increased 2-fold from 1993 to 2002 (from 12.3 to 28.9 per 1000 deliveries). Pregnancy-associated hypertension remains an important cause of maternal and fetal morbidity and mortality,² and more evidence has confirmed that pregnancy-associated hypertension could cause early childhood cardio-metabolic disorder.^{3,4} The majority of women with controlled-chronic hypertension under appropriate management will have successful outcomes, however, pre-pregnancy hypertensive women with poorly-controlled blood pressure in the first trimester have significantly increased risk of target organ damage in both mothers and foetuses, low birth weight, pre-eclampsia and other adverse outcomes. Most current guidelines and clinical trials focus on the management and treatments for hypertension during pregnancy and breast-feeding, while limited evidence could be applied to the management of hypertension before pregnancy.

Epidemiology

There are three types of hypertensive disorders of pregnancy: chronic hypertension, gestational hypertension and pre-eclampsia. Pre-eclampsia is a leading cause of pre-term birth and cesarean delivery.⁵ Chronic hypertension is defined as a BP \geq 140/90 mmHg, recorded before pregnancy and before 20 weeks of gestation.⁶ The incidence of this disorder is higher in women who are older, obese or black.⁷

Chronic hypertension is associated with an increased risk of pre-eclampsia, growth restriction and congenital heart disease.^{8–10} Even in the absence of superimposed pre-eclampsia, women with chronic hypertension have a higher risk of adverse outcomes.¹¹ Chronic hypertension complicates 3–5% of pregnancies,¹² but the number is rising over time, along with the trend of women postponing childbirth into their 30s or 40s^{13,14} as well as obesity.¹⁵ A systematic review reported chronic hypertension associated with many adverse outcomes, including superimposed pre-eclampsia, cesarean delivery, pre-term delivery (<37 weeks), low birth weight (<2500 g), neonatal intensive care and perinatal death.¹⁶

The presence of mild-to-moderate pre-existing hypertension (systolic blood pressure (SBP) 140–159 mmHg or diastolic blood pressure (DBP) of 90–99 mmHg) increases the risk of pre-eclampsia, placental abruption and growth restriction in the fetus. In a prospective study including 222 women with mild-to-moderate hypertension, the non-treatment group experienced higher complication rates than did the treatment group for severe hypertension (66.9% vs. 25%, odds ratio (OR) 0.37(0.22–0.63)), renal impairment (72.8% vs. 23.1%, OR 0.32(0.19–0.52)), ECG changes (71.18% vs. 25% OR 0.35(0.21–0.59)), placental abruption (22.03% vs. 7.6% OR 0.35(0.15–0.8)) and repeated hospital admissions for blood-pressure control (54.2% vs. 5.7% OR 0.11(0.04–0.26)); there were comparable rates for the development of pre-eclampsia (47.4% vs. 30.7%) and hepatic impairment (23.7% vs. 21.15%).¹⁷

However, when chronic hypertension is severe (>170/110 mmHg), the risk of pre-eclampsia is as high as 46%, with resulting raised maternal and

fetal risks. In Chappell's study, which collected data from 822 women with chronic hypertension, the prevalence of infants born small-for-gestational age or pre-term was higher than the background rates (48% vs. 21%).¹⁸ Thus, the management of pre-pregnancy blood pressure is of great importance to achieve an optimal pregnancy outcome.

Guidelines for pre-pregnancy hypertension treatment

Most guidelines gave the pre-pregnancy antihypertensive advice based on the evidence from pregnancy chronic hypertension guidelines. Internationally, the guidelines vary for the management of chronic hypertension during pregnancy. It must be stressed that none of the many antihypertensive agents used in routine practice have been shown to be teratogenic to be taken safely (Table 1). The majority of the guidelines recommend that women on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and planning to become pregnant have to discuss with their doctor prescription of an alternative.¹⁹ Antihypertensive treatment should be discontinued in women taking ACE inhibitors or ARBs if they become pregnant (preferably within two working days of notification of pregnancy) as ACE inhibitors and ARBs are teratogenic, with increased risk of congenital abnormalities if taken during early pregnancy, and they are therefore contraindicated.²⁰⁻²³

Methyldopa is often considered the first-line therapy for pre-pregnancy antihypertensive treatment^{24,25} with the largest quantity of data regarding fetal safety since it has been used for pregnancy hypertension since 1960s²⁶ even in the first trimester.²⁷ In a 7.5-year follow-up study, there were no adverse growth or developmental outcomes in children whose mothers received methyldopa during pregnancy.²⁸ Many clinicians opt to change women's antihypertensive therapy to methyldopa prior to conception, especially if they require more than one drug and it is unlikely that they will be able to discontinue therapy in early pregnancy. Labetalol, a combined alpha-blocker and beta-blocker, is an alternative to methyldopa, as it is well-tolerated with an easier

twice-a-day dosing schedule than methyldopa,²⁹ particularly for severe hypertension.

Beta-blockers is generally safe, but intrauterine growth retardation and pre-term birth have been reported.³⁰ Calcium channel blockers (CCBs) such as nifedipine are frequently used because of their use in stopping premature labor. A randomized controlled trial conducted by Webster L demonstrated that nifedipine controlled BP of chronic hypertension in pregnancy and reduced the incidence of severe hypertension without an increase in adverse perinatal outcome.³¹ The use of sublingual nifedipine, however, should be avoided to minimize the risk of sudden maternal hypotension and fetal distress, caused by placental hypoperfusion. Amlodipine has been used in pregnancy but safety data are lacking.

There is increasing debate regarding discouraging the use of diuretics. The European Society of Hypertension/European Cardiology Society (ESH/ECS) 2013 guidelines state that the use of diuretics in pregnancy should be considered a possible or relative contraindication, while the British Hypertension Society (BHS) deemed the use of diuretics as a controversial issue associated with potential harmful effects on maternal and fetal outcomes. There could also be an increased risk of congenital abnormalities and neonatal complications if chlorothiazide is taken.

Blood-pressure goals

There is also controversy regarding antihypertensive benefits for mild-to-moderate hypertension based on the unpredicted adverse outcomes of these antihypertensive drugs, particularly for those that aggressively lower blood pressure. A systemic review from the Lancet claims that the evidence base regarding pharmacologic management of chronic hypertension during pregnancy is too small to either prove or disprove moderate-to-large benefits of antihypertensive therapy; every 10-mmHg drop in blood pressure in women taking antihypertensives was associated with a 145-g decrease in birth weight.³² The American College of Obstetricians and Gynecologists (ACOG) practice bulletin also states that there is no evidence that antihypertensive treatment for mild-to-moderate

Table 1 Summary of antihypertensive treatment for pre-pregnancy hypertension

Variable	Recommendation	Controversy
Medications	Methyldopa or labetalol Avoid ACE inhibitors	Diuretics
Blood-pressure goals	Women with mild-moderate hypertension and a normal BMI may choose to discontinue the use or reduce the doses of antihypertensive agents.	Specific blood-pressure levels for treatment and goal
Evaluation before pregnancy	Evaluate for secondary causes in presence of suggestive symptoms or signs. In women with a history of hypertension for several years, evaluate for target-organ damage, including left ventricular hypertrophy, retinopathy.	
Supplementations		Calcium, antioxidants, low-dose aspirin (60 mg daily)
Lifestyle	Healthy body weight. Adequate sodium and potassium intake.	The dose of sodium or potassium intake

ACE denotes angiotensin-converting enzyme, BMI body mass index.

hypertension improves maternal or fetal outcomes, even for women who are already receiving hypertension treatment.³³ Magee et al provided important data from the Control of Hypertension in Pregnancy Study (CHIPS) showing that less-tight control of maternal hypertension (control of DBP values) in pregnancy as compared with tight control resulted in no significant difference in the risk of adverse perinatal outcomes, although less-tight control was associated with a significantly higher frequency of severe maternal hypertension.³⁴ On the other hand, in a prospective population-based cohort study including 43 718 Chinese women, investigators found that blood pressure before pregnancy was not associated with increased risk of low birth weight or small-for-gestational age, even in the hypertensive groups.³⁵

Regarding these opinions, we should pay more attention to the blood-pressure goal before pregnancy. One reason is that blood pressure, including SBP, DBP, mean arterial pressure and central SBP, has been confirmed to decrease in the early stage in the first trimester³⁶; and the majority of the decrease occurs early in pregnancy (6–8 week gestational age).³⁷ However, women with a body mass index (BMI) over 25 kg/m² before pregnancy have been shown by some to have significantly higher SBP, DBP and mean arterial pressure during the pregnancy and the postpartum period than women

with lower body mass.³⁸ In a population-based cohort study, obese and overweight women had higher blood pressure in the first trimester than normal-weight women.³⁹ Second, various guidelines provided disparate recommendations regarding starting antihypertensive therapy, ranging from a blood pressure of >159/89 mmHg to >169/109 mmHg, and the target blood pressure after antihypertensive treatments ranged from <140/90 mmHg to <160/110 mmHg.

Accordingly, for women with hypertension who wish to become pregnant, a less restricted blood-pressure goal could be set. Women with mild-to-moderate hypertension and a normal BMI may choose to discontinue the use or reduce the doses of antihypertensive agents.

Education

The most difficult problem for the management of pre-pregnancy hypertension was that the majority of women with chronic hypertension who became pregnant did not know their blood pressure and did not start hypertension management before pregnancy or when they are planning to become pregnant. Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the normal fall in blood pressure, commencing in the first trimester.

This may mask pre-existing hypertension, and when blood pressure is recorded later in the pregnancy it may be interpreted as gestational hypertension.

Since nearly 50% of pregnancies in USA are unplanned, it is very important to counsel women of reproductive age regarding both the importance of the blood pressure control and the adverse effects of the antihypertensive agents. Those with high blood pressure should be screened for underlying secondary causes and endocrine causes such as hyperaldosteronism.⁴⁰ This recommendation is enhanced by the Canadian (34), Australasian and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) eight evidence guidelines for the management of high blood pressure in adults (35), reinforcing the importance of looking for signs and symptoms of secondary hypertension in women with chronic hypertension who seek preconception counseling. Particularly, the presence of resistant hypertension, hypokalaemia (potassium levels <3.0 mEq/l), elevated serum creatinine level (>1.1 mg/dl) and family history of kidney disease are important suggestive findings of secondary hypertension.

In addition, age is the strongest risk factor for the occurrence of hypertension.⁴¹ The prevalence of hypertension was 30% among adults over 18 years old in the USA, and in some other countries, as African American women have a higher prevalence of hypertension and at younger ages.^{42,43} First birth rates for women 35–39 years old generally increased from the mid-1970s to 2012, while steady increases for women 40–44 years old began later in the 1980s, which may cause the increased risk of pregnancy-associated hypertension and related adverse delivery outcomes. Childbirth at earlier ages could bring much more benefits for decreasing the risk of delivery complications and improving childhood developmental outcomes.

Women with long-term hypertension

Long-term hypertension induces damage to the vasculature,⁴⁴ myocardium, kidney⁴⁵ and other organs.⁴⁶ Thus, before pregnancy, women with long-term hypertension (usually more than 4 years), are

recommended to undergo assessment of left ventricular function with echocardiography or electrocardiography,¹⁹ according the guidelines from ACOG, 2013. Additionally, if the urinalysis is positive for protein, then a 24-h urine collection for protein analysis or measurement of spot urine protein-to-creatinine ratio should be assessed.^{47,48} For those with target organ damage, contraception (the Copper T380A) is important for helping them achieve optimal timing of pregnancy in relation to the optimal control of their condition.⁴⁹

Supplementations

Calcium supplementation (1.5–2 g daily) in the second half of pregnancy is currently recommended by the World Health Organization (WHO) for women with low dietary calcium intake.⁵⁰ Low dietary calcium intake has been confirmed to be associated with high blood pressure in the general population.⁵¹ In Griffith's systematic review, dietary calcium supplementation was associated with a 1.44-mmHg reduction in SBP and a 0.84-mmHg reduction in DBP⁵²; the benefits of calcium supplementation in the second half of pregnancy for the prevention of severe morbidity or mortality associated with pre-eclampsia has also been confirmed in a Cochrane review.⁵³ There is no study focused on the potential benefits of pre-pregnancy calcium supplementation or food fortification in the prevention of pre-eclampsia or other hypertensive disorders, maternal morbidity and mortality and fetal and neonatal outcomes. Only one randomized controlled trial looked at the effect of calcium (800 mg) plus additional supplements in the early stages of pregnancy,⁵⁴ but no studies of calcium alone were found. Based on the fact that whether calcium supplementation could reduce blood pressure in hypertensive female patients remains unclear,⁵⁵ we currently cannot conclude whether the use of calcium in pre-pregnancy women is effective.⁵⁶ Further research is needed to determine whether pre-pregnancy calcium supplementation is recommended for hypertensive women as well.

Antihypertensive effects of antioxidants such as vitamin C and resveratrol were hypothesized and

tested in many laboratory⁵⁷ and human studies^{58–60} because of their antioxidative effects in reducing oxidative stress and enhancing endothelial function. However, the evidence for blood-pressure-lowering effects of these antioxidants in clinical trials is inconsistent.⁶¹ It has been proposed that pre-eclampsia is a disorder of increased oxidative stress, offering the possibility of targeted therapy aimed at oxidative stress reduction with antioxidants.⁶² Although the antihypertensive effect of antioxidants is limited, they are also recommended to potentially reduce the risk of pre-eclampsia in pre-pregnant patients with chronic hypertension. However, studies have shown a lack of efficacy of vitamin C or E administered from the second trimester to reduce the rates of either pre-eclampsia or other adverse outcomes.^{63,64} The result of a multicentre, randomized, double-blind trial involving nulliparous women at low risk for pre-eclampsia showed no significant differences between vitamin C (1000 mg) and E (400 IU) or placebo initiated in early pregnancy (the 9th to 16th week) of pregnancy on rates of primary outcome (6.1% vs. 5.7%) or pre-eclampsia (7.2% vs. 6.7%).⁶⁵ The dose and the timing of administration of antioxidants are important and should be investigated in further clinical trials, particularly in women with mild-to-moderate hypertension who wish to become pregnant.

Another supplement that may have the same effect to prevent pre-eclampsia is low-dose aspirin (60 mg daily). Low-dose aspirin therapy inhibits thromboxane production more than prostacyclin production and therefore should protect against vasoconstriction and pathologic blood coagulation in the placenta.⁶⁶ Although there has been no clinical trial conducted to identify whether low-dose aspirin used before pregnancy is useful, data from large RCTs do not suggest greater benefits of aspirin when started before 17 weeks' gestation for the prevention of pre-eclampsia, as a result of a meta-analysis (relative ratio (RR): 0.93; 95% confidence interval (CI): 0.75–1.15).⁶⁷ Low-dose aspirin is not recommended as prophylaxis if the risk for pre-eclampsia is relatively low.

Lifestyle change

Healthy body weight

Numerous studies have demonstrated the importance of body weight or weight loss to control of blood pressure during pregnancy.^{68,69} A prospective study included 2252 pregnant women to evaluate the association between pre-pregnancy BMI and blood pressure during pregnancy. They found that pre-pregnancy BMI determines the level but not the change of blood pressure during pregnancy.⁷⁰ Although this study did not restrict women's blood pressure level, we must notice that obese and overweight women of reproductive age should be encouraged to practice a healthy lifestyle, including weight reduction prior to pregnancy. Another study from Australia excluded women with a history of hypertension before pregnancy, and the result was inconsistent with the above conclusion.⁷¹ The result showed that pre-pregnancy weight gain but not the baseline weight was associated with an increased risk of hypertensive disorders in pregnancy, whereas early adult weight loss was associated with lower risk of pregnancy hypertension. A Chinese study showed both pre-pregnancy BMI as well as gestational weight change were positively associated with the risk of hypertensive disorders in pregnancy (39).

Diet

Dietary intake during pregnancy was proposed to play a role in the etiology of pregnancy hypertensive disorders, but the evidence for the relation between diet and the prevention of hypertensive disorders remains inconclusive.⁷² There are no studies including pre-pregnancy hypertensive women to follow up the results of the delivery outcomes as well as the adverse events during pregnancy. In a population-based study enrolling participants in the Australian Longitudinal Study on Women's Health, pre-pregnancy consumption of a Mediterranean-style dietary pattern (characterized by vegetables, legumes, nuts, tofu, rice, pasta, rye bread, red wine and fish) was found to be associated with lower risk

of developing hypertensive disorders (RR: 0.58; 95% CI: 0.42–0.81).⁷³

Dietary sodium and potassium intake are also believed to significantly contribute to the change in blood pressure in both general and hypertensive population. In a recent Cochrane Database systemic review,⁷⁴ sodium reduction from an average high usual sodium intake level (201 mmol/day) to an average level of 66 mmol/day, below the recommended upper level of 100 mmol/day (5.8 g/day), resulted in a decrease in SBP/DBP of 1/0 mmHg in white participants with normotension and a decrease in SBP/DBP of 5.5/2.9 mmHg in white participants with hypertension. In another meta-analysis, potassium supplementation was found to decrease SBP of 4.48 mmHg (95% CI: 3.07–5.90) and DBP of 2.96 mmHg (95% CI: 1.10–4.82).^{75,76} The authors suggested an adequate dietary intake of potassium, on the order of 90 mmol/day (3510 mmHg), to achieve blood pressure control as recommended by the WHO.⁷⁷ For pregnant women, there are paradoxical studies regarding salt consumption and the risk of pre-eclampsia.^{78,79} Although some limited data evaluated the effects of potassium intake on blood pressure development in pregnant women, the association remains a controversial matter for clinicians. There are no trials of sodium or potassium intake for reducing the relative risks for hypertensive women before pregnancy.⁸⁰ To date, information about the association between sodium and potassium is insufficient to make an accurate conclusion for a recommendation. As overall dietary patterns remain relatively stable from pre-pregnancy and throughout pregnancy, a large nationwide randomized trial is underway.

Conclusion

For women with hypertension who wish to become pregnant, antihypertensive treatment should be discontinued in those taking ACE inhibitors or ARBs (even chlorothiazide), and methyldopa should be used as an alternative. Women with chronic hypertension should be encouraged to maintain low dietary sodium intake. Moreover, large, multicentre, randomized trials should be conducted to determine

the efficacy of supplements such as antioxidants and calcium used from the pre-pregnancy stage.

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Conflict of interest statement

The authors have no potential conflicts of interest.

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