Antihypertensives in pregnant women with mild chronic hypertension.

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December 8, 2022

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Disclosure: ¨The authors report no conflict of interest¨

Funding: NO

Word count: Abstract: 94 Main Text: 1085

Running Title: Treatment of pregnancy with chronic hypertension.

Abstract

Pregnant women with chronic hypertension have increased worldwide and with it more maternal and perinatal complications such as hypertensive crisis, preeclampsia, placental abruption, growth restriction, prematurity, perinatal mortality. In addition to correct diagnosis and strict follow-up during the pregnancy, antihypertensive drugs have been controversially used. An adequate randomized controlled study recently published shows the benefit of antihypertensives. The antihypertensive drug used seems to be the explanation why previous studies were not conclusive in denoting benefits. The drugs that have shown benefits are beta-blockers (labetalol), calcium channel blockers (nifedipine, amlodipine) and with minimal effectiveness methyldopa.

Keywords: Chronic hypertension, pregnancy, antihypertensive drugs, labetalol, methyldopa.

Pregnant women with chronic hypertension increase considerably in the world. This group of patients and especially the black population have a higher risk of presenting obstetric complications such as preeclampsia, placental abruption, growth restriction, prematurity, perinatal mortality. In addition, there are more maternal risks such as acute pulmonary edema, kidney damage, heart failure, stroke and death.[1,2]. The management of the patient with chronic hypertension requires follow-up, evaluations and the main management focuses on giving antihypertensive drugs. When these patients become pregnant or chronic hypertension is diagnosed for the first-time during pregnancy, there was no convincing evidence on the usefulness and necessity of giving antihypertensive treatments if the hypertension is not severe, which is usually defined as a blood pressure of <160/110 mm Hg. A recently published study shows convincing evidence on the need to give antihypertensive drugs in this population group.[3]. Until before this study [3], a Cochrane systematic review (CSR) [4] including in the meta-analysis 58 studies (5909 women) showed controversial results that prevented a clear recommendation, also a randomized study[5] of adequate quality published in 2015, in which strict blood pressure control was done or not, it failed to prove benefits in perinatal or maternal outcomes, except less severe hypertension in the group with strict control of blood pressure. The findings of the CSR [4] and

the study by Tita et al.[3] show that the possible explanation for the controversial findings is the drugs used to treat hypertension.

Most of the randomized studies examining the effectiveness of drugs in the management of pregnant women with non-severe chronic hypertension have small numbers of patients. There are only 4 studies that have evaluated at least 300 patients, two of them analyzed in CSR[4] (one in the USA in 1990 with 300 women and the other in Pakistan in 2016 with 314 women), the study by Magge et al.[5] published in 2015 with 981 women and the study by Tita et al. [3] published in the year 2022 with 2408 pregnant women. The study by Magee et al. [5], used antihypertensives in both groups, without randomization to the type of antihypertensives and therefore is not analyzed in the CSR[4] and the study by Tita et [3] was published after the CSR [4]. We currently have three big studies: a systematic review with 5909 women, a randomized study with 981 patients using antihypertensives in both groups, and a randomized study with 2408 women comparing using versus not using antihypertensives. Due to the relevance of the topic and the findings of these three studies, a narrative description and comments are necessary.

The outcomes of maternal and perinatal complications according to the medication used to manage hypertension are described according to the findings of each of the three studies, table 1.

Hypertensive crisis (systolic blood pressure [?]160 mm Hg and/or diastolic blood pressure [?] 110 mmHg): The reduction in hypertensive crises using antihypertensives was demonstrated in the CSR [4] and in the two big and randomized studies already mentioned[3,5]. The study by Magee et al. [5], for the strict control of hypertension, labetalol was used as the main antihypertensive, however, methyldopa was used in more than 40% of the population studied. The findings show that there is a significant decrease in hypertensive crises. The CSR [4] showed a decrease in hypertensive crises independent of the antihypertensive used, but a better result is observed when using beta-blockers. In addition, the CRS shows that in two studies (310 women) with methyldopa, hypertensive crises were also reduced. The Tita et al study[3] shows a significant decrease in hypertensive crises and they used labetalol, nifedipine and amlodipine in 99% of patients in the treatment group, methyldopa was only used in 0.3%. The results of these investigations suggest benefits in avoiding hypertensive crises using beta-blockers, calcium channel blockers and methyldopa.

Preeclampsia/severe preeclampsia and premature birth: The study by Tita et [3] shows significant decrease in severe preeclampsia and births before 35 weeks and the CSR [4] showed a decrease in preeclampsia only when using beta-blockers and a slight increase is observed when using calcium channel blockers, this systematic review does not find a decrease in preterm deliveries. The study by Magee et al. [5] showed no benefit in those outcomes. The findings of these studies show us that using methyldopa as an antihypertensive does not reduce preeclampsia or prematurity.

Placental abruption, fetal/perinatal death: The CSR [4]and the other two randomized studies [3,5] did not find any change in these findings, so there seems to be no benefit for these variables when antihypertensives are used in pregnant women with mild/moderate chronic hypertension. Nevertheless, the Tita et al study[3] shows a significant decrease when adding both findings as a component of the set of primary results.

Neonatal complications (respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, hypoglycemia, bradycardia, seizure, hypotension): The study by Tita et al [3] does not show differences in these variables when giving you antihypertensive treatment, nor did the study by Magee et al. [5]. The CSR [4] shows similar results to the two randomized studies, except that less respiratory distress syndrome is observed at the expense of the group that received antihypertensive treatment with beta-blockers.

Small for gestational age: This is a result that has been questioned as a possible adverse effect of antihypertensives, however, the CSR[4] and the two randomized studies [3,5]they found no change in fetal growth.

Cesarean section: Cesarean births did not vary significantly in the two randomized studies [3,5], however, in a sub-analysis of the CSR [4] shows that there is a significantly higher chance of cesarean section if the antihypertensive used is methyldopa, this emerges from the analysis of 13 studies with 1330 women.

Conclusion: Antihypertensives generate benefits in pregnant women with mild chronic hypertension. The main antihypertensives used in these patients are labetalol, nifedipine, amlodipine, and methyldopa; these drugs reduce severe hypertension. Preeclampsia and especially severe preeclampsia is reduced by beta-blockers and calcium channel blockers. Using methyldopa there is no decrease in preeclampsia, there is a greater possibility of cesarean section and there are side effects such as sedation, depression, dizziness. In addition, the randomized controlled trial that includes the largest number of pregnant women with mild chronic hypertension, demonstrating several benefits with antihypertensives, did not use methyldopa. Methyldopa should not be considered as an antihypertensive in pregnant women with mild chronic hypertension due to its minimal usefulness and the existence of other more effective drugs.

Table 1.

Antihypertensives used in chronic hypertension without hypertensive crisis

Complications	Beta-blockers	CCB	Methyldopa	Observations
Severe hypertension *	decreases	decreases	decreases	Better results with labetalol ar
Preeclampsia with or without severity criteria	decreases	decreases	No changes	CSR [4] shows increase preeclan
Premature birth	decreases	decreases	No changes	
Placental abruption	No changes	No changes	No changes	The study by Tita et al [3] (bet
Fetal or perinatal death	No changes	No changes	No changes	The study by Tita et al [3] (bet
Fetal complications +	No changes	No changes	No changes	CSR[4] shows decreased neonata
Small for gestational age	No changes	No changes	No changes	
Caesarean section	No changes	No changes	Increases	

CCB = Calcium channel blockers; CSR = Cochrane systematic review; * Systolic blood pressure [?]160 mmHg and/or diastolic blood pressure [?]110 mmHg; + respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, hypoglycemia, bradycardia, seizure, hypotension.

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