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Chronic hypertension: effect of blood pressure control on pregnancy outcome

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Short Title: Chronic hypertension and blood pressure control

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ABSTRACT

Context: In pregnancies with chronic hypertension (CH), compared to those without CH, there is a 10-fold increase in the risk of preeclampsia (PE) and two-fold increase in risk of small for gestational age (SGA) neonates.

Objective: To examine the evidence of whether in patients with CH and mild to moderate hypertension the level of control of blood pressure during pregnancy has a beneficial or adverse effect on the risk of PE or SGA.

Method: We performed a systematic review and meta-analysis of randomized controlled trials of patients with mild to moderate CH in pregnancy that reported the impact of different levels of control of blood pressure on the risk of PE or SGA. We completed a literature search through PubMed, Embase, Cinahl, Web of science, Cochrane CENTRAL Library from their earliest entries to July 2017 and from references of other

systematic reviews. No language restrictions were applied. Relative risks with random effect were calculated with their 95% confidence intervals (95% CI).

Results: Six trials including 495 participants provided data on BP after entry to the study. In four studies there was comparison between one or more antihypertensive agents and no treatment and in the other two use of antihypertensives was compared to placebo. All trials were considered to be at high risk of bias, because they were conducted between 1976 and 1990 and since that time medical practice regarding the control of hypertension during pregnancy could have changed and the definitions for diagnosis of superimposed PE varied between studies. In the case of SGA only one of the six studies reported the definition for such diagnosis. There was high heterogeneity between studies for mean arterial pressure (MAP) after randomization (I^2=87%) and SGA (I^2=60%), but not for PE (I^2=0%). Moreover, there were large differences between studies in the inclusion criteria, antihypertensive regimens, targets of therapy, and wide gestational age range at entry to the trials. In women receiving antihypertensive therapy, compared to those receiving placebo or no treatment, the MAP after entry to the trial was significantly lower (mean difference -4.2 mmHg, 95% CI -6.6 to -1.8; p=0.006). However, there was no significant reduction in the risk of PE (RR 1.03, 95% CI 0.63 to 1.68; p=0.90) or SGA (RR 1.01, 95% CI 0.35 to 2.93; p=0.99).

Conclusion: The findings of the meta-analysis suggest that lowering the blood pressure by antihypertensive medication in women with mild to moderate hypertension in the context of CH has no significant effect on the risk of SGA or PE.

Key Words: Chronic hypertension; blood pressure control; preeclampsia; small for gestational age; systematic review; meta-analysis; randomized controlled trial.

Introduction

Chronic hypertension (CH) is found in 1-2% of pregnancies. In pregnancies with CH, compared to those without CH, there is a 10-fold increase in the risk of preeclampsia (PE) and two-fold increase in risk of small for gestational age (SGA) neonates.[1,2] A study of 74,226 pregnancies, including 1,052 (1.4%) with CH, attending for routine care reported that the risk of PE and SGA in all pregnancies increased with the level of mean arterial pressure (MAP) at 11-13 weeks' gestation and this increase was particularly marked in women with CH.[1]

In patients with CH it is recommended that severe hypertension should be controlled to reduce the risk of maternal death and morbidity. However, in the case of mild to moderate hypertension it is uncertain whether normalization of blood pressure (BP) is beneficial and whether such therapy would reduce the associated increased risk of PE and SGA. Meta-analysis of trials evaluating antihypertensive treatment vs. placebo or no treatment in pregnancies with CH reported no significant differences between the groups in risk of superimposed PE or SGA.[3] However, the real issue is whether normalization in BP, rather than treatment *per se*, is beneficial or not.

This review examines the evidence of whether in patients with CH and mild to moderate hypertension the level of control of BP during pregnancy has a beneficial or adverse effect on the risk of PE or SGA.

Methods

This is a systematic review and meta-analysis of randomized controlled trials of patients with mild to moderate CH in pregnancy. We aim to examine the impact of different levels of control of BP on the risk of PE or SGA. No ethical approval was required.

Search strategy

MeSH terms and keywords related to CH in pregnancy and treatment were searched

through PubMed, Embase, Cinahl, Web of science, Cochrane CENTRAL Library from their earliest entries to July 2017 and from references of other systematic reviews. No language restrictions were applied.

Selection of the articles

The inclusion criteria were randomized controlled trials of pregnant women with mild to moderate CH comparing treatment versus no treatment or placebo in which control of BP after randomisation was documented. Studies including women with gestational hypertension and CH were excluded unless they reported data separately for CH.

All citations were examined to identify potentially relevant studies; the abstracts were revised by two independent reviewers (AMP and SR) who selected eligible studies for full assessment of the complete article. Any disagreements were resolved by discussion with a third party (KN).

Outcome measures

The outcome measures for this analysis were superimposed PE and SGA. We adopted a pragmatic approach of accepting these outcomes as defined in each study and the definitions were documented. We examined these outcome measures in relation to the level of control in BP, which was defined as the difference in mean arterial pressure (MAP) after enrolment between the treated group and the controls.

Quality evaluation

PRISMA tool was used to assess the quality of the study and the Cochrane Handbook criteria were used to assess the risk of bias.[4,5]

Analyses

Relative risks (RR) and mean differences were calculated with their 95% confidence intervals (CI) using random effects.[6] Assessment for publication bias was by funnel plots and heterogeneity with Higgins's I^2; the latter was high if $\geq 50\%$.[7,8] Analyses were carried out with Review Manager 5.3 software (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark).

Results

The literature search identified 4,260 citations and 47 of these were selected for final evaluation (Figure 1). There were six trials (495 participants) investigating the effect of treatment of mild to moderate hypertension in pregnant women with CH in which we could extract data for mean MAP after entry to the study.[9-14] In four studies there was comparison between one or more antihypertensive agents and no treatment and in the other two use of antihypertensives was compared to placebo. Details of individual studies are provided in Table 1. Appendix 1 reports the 41 studies that were excluded and the reasons for their exclusion.

All trials were considered to be at high risk of bias, because they were conducted between 1976 and 1990 and since that time medical practice regarding the control of hypertension during pregnancy could have changed and the definitions for diagnosis of superimposed PE varied between studies (Figure 2). In the case of SGA only one of the six studies reported the definition for such diagnosis.

There was high heterogeneity between studies for MAP (I^2=87%) and SGA (I^2=60%), but not for PE (I^2=0%). Moreover, there were large differences between studies in the inclusion criteria, antihypertensive regimens, targets of therapy, and wide gestational age range at entry to the trials. Publication bias cannot be excluded because the number of included studies was too small to allow assessment of the funnel plot.

In women receiving antihypertensive therapy, compared to those receiving placebo or no treatment, the MAP after entry to the trial was significantly lower (mean difference -4.2 mmHg, 95% CI -6.6 to -1.8; p=0.0005; Figure 3). However, there was no significant reduction in the risk of PE (RR 1.03, 95% CI 0.63 to 1.68; p=0.90; Figure 4) or SGA (RR 1.01, 95% CI 0.35 to 2.93; p=0.99; Figure 5).

Discussion

Principal findings of this study

The findings of our meta-analysis suggest that lowering the MAP by antihypertensive medication in women with mild to moderate hypertension in the context of CH has no significant effect on risk of SGA or PE.

The study has also highlighted that first, the effect of antihypertensive medication in terms of lowering the BP is significant but very small and second, in most trials the average BP in the placebo or no treatment group was <140/90 mmHg . In the largest of the six trials, which included 263 patients, the overall BP in the no treatment group was 136/85 mmHg, compared to 128/80 mmHg in those receiving antihypertensive drugs.[14] A BP of 140/90 mmHg is equivalent to the MAP of 107 mmHg and the average MAP during pregnancy in the placebo or no treatment arm of each trial was 102,[9] 106,[10] 109,[11] 104,[12]99[13] and 102.[14]

Limitations of the study

The meta-analysis included a small number of trials with large heterogeneity between the studies in terms of inclusion criteria, antihypertensive regimens, targets of therapy, gestational age range at entry to the trials and definitions of superimposed PE. Age of the studies can also limit the external validity since medical practice could have changed in the last 27-38 years since publication of these trials. However, regarding the literature, this is the actual best evidence we have now.

Comparison with findings of other studies

The findings of our meta-analysis are concordant with those of a subgroup analysis of the CHIPS trial which showed that in 736 women with CH and diastolic BP of 90-105 mm Hg at entry to the study, there was no significant difference in the risk of either SGA or PE between a policy of tight control in BP with a target diastolic BP of 85 mm Hg compared to a policy of less-tight control with target diastolic BP of 100 mm Hg.[15]

Clinical implications of the study

The American College of Obstetricians and Gynecologists (ACOG) recommends that patients with CH should only receive antihypertensive medication if the disease is severe with systolic BP of >160 mm Hg or diastolic BP of >105 mm Hg, but not if the disease is mild to moderate with systolic BP of 140-159 mm Hg or diastolic BP of 90-109 mm Hg.[16]Similarly, in the UK, the National Institute for Health and Clinical Excellence (NICE) guideline recommends the use of antihypertensive drugs only when the BP is greater than 150/100 mm Hg.[17] The reluctance of professional bodies to recommend

therapy for mild to moderate hypertension was based on evidence that such therapy does not improve perinatal outcome and may increase the risk of SGA.[18,19]

Our finding that lowering the MAP by antihypertensive medication in women with mild to moderate hypertension does not increase the risk of SGA is reassuring. However, we did not provide evidence that such therapy improves perinatal outcome and it certainly does not appear to reduce the risk of PE. Consequently, our results do not support a need for change of the recommendations by ACOG and NICE concerning the management of mild to moderate hypertension.

Future research

In pregnancies with CH there is a high risk for development of PE and delivery of SGA neonates and these risks increase with increasing MAP at 11-13 weeks' gestation.[1,2] This meta-analysis suggests than lowering the BP does not reduce the risks of PE and SGA. In most of the trials included in our analysis[9,11,12,13] and in the CHIPS trial[15] treatment was initiated after the first trimester and it could therefore be argued that any detrimental effect of hypertension on placentation could not have been reversed. However, the two trials where treatment was initiated within the first trimester have also reported no benefit in reducing the risk of PE or SGA.[10,14] It is also of interest that in the ASPRE trial, which reported that aspirin (150 mg/day) from 11-14 to 36 weeks' gestation in pregnancies at high-risk for PE was associated with >60% reduction in the risk of preterm-PE, the beneficial effect of aspirin did not apply in pregnancies with CH.[20,21]

In CH there is remodeling of small arterial resistance vessels leading to relative thickening of the muscular media, vasoconstriction and decreased capacity for vasodilation.[22] Such features could cause impaired placental perfusion and the cascade of events leading to PE and SGA. In addition, some women with medical disorders, such as CH, have endothelial dysfunction before pregnancy and it was proposed that in such cases PE can develop even in the absence or mild degrees of impaired placentation.[23-26]

The extent to which in CH normalization of BP before conception could improve placentation and / or cardiovascular function with consequent prevention of PE and SGA remains to be determined. Another area of research is the investigation of the extent to

which in pregnancies with CH placentation could be improved through such medications as pravastatin, which stimulates release of proangiogenic placental growth factor (PLGF) and inhibit secretion of the angiogenic factor soluble Fms-like tyrosine kinase-1 (sFLT-1).[27,28]

Figure legend

Figure 1. Flow chart for the systematic review.

Figure 2. Summary of the quality of included studies.

Figure 3: Forest plots of the mean arterial pressure (MAP) after randomization. Comparison between treated versus control groups.

Figure 4: Forest plots of the risk of preeclampsia. Comparison between treated versus control groups.

Figure 5: Forest plots of the risk of small for gestational age. Comparison between treated versus control groups.

Table 1. Characteristics of studies included in the meta-analysis

Study	N	Inclusion criteria	Intervention: dugs vs. placebo or no treatment	GA at entry (w)	Mean arterial pressure (mmHg)		Definition of PE	Definition of SGA
					Entry	Later		
Arias, *et al*, 1979[9]	58	History of hypertension before pregnancy or hypertension <20 weeks with BP >140/90-99 mmHg on two occasions >24 h apart	**Drugs:** Methyldopa (750-2000 mg/day) and / or Hydralazine (75-250 mg/day) and / or Hydrochlorthiazide (50 mg/day) **Control:** No treatment	<20	100.6 (1.97) vs. 97.1 (1.35)	99.6 (2.97) vs. 102.1 (1.52)*	Proteinuria of >2+ in random samples, or >300 mg/L in 24 h collection	Not stated
Sibai, *et al*, 1984[10]	20	History of hypertension before pregnancy receiving diuretics plus diastolic BP >90 and <110 mmHg	**Drugs:** Diuretics (continuation of pre-pregnancy treatment) **Control:** No treatment (diuretics discontinued)	<14	105 vs.102	108 (10) vs. 106 (7) †	Not stated	Not stated
Kahhale, *et al*, 1985[11]	100	Hypertension <22 weeks with BP >140/90 mmHg on two occasions	**Drugs:** Pindolol (10-30 mg/day) **Control:** No treatment	<22	125.6 (17.2) vs. 113.8 (11.8)	107.3 (16.3) vs. 109.1 (9.2)	-	Not stated
Weitz, *et al*,	25	Presumed CH <34	**Drugs:** Methyldopa (750-2000	20-34	106.8 (3.3)	96 (3.3)	Rise in systolic BP	-

1987[12]		weeks with BP >140/90 mmHg on two occasions 6 h apart	mg/day) **Control:** Placebo		vs. 97.6 (9.9)	vs. 104 (9.9)*	by 30 mmHg or diastolic BP by 15 mmHg and weight gain (>2 lbs per week) or proteinuria (>2+ on urine dipstick)	
Butters, *et al*, 1990[13]	29	Hypertension <24 weeks with BP >140-170/90-110 mmHg on two occasions >24 h apart	**Drugs:** Atenolol (50-200 mg/day) **Control:** Placebo	15.8 (12-24)	105 vs. 107	93 (5) vs. 99 (5)* †	-	BW <10th centile
Sibai, *et al*, 1990[14]	263	History of hypertension before pregnancy	**Drugs:** One group - Methyldopa (750-4000 mg/day) Second group - Labetalol (300-2400 mg/day) **Control:** No treatment	11.2 (6-13)	108.3 (0.7) vs. 107.0 (0.7)	96 (0.4) vs. 102 (0.6)*	Proteinuria >1 gm / 24 h or uric acid >6 mg/dL	Not stated

BW = birth weight; * $p<0.01$; † standard deviation extrapolated from a figure given in the publication

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