

Mild chronic hypertension in pregnancy: to treat or wait?

Costas Thomopoulos^a, Jana Brguljan^b, Renata Cífková^{c,d}, Alexandre Persu^e and Reinhold Kreutz^f

^aDepartment of Cardiology, Helena Venizelou General & Maternity Hospital, Athens, Greece;

^bHypertension Department, Medical University Ljubljana, University Medical Centre Ljubljana, Ljubljana, Slovenia; ^cCenter for Cardiovascular Prevention, First Faculty of Medicine and Thomayer University Hospital, Charles University in Prague, Prague, Czech Republic; ^dDepartment of Medicine II, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; ^eDivision of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium; ^fInstitute of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, Berlin, Germany



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Context

The optimal blood pressure (BP) targets during pregnancy in women with pre-existing (i.e. chronic) or new (after the 20th week, i.e. gestational) hypertension remain by and large empirically determined. Indeed, the evidence of different international guideline recommendations for antihypertensive treatment in pregnancy is mainly based on expert opinions. While in pregnant women with severe hypertension, the benefits of pharmacological BP-lowering treatment were clear, no evidence in pregnant women with mild hypertension was available until recently [1].

Seven years ago, the Control of Hypertension in Pregnancy Study (CHIPS) [2] evaluated whether less or more tight control of hypertension (i.e. achieved diastolic BP values less than 100 or 85 mmHg, respectively) was associated with different perinatal and maternal outcomes. In CHIPS, 987 pregnant women with non-severe and non-proteinuric chronic (75%) or gestational (25%) hypertension were enrolled at 14–33 weeks of gestation [2]. The primary outcome was a composite of pregnancy loss or substantial long-standing intensive neonatal care, with serious maternal complications as a secondary outcome. Both outcomes were not different for an average diastolic BP reduction of 4.6 mmHg between the tight and

less-tight BP control groups during follow-up. However, as expected from previous studies [3], the development of severe hypertension, a non-prespecified secondary outcome, was 1.8-fold more frequent in the less tight compared to the tight diastolic BP control group [2]. Finally, in the subgroup of women with chronic hypertension, less tight BP control was associated with lower rates of small-for-gestational-age newborns ($p = 0.04$) than tight BP control [4]. Clearly, CHIPS is an important study, but some limitations should be noted: (1) the sample size was limited and several important analyses including the rates of small-for-gestational-age newborns were underpowered; (2) women with chronic or gestational hypertension were analysed in one group, which represents a potential bias for the clinical interpretation of the data; (3) women presenting with new chronic hypertension earlier in pregnancy than the 14–33 weeks enrolment window were not included; (4) although labetalol was considered the drug of choice, it was only used by two-thirds of women; (5) systolic BP control was not considered for the association with outcomes although it was monitored to detect more severe hypertension and (6) women with prior severe hypertension were more frequently randomised to less-tight control.

CONTACT Costas Thomopoulos  thokos@otenet.gr  Department of Cardiology, Helena Venizelou General & Maternity Hospital Athens, Athens, Greece

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New evidence from CHAP

In April 2022, an important open-label multicentre randomised trial, the Chronic Hypertension and Pregnancy (CHAP), was published [5]. The CHAP trial addressed the outcomes and safety of antihypertensive drug treatment in singleton-pregnancy women with mild chronic hypertension (Table 1). Antihypertensive drug treatment with a target below 140/90 mmHg (active-treatment group) was compared to a conservative strategy of withholding or stopping such treatment unless severe hypertension developed (control group). The CHAP trial outcomes were (1) preeclampsia with severe features or preterm delivery or placental abruption or foetal/neonatal death (primary outcome); (2) small-for-gestational-age newborn (safety outcome); and (3) serious neonatal or maternal complications or preeclampsia or preterm birth (secondary outcomes).

Of the 2408 participants, a majority of the population was Non-Hispanic Black (48%), while Non-Hispanic White and Hispanic women represented 28.7 and 19.7%, and 45 and 77% used aspirin at baseline or pre-delivery. The participants were enrolled before the 23rd week of gestation, and those at higher risk for severe hypertension development (i.e. treated with more than one antihypertensive agent at baseline) were excluded. The preferred drugs were labetalol or extended-release nifedipine (97% of participants). A combination drug treatment was only used after monotherapy dose escalation. The control

group received similar antihypertensive medications only if severe hypertension developed (defined as systolic/diastolic BP 160/105 mmHg or more), otherwise remained untreated. During the in-pregnancy follow-up period, the achieved systolic/diastolic BP difference was 3.1/2.3 mmHg lower in the active treatment than in the control group. The composite primary outcome occurred 18% less frequently in the active-treatment group than in controls (95% confidence interval [CI], 8–27%), translating to a number of women ‘needed to treat’ to prevent one primary outcome event of 14. In subgroup analyses, placental abruption and foetal/neonatal deaths were not different between groups, but both of the following primary outcome components were reduced in the active treatment compared to the control group: (1) preeclampsia with severe features by 20% (95% CI, 8–30%) and (2) preterm birth for medical reasons by 27% (95% CI, 11–40%). The pre-specified composite maternal or neonatal secondary outcomes were not different between groups, including small-for-gestational-age newborns. Severe hypertension developed 18% less frequently in the active treatment compared to the control group (95% CI, 0.74–0.90), however, no stroke event occurred in either study group during the trial.

The CHAP trial adds thus important new randomised evidence to the body of knowledge of antihypertensive treatment during pregnancy, and the authors are to be commended for the successful conduction of this very important trial. However, despite our

Table 1. Contemporary randomised studies of women with hypertension in pregnancy.

Items of interest	CHIPS (2015)	CHAP (2022)
Design	More tight vs. Less tight	Active vs. no treatment
Condition	Gestational hypertension (1/3) Chronic hypertension (2/3)	Chronic hypertension
Study participants, <i>n</i>	987 (736 with chronic hypertension)	2408
Entry BP levels, mmHg	Diastolic: 90–105 no meds or 85–100 on meds	140–159/90–104 no meds Or <160/105 on meds
Entry period, weeks	14–33	0–23
Key exclusion criteria	Severe hypertension Proteinuria Non-singleton pregnancy	At-risk or with severe hypertension Proteinuria Non-singleton pregnancy
Preferred drug(s)	Labetalol	Labetalol Nifedipine (extended-release) ^c
BP measurements	Auscultatory method	Auscultatory method Automated device (ancillary research purposes)
Achieved systolic/diastolic BP, mmHg	138.8/89.9 vs. 133.1/85.3	129.5/79.1 vs. 132.6/81/5
Achieved systolic/diastolic BP difference, mmHg	–5.8/–4.6	–3.1/–2.3
Outcomes ^a		
• Primary ^b	0.65 (0.48–0.88)	0.82 (0.74–0.92)
• Preeclampsia with severe features	0.66 (0.48–0.91)	0.80 (0.70–0.92)
• Small for gestational age newborns (10th percentile)	1.52 (1.01–2.22)	1.04 (0.82–1.31)

BP: blood pressure; CHAP: Chronic Hypertension and Pregnancy; CHIPS: Control of Hypertension in Pregnancy Study; *n*: number; vs.: versus

^aOutcomes for both trials are reported according to the definition of the CHAP protocol but limited to women with chronic hypertension (after the exclusion of women with gestational hypertension recruited in the CHIPS).

^bPrimary outcome was the composite of preeclampsia with severe features, medically indicated preterm birth at less than 35 weeks gestation, placental abruption or foetal or neonatal death.

^cAmlodipine and α -methyl-DOPA were used in 1.0% and 0.3% of the participants, respectively.

enthusiasm, we wish to note a number of limitations of the CHAP trial and still unanswered questions.

First, BP differences were most evident during the first half of the pregnancy, while in the second half, close to most outcomes adjudication, BP differences were less pronounced. A possible explanation might be that the active drug treatment strategy was of a limited intensity, and drug combinations were used only as a third-line step after the implementation of full-dose monotherapy. Second, given the design of the study and the high ratio of women excluded during pre-randomisation screening, the results cannot be generalised to all women with mild chronic hypertension, especially to those diagnosed (1) after the 23rd week of gestation, (2) during the second trimester but with BP levels below the threshold (because of the masking effect of physiological BP drop) and (3) in the context of multiple baseline antihypertensive treatment prone to severe hypertension later in pregnancy. Third, the lower safety margin, i.e. the BP level that is too low and potentially hazardous, still remains unclear. Fourth, while a strength of CHAP is the inclusion of a substantial number of women from three different ethnic groups (Non-Hispanic Black, Non-Hispanic White and Hispanic), the proportion of Asian women included was very low. Finally, the cross-over rate between groups would be interesting to add in a future communication.

Recent reviews, including a Cochrane analysis [3], concluded insufficient data to determine the benefits and risks of antihypertensive therapy for mild-to-moderate hypertension in pregnancy (defined as systolic BP of 140–169 mmHg and diastolic BP of 90–109 mmHg). In addition, different guidelines for the treatment of hypertension in pregnancy vary concerning thresholds for starting treatment and BP goals (Table 2).

According to the current European Society of Cardiology/European Society of Hypertension guidelines for the management of Hypertension [6], the systolic/diastolic BP thresholds at which to start antihypertensive treatment are 140/90 mmHg in women with:

- Gestational hypertension with or without proteinuria;
- Pre-existing hypertension and superimposed gestational hypertension;
- Pre-existing hypertension with hypertension-mediated organ damage.

In other circumstances [6], the above thresholds become more conservative (i.e. 150/95 mmHg). The

Table 2. Management of hypertension in pregnancy.

Guidelines/country, year	BP threshold, mmHg	BP target, mmHg
ESC/ESH, 2018	≥150/95	Not defined
NICE, 2019	≥140/90	135/85
Germany, 2013	≥150/100	<150/80–100
Ireland, 2016/2019		
ISSHP, 2018	≥140/90	110–140/85
ACOG, 2019	≥160/110	<160/110
Canada, 2018	≥140/90	No recommendation/85
SOMANZ, 2014	≥160/110	<160/110
Queensland, 2020	≥140/90	<140/90
Brazil, 2016	≥150/100	130–150/80–100

ACOG: American College of Obstetricians and Gynaecologists; BP: blood pressure; ESH/ESC: European Society of Cardiology/European Society of Hypertension; ISSHP: International Society for the Study of Hypertension in Pregnancy; NICE: National Institute for Health and Care Excellence; SOMANZ: Society of Obstetric Medicine of Australia and New Zealand

critical appraisal of most recent trials may change BP thresholds in future guidelines.

Conclusion

CHAP is a very important study that provides further evidence for the management of mild chronic hypertension during pregnancy, a setting that is inherently difficult to study. The results of the study suggest that antihypertensive drug treatment for women with mild chronic hypertension with a BP target of less than 140/90 mmHg is advantageous and safe, but some limitations of the trial and unanswered questions remain. Physicians may consider the following: (1) identify and treat those at risk of severe hypertension; (2) advise the use of low-dose aspirin, ideally before the second half of the second trimester [7]; (3) regularly monitor BP levels by using the recommended methodology for women in pregnancy [6], especially in the second trimester to avoid overtreatment, placental hypoperfusion and loss of pregnancy, although we note that no randomised evidence is available to support this practice.

The ESH has just started a new Working Group Section (see ESH News Corner) to highlight issues related to the management of hypertension in women, including but not limited to pregnancy. The current ESH Clinical Update briefly reports the results of an important trial in hypertension in pregnancy, drawing attention to the fact that additional randomised trials in the field are desirable in different study populations.

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Key points

- The CHAP trial shows that target BP in pregnant women with mild chronic hypertension should be less than 140/90 mmHg to improve maternal and foetal/neonatal outcomes.
- However, the lower safety margin, i.e. a BP level that is too low and potentially hazardous, remains still unclear.
- The findings of the CHAP trial should be extrapolated with caution to women of Asian ancestry.
- Studies on the long-term effects of antihypertensive drug treatment in women with mild chronic hypertension and their offspring are lacking.
- Whether pregnancy-validated automated devices may replace the traditional auscultatory BP measurements should be examined in future trials. Secondary analyses of the CHAP data comparing outcomes based on standardised pragmatic clinic BP vs. standardised automated clinic BP are awaited.

ESH News Corner: Call for members in a new ESH working group section

ESH will establish within the ESH Working Group (WG) on Hypertension and Cardiovascular Diseases in Special Populations a new WG Section on the topic of ‘**Hypertension in Women**’. Colleagues who wish to join this WG may contact ESH-coordinator Mandy Elgner via email:

eshcoordinator@eshonline.org

The founding meeting of this Section will take place during the 31st ESH Annual Meeting in Athens, 17-20 June 2022.



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