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Management of non-severe pregnancy hypertension – A summary of the CHIPS Trial (Control of Hypertension in Pregnancy Study) research publications☆

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ABSTRACT

The international CHIPS Trial (Control of Hypertension In Pregnancy Study) enrolled 987 women with chronic (75%) or gestational (25%) hypertension. Pre-eclampsia developed in 48%; women remained on their allocated BP control and delivered an average of two weeks later. 'Less tight' control (target diastolic BP 100 mmHg) achieved BP that was 6/5mmHg higher ($p < 0.001$) than 'tight' control (target diastolic 85 mmHg, BP achieved 133/85 mmHg). 'Less tight' (vs. 'tight') control resulted in similar adverse perinatal outcomes (31.5% vs. 30.7%; $p = 0.84$) that balanced birthweight < 10th percentile (16.1% vs. 19.8%; $p = 0.14$) against preterm birth (35.6% vs. 31.5%; $p = 0.18$). 12-month follow-up revealed no compelling evidence for developmental programming of child growth. However, 'less tight' (vs. 'tight') control resulted in more severe maternal hypertension (40.6% vs. 27.5%; $p < 0.001$), and more women with platelets < 100×10^9/L (4.3% vs. 1.6%; $p = 0.02$) or symptomatic elevated liver enzymes (4.3% vs. 1.8%; $p = 0.03$), with no difference in serious maternal complications (3.7% vs. 2.0%; $p = 0.17$). Labetalol was the drug of choice. Methyldopa did not result in inferior outcomes. Post-hoc, severe hypertension, independent of pre-eclampsia, was associated with heightened increased risk of adverse outcomes, and in 'less tight' control, of serious maternal complications. At no gestational age at initiation of BP control was 'less tight' superior to 'tight'. Women in both groups were equally satisfied with care. 'Less tight' control tended to be more expensive by CAD$6000 ($p = 0.07$) based on neonatal care costs. Collectively, CHIPS publications have provided evidence that women with non-severe pregnancy hypertension should receive 'tight' BP control achieved by a simple algorithm.

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1. Introduction

Blood pressure (BP) targets for women with hypertension in pregnancy has been long-debated. The historical concern that lowering of maternal BP may decrease uteroplacental perfusion and have a negative impact on fetal growth and well-being, has resulted in variable recommendations in international clinical practice guidelines [1]. Many societies have recommended observation for BP values < 160/110 mmHg and then urgent treatment at ≥160/110 mmHg, an approach that has been described as "logically inconsistent" [2].

The international CHIPS Trial (Control of Hypertension In Pregnancy Study) was designed to test whether minimisation of antihypertensive use by 'less tight' control and a target diastolic BP (dBP) of 100 mmHg, compared with normalisation of BP by 'tight' control and a target dBP of 85 mmHg, would be better for the baby without increasing risk to the mother [3]. The CHIPS Trial provided evidence that antihypertensive treatment to a lower BP target is of benefit to the mother, without associated perinatal risk.

In reference to publication of the main results of trials, it has been stated that, "rarely does a trial's clinically important message jump out fully formed. Instead, the process requires detailed analyses that weigh the risks and benefits of the study intervention as translated into a clinical care setting…" [4]. This was certainly true of the main CHIPS results, published in 2015 [5] and followed by numerous secondary analyses that have built on results in the supplementary online appendix of the original publication and refined the study findings, addressing in particular, the importance of severe hypertension as a clinical outcome and why any potential effect of BP control on birthweight was balanced by prematurity and did not translate into an effect on perinatal death or morbidity. As the results of the CHIPS Trial are now being adopted into international guidelines [6–8], it is timely to summarise the published evidence from CHIPS, supplemented by additional data, to provide clinicians with an overview that can best inform implementation of evidence into practice.

2. CHIPS background and general information

The normal placenta does not regulate uteroplacental blood flow because of normal loss of endothelial smooth muscle during placental development. While it is known that the breadth and depth of vascular change is reduced in pre-eclampsia, concern about antihypertensive therapy has been expressed for all types of pregnancy hypertension.

Antihypertensive treatment of pregnancy hypertension has been the subject of many randomised controlled trials (RCTs) [9]. Trials have enrolled women with a variety of hypertensive disorders, usually without co-morbidities; when women were enrolled at ≥20 weeks' gestation, trials often did not or could not distinguish between women with chronic hypertension and women with gestational hypertension or pre-eclampsia that, by definition, arose at ≥20 weeks. Based on the results of these trials, global guideline consensus is that clinicians respond to absolute BP levels, regardless of the underlying hypertensive disorder.

Most trials have been small and of low quality [9]. They showed that antihypertensive therapy, compared with no treatment or placebo, decreased the risk of severe hypertension. However, this was considered insufficient to guide practice because of unresolved concerns about perinatal outcomes, highlighted by meta-regression analyses that associated greater antihypertensive-induced falls in mean arterial pressure with decreased fetal growth velocity [10,11].

The international CHIPS Trial enrolled 987 women with chronic or gestational hypertension, all without co-morbidities (an exclusion criterion). CHIPS randomised women to a dBP target of 100 mmHg ('less tight' control) vs. 85 mmHg ('tight' control). Standardised measurement of BP was performed in outpatient settings by health professionals who obtained three BP measurements. The average of the second and third diastolic measurements was considered to be the diastolic BP for that visit, and recorded in a patient-held diary. Few women (< 3%) discontinued their assigned BP treatment before delivery, but regardless, they were included in their allocated group according to an intention-

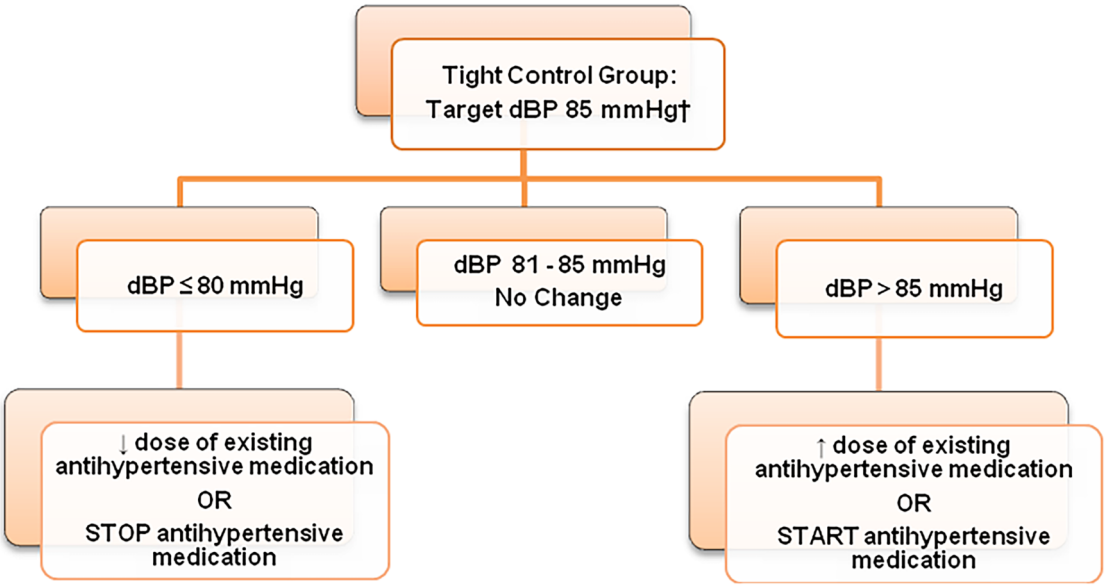


Fig. 1. 'Tight' control of BP, according to the target diastolic blood pressure (dBP) and appropriate responses to it with regards to antihypertensive therapy. dBP (diastolic blood pressure), sBP (systolic blood pressure). (From The New England Journal of Medicine, Magee LA (on behalf of the Control of Hypertension in Pregnancy Study [CHIPS] Study Group, ClinicalTrials.gov number, NCT01192412), von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies JM, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Logan AG, Ganzevoort JW, Welch R, Thornton JG, Moutquin JM, Less-tight versus Tight Control of Hypertension in Pregnancy, 372, 407–17. Copyright@2015 Massachusetts Medical Society. Reprinted with permission.) [5]. †If sBP ≥ 160 mm Hg, increase dose of existing medication or start new antihypertensive medication to get sBP < 160 mm Hg.

to-treat analysis. At ~6–12 wks postpartum, CHIPS site co-ordinators administered a structured questionnaire to record any post-discharge morbidities and obtain maternal views about trial participation.

The baseline characteristics of women in the two groups were generally similar. On average, women were randomised at about 24 weeks. Most women (about 75%) had chronic hypertension. Baseline BP was about 140/92 mmHg, and just over half of women were on antihypertensive therapy at the time, usually (> 80%) labetalol or methyldopa. Few women were either smokers or had gestational diabetes (about 6% each).

Between randomisation in CHIPS and giving birth, BP was a mean of 5.8/4.6 mmHg higher in women receiving 'less tight' (138.8 ± 0.5/89.9 ± 0.3 mmHg) vs. 'tight' control (133.1 ± 0.5/85.3 ± 0.3 mmHg) ($p < 0.001$) that was achieved through use of a simple algorithm (Fig. 1). There was no difference between groups in potential co-interventions for the mother (such as outpatient visits or home BP monitoring) or fetus (such as ultrasounds).

3. Outcomes for the fetus, newborn, and infant

In 'less tight' (vs. 'tight') control groups, the primary outcome of perinatal death or high-level neonatal care for > 48 h did not differ between groups (155, 31.4% in 'less tight' vs. 150, 30.7% in 'tight') [5]. For 'less tight' (vs. 'tight') control, the components of the primary outcome showed the same direction of effect as the overall results, for pregnancy loss [15, 3.0% vs. 13, 2.7% respectively, overall, and stillbirth (12 vs. 7) and neonatal death (2 vs. 4) specifically], and high-level neonatal care for > 48 h (141, 29.4% vs. 139, 29.0%). There were no subgroups (including the type of hypertension) for which the intervention was more or less effective.

High-level neonatal care for > 48 h (among liveborns) was most commonly required only during the delivery admission (131, 28.6% in 'less tight' vs. 124, 25.4% in 'tight' control), rather than following primary hospital discharge but within 28 days of life (10, 2.1% vs. 15, 3.1%, respectively) (previously unpublished). Indications for the initial high-level neonatal care for > 48 h were not mutually exclusive, and were most commonly for early gestational age (100/133 in 'less tight' vs. 59/131 in 'tight' control) or birth weight (low or high, 65/133 vs. 59/131, respectively) during the delivery admission [5]. Indications for re-admission for > 48 h were usually jaundice (6/10 in 'less tight' vs. 6/15 in 'tight'), feeding difficulties (1/10 vs. 4/15, respectively), or fever/infection (2/10 vs. 2/15, respectively) (previously unpublished).

Attention has focussed on the 'other' outcome of fetal growth for which there was no significant between-group difference, assessed by a number of outcome measures, all specified and published *a priori* in the study protocol: birth weight (g), birth weight < 2500 g or < 1250 g, or birth weight < 10th or < 3rd centile for gestational age and gender, based on a Canadian multi-ethnic standard [5,12] (Table 1). There was no between-group difference in birthweight < 3rd centile, a surrogate marker for neurodevelopmental abnormalities. There was no between-group difference in an additional *post-hoc* measure of birthweight corrected for the mean birthweight at that gestational age (Table 1) (previously unpublished). However, concern has been raised that CHIPS was underpowered to detect a potentially clinically important between-group difference in birthweight < 10th centile (16.1% vs. 19.8% in 'less tight' vs. 'tight' control, respectively; $p = 0.14$).

Importantly, little attention has been focussed on the additional perinatal outcome of preterm birth. While there was no significant between-group difference (35.6% in 'less tight' vs. 31.5% in 'tight'; $p = 0.18$), and the vast majority of those preterm births were iatrogenic (i.e., followed induction or Caesarean without labour, in 84.0% vs. 84.3%, respectively) (previously unpublished), any apparent difference was similar in magnitude and in the direction opposite to the effects of 'less tight' (vs. 'tight') control on fetal growth.

A secondary analysis that explored the relationship of fetal growth to preterm birth showed no benefit of a strategy of 'less tight' (vs. 'tight') control, regardless of the gestational age at which the intervention of 'less tight' (vs. 'tight') control was begun [13]. This finding held true for women with either chronic or gestational hypertension. In brief, the odds ratio for the effect of 'less tight' (vs. 'tight') control on outcomes was adjusted for baseline factors as in the primary CHIPS analysis (i.e., stratification factors of hypertension type and centre [as a random effect], prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes mellitus at enrolment, and antihypertensive therapy at enrolment) and those that were different between 'less tight' and 'tight' control in any gestational age quartile (i.e., ethnicity, aspirin at enrolment, perinatal mortality ratio of recruiting country, and systolic BP within one week before randomisation); also, an interaction term between gestational age at randomisation and treatment group was included to examine treatment effect as a function of gestational age at randomisation. 'Less tight' (vs. 'tight') control commenced before 24 weeks was associated with *fewer* babies born with birth weight < 10th centile, but *more* babies born at < 37 weeks; importantly, there was no overall effect on the primary outcome of pregnancy loss or high-level neonatal care for > 48 h (Fig. 2a); also, there were more mothers who developed severe hypertension in the group with 'less tight' BP control (Fig. 2b). In fact, more severe hypertension was associated with 'less tight' (vs. 'tight') control when commenced at up to 28 weeks; the pattern of effect for pre-eclampsia was similar but not significant, and serious maternal complications were not significantly different at any gestational age, although the lower boundary of the 95% CI was just below 1.0 after 28 weeks.

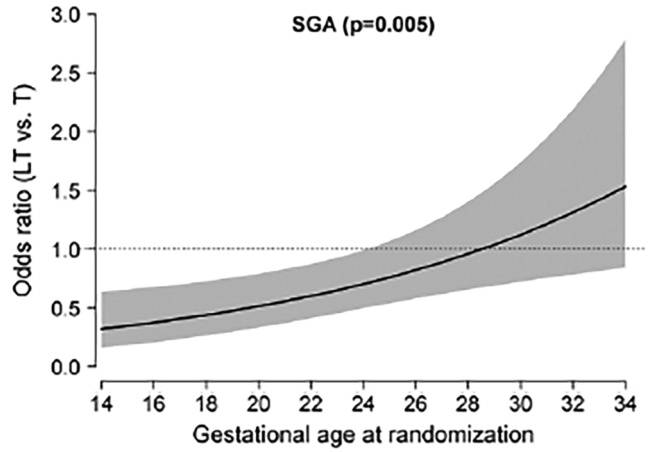
Longer-term follow-up of babies born in the CHIPS trial was of interest and feasible at 59 of the 94 CHIPS sites (with 760/987, 77.0% of the CHIPS participants) as part of the separate CHIPS-Child study. CHIPS-Child investigated potential developmental programming of maternal BP control in pregnancy, independent of genetic variability and prenatal nutrition, by examining measures of postnatal growth rate [14]. Our hypothesis was that if 'less tight' (vs. 'tight') control were associated with better antenatal nutrition, babies so exposed should

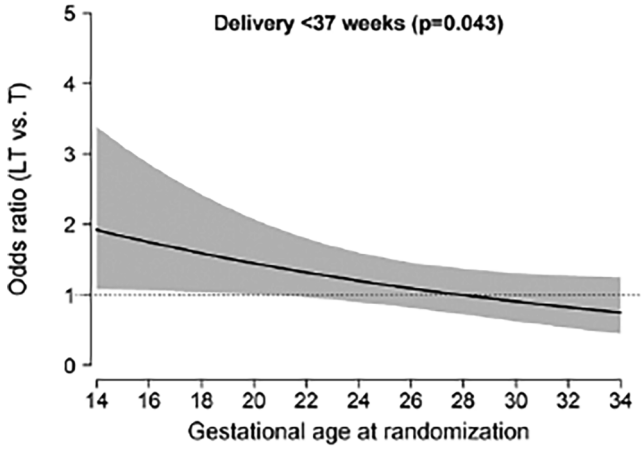
Table 1
Birthweight (N (%) or median [IQR], as appropriate).

	'Less tight' control (N = 493)	'Tight' control (N = 488)	aOR [95% CI]*	p value
Birthweight (g)	2998 [2235, 3451]	2993 [2390, 3430]	–	0.94
< 2500 g	148 (30.1%)	136 (28.0%)	1.10 [0.83,1.46]	0.47
< 1250 g	33 (6.7%)	28 (5.8%)	1.14 [0.67,1.94]	0.54
SGA newborns				
Birth weight < 10th centile	79 (16.1%)	96 (19.8%)	0.78 [0.56,1.08]	0.14
Birth weight < 3rd centile	23 (4.7%)	26 (5.3%)	0.92 [0.51,1.63]	0.64
Birthweight/population mean at the GA at birth (by day)	0.94 [0.83, 1.04]	0.93 [0.82, 1.03]	–	0.09

aOR (adjusted odds ratio), CI (confidence interval), IQR (interquartile range), SGA (small for gestational age).

* The mixed-effects logistic-regression model was adjusted for stratification factors (type of hypertension [chronic vs. gestational] and centre), use of any antihypertensive therapy at randomisation, previous BP ≥ 160/110 mmHg during this pregnancy, gestational diabetes, and weeks of gestation at randomisation.





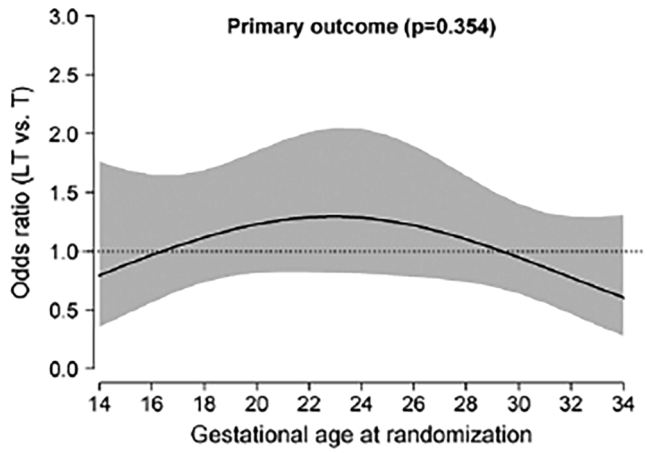
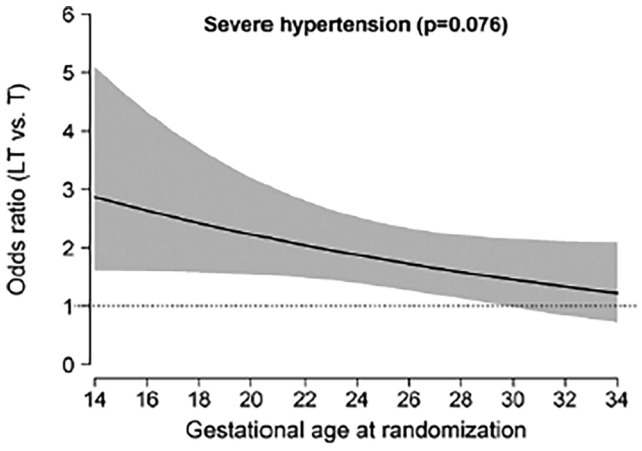
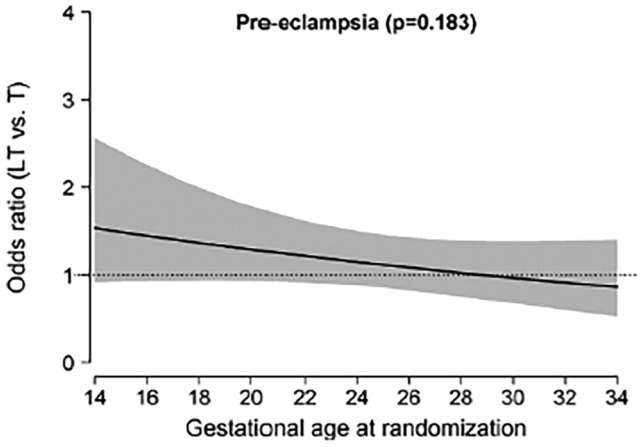


Fig. 2a. Relationship between gestational age at initiation of 'less tight' (vs. 'tight') control (i.e., randomisation in CHIPS) and adverse perinatal outcomes [13]. LT ('less tight'), SGA (small for gestational age), T ('tight'). TORs for the effect of 'less tight' (vs. 'tight') control on outcomes were adjusted for baseline factors as in the primary CHIPS analysis (i.e., stratification factors of hypertension type and centre [as a random effect], prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes mellitus at enrolment, and antihypertensive therapy at enrolment) and those that were different between 'less tight' and 'tight' control in any gestational age quartile (i.e., ethnicity, aspirin at enrolment, perinatal mortality ratio of recruiting country, and sBP within one week before randomisation); also, an interaction term between gestational age at randomisation and treatment group was included to examine treatment effect as a function of gestational age at randomisation.





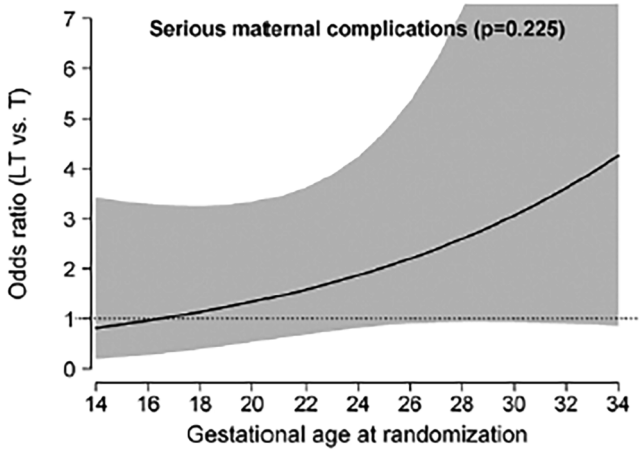


Fig. 2b. Relationship between gestational age at initiation of 'less tight' (vs. 'tight') control (i.e., randomisation) and adverse maternal outcomes [13]. LT ('less tight'), SGA (small for gestational age), T ('tight'). ORs for the effect of 'less tight' (vs. 'tight') control on outcomes were adjusted for baseline factors as in the primary CHIPS analysis (i.e., stratification factors of hypertension type and centre [as a random effect], prior severe hypertension in this pregnancy, in-hospital at enrolment, gestational diabetes mellitus at enrolment, and antihypertensive therapy at enrolment) and those that were different between 'less tight' and 'tight' control in any gestational age quartile (i.e., ethnicity, aspirin at enrolment, perinatal mortality ratio of recruiting country, and sBP within one week before randomisation); also, an interaction term between gestational age at randomisation and treatment group was included to examine treatment effect as a function of gestational age at randomisation. (From Hypertension, Pels A, Mol BWJ, Singer J, Lee T, von DP, Ganzevoort W, et al. Influence of Gestational Age at Initiation of Antihypertensive Therapy: Secondary Analysis of CHIPS Trial Data [Control of Hypertension in Pregnancy Study]. Hypertension 2018 Jun;71(6):1170–7. Copyright @ 2018 American Heart Association. Reprinted with permission.) [13].

exhibit a slower rate of postnatal growth compared with babies exposed to 'tight' control who would exhibit accelerated postnatal 'catch-up' growth. Of 683 eligible babies followed-up, 414 parents (60.6%) consented to follow-up, and 372 (89.9%) had their weight measured at 12 ± 2 months of age. The primary outcome of 'change in z-score for weight' between birth and 12 ± 2 months was similar following exposure to 'less tight' (vs. 'tight') control before birth, and no differences in growth rate could be demonstrated up to 5 years (Fig. 3). Few children (N = 35) were able to attend a study visit at 12 ± 2 months to examine hypothalamic-pituitary adrenal (HPA) axis activation (through hair cortisol measurements) and epigenetic change (by analysis of buccal cell swabs, N = 16).

4. Outcomes for the mother

In 'less tight' (vs. 'tight') control groups, the secondary maternal outcome of serious maternal complications did not differ between groups (18, 3.7% vs. 10, 2.0%, respectively; p = 0.17). Most of the serious complications were blood transfusion (16 vs. 8), consistent with an excess in 'less tight' (vs. 'tight') control of platelets < $100x10^9$/L (21, 4.3% vs. 8, 1.6%) and elevated liver enzymes with symptoms (21, 4.3% vs. 10, 2.0%) (both p < 0.05). There were no subgroups (including the type of hypertension) for which the intervention had an effect different from that overall. However, there were too few serious matearnal complications to rule out the possibility of a clinically important increase with 'less tight' control, of which the observed difference of 1.7% would be. The ongoing Chronic Hypertension And Pregnancy Trial (NCT02299414) is collecting data on blood transfusion, so more information will be available in the future about whether 'less tight' control of chronic hypertension increases serious maternal complications [5].

'Less tight' control was associated with significantly more severe maternal hypertension (200, 40.6% vs. 134, 27.5%; adjusted OR 1.80, 95% CI 1.36, 2.38); this means that eight women would need to be treated with 'tight' BP control to prevent one from developing severe hypertension. Of note, the distribution of BP values was similar between groups, across the range of systolic and diastolic values observed (Fig. 4). This occurred despite almost half of women in both groups using home BP monitoring post-randomisation (231, 46.5% vs. 225, 46.0%) and attending frequent antenatal visits from a mean of 24 weeks' gestation (median N visits [interquartile range] per woman: 7.0 [4.0, 11.0] in both groups). The CHIPS intervention was applied from randomisation until birth, so it is not known whether 'tight' (vs. 'less tight') control may also decrease the incidence of postpartum hypertension that may prolong hospitalisation and elevate long-term cardiovascular risk if unresolved [15]. What can be said is that if hypertension is treated before birth for maternal reasons, it makes sense to continue such an approach postpartum when maternal risk is the primary consideration, the duration of hypertension is short (days to weeks), and so many agents are acceptable for use during breastfeeding [16].

While pre-eclampsia is regarded as a surrogate for adverse maternal and perinatal outcome, the same has not been true of severe hypertension. Almost all international guidelines recognise severe hypertension as a treatment urgency. Failure to identify and treat severe hypertension is the single most important failing in the care of women with pregnancy hypertension who have died in the UK [17]. However, some experts regard severe hypertension as something that does not need to be prevented but rather, can be detected and treated. In response to these concerns about the importance of severe hypertension as an outcome [18], we explored the association of severe hypertension, independent of pre-eclampsia, on maternal and perinatal outcomes in CHIPS in a *post-hoc* secondary analysis using logistic regression. Severe hypertension was associated with more subsequent adverse perinatal and maternal outcomes, after adjustment for allocated group, prognostic factors, *and* pre-eclampsia, itself a recognised surrogate marker for adverse outcomes [19]. Similar effects were seen for the impact of pre-eclampsia on outcomes, adjusting for severe hypertension.

It is noteworthy that pre-eclampsia developed commonly, whether defined broadly by one/more end-organ complications, including proteinuria (241, 48.9% vs. 223, 45.7%; aOR 1.14, 95% CI 0.88, 1.47) or restrictively only by new proteinuria (148, 30.0% vs. 132, 27.0%; aOR 1.08, 95% CI 0.74, 1.59). Women who developed pre-eclampsia remained on their allocated BP control, and delivered an average of two weeks following development of pre-eclampsia, as would be expected when pre-eclampsia is expectantly managed. As such, the findings of CHIPS have been extrapolated to women with pre-eclampsia [8].

It is accepted that there is a general reluctance of women to take medication in pregnancy. As such, it is noteworthy that women who received less tight' (vs. 'tight') control were not more satisfied with care, defined as either a willingness to have the same treatment in another pregnancy (423, 92.4% 'less tight' vs. 434, 95.8% 'tight'; p = 0.14) or a willingness to recommend the same treatment to a friend (428, 93.4% 'less tight' vs. 435, 96.0% 'tight'; p = 0.17). The slightly higher satisfaction rate (by a mean of 2.6–3.4%) among women who received 'tight' BP control is of potential clinical (albeit not statistical) significance.

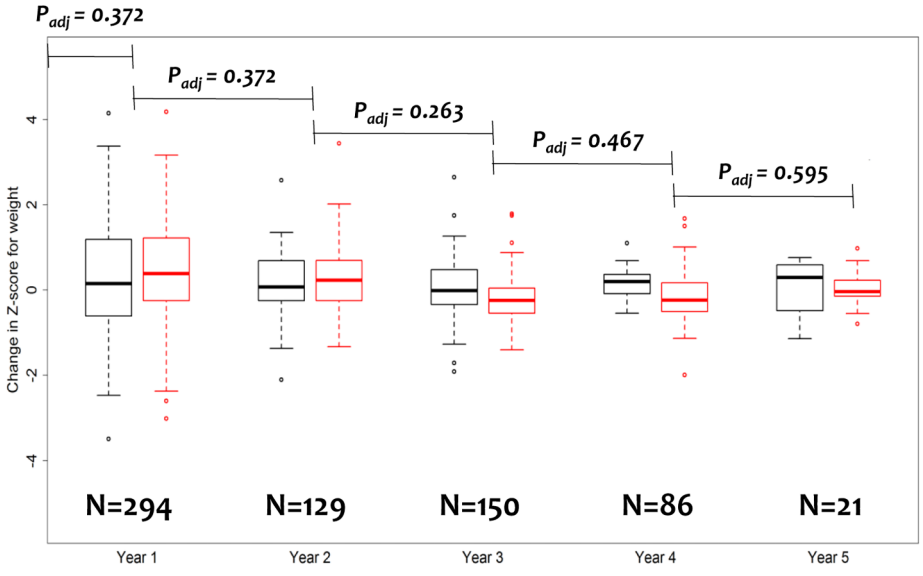


Fig. 3. Change in z-score for weight' relative to birth or the year prior (median, interquartile range and outliers for each group) [14]. Padj (p value adjusted), z-score (number of standard deviations from the mean). Data for children exposed to 'less tight' (in black) vs. 'tight' (in red) control groups are shown until the age of 5 years. The N children evaluated at each time point relative to the year before is presented at the bottom of each set of box plots. The p values for 'less tight'(vs. 'tight') control comparisons are from mixed effects linear regression with centre and subject as random effects, and following adjustment for the maternal pre-randomisation factors of type of hypertension, type of antihypertensive, and maternal body mass index (BMI). (From Pregnancy Hyprtension: A Journal of Cardiovascular Women's Health, Magee LA, Synnes AR, von DP, Hutfield AM, Chanoine JP, Cote AM, et al. CHIPS-Child: Testing the developmental programming hypothesis in the offspring of the CHIPS trial. Pregnancy Hypertens 2018 Oct;14:15–22. Copyright @ 2018 Elsevier. Reprinted with permission.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

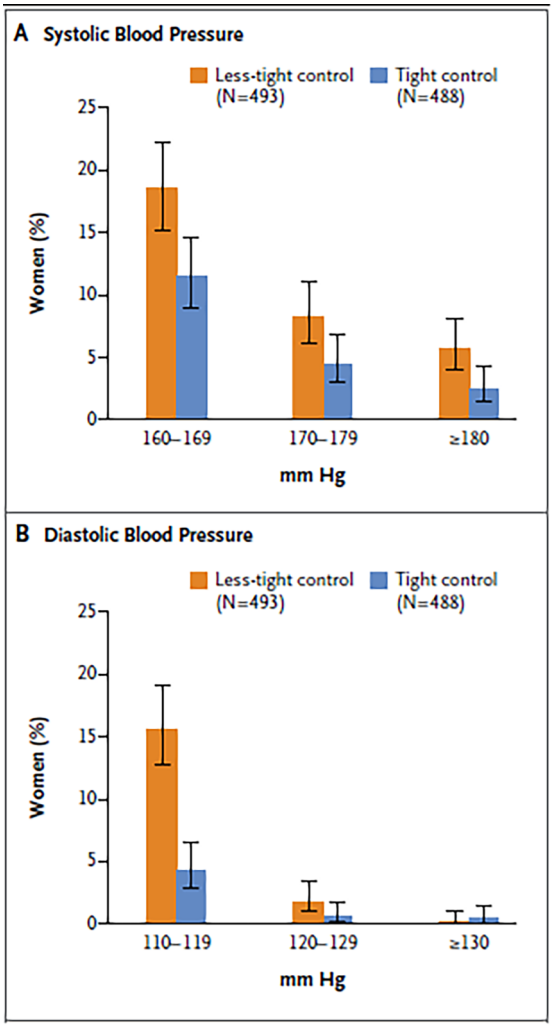


Fig. 4. BP values among women with severe hypertension. Panel A shows the percentage of women with systolic blood pressure ≥ 160 mmHg. Panel B shows the percentage of women with diastolic blood pressure ≥ 110 mmHg. The vertical bars represent the 95% confidence intervals. (From The New England Journal of Medicine, Magee LA (on behalf of the Control of Hypertension in Pregnancy Study [CHIPS], ClinicalTrials.gov number, NCT01192412), von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies JM, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Logan AG, Ganzevoort JW, Welch R, Thornton JG, Moutquin JM, Less-tight versus Tight Control of Hypertension in Pregnancy, 372, 407–17. Copyright@2015 Massachusetts Medical Society. Reprinted with permission.) [5].

In summary, no evidence was found to suggest harm to the neonate or child associated with 'tight' control, and these findings increase confidence to implement a policy of 'tight' control for women in pregnancy with the intention of improving maternal outcomes.

5. Choice of antihypertensive agent

In the CHIPS protocol, labetalol was the drug of choice for consistency, but other agents could be used according to clinicians' and/or women's preferences. Of 987 women in CHIPS, antihypertensive therapy was taken by 566 (57.3%) women at randomisation; most took labetalol (111, 22.3% in 'less tight' vs. 127, 25.9% in 'tight' control) or methyldopa (126, 25.4% vs. 117, 23.9%, respectively). After randomisation, 815 women took antihypertensive therapy, usually labetalol (186, 37.7% in 'less tight' vs. 247, 50.7% in 'tight' control) rather than methyldopa (98, 19.9% vs. 126, 25.9%, respectively) [20]. Adjusting for allocation to 'less tight' or 'tight' control, and baseline prognostic factors, methyldopa was associated with better outcomes than labetalol, particularly when women were classified according to the drug that they took post-randomisation [21]. Outcomes were better for the mother (i.e., lower incidence of severe hypertension, pre-eclampsia, and preterm delivery) and for the baby (i.e., CHIPS primary outcome and birth weight < 10th centile) even after adjusting for baseline characteristics. While caution must be exercised in interpreting these results, as non-randomised comparisons are subject to residual confounding and there was a clear preference within centres for labetalol or methyldopa, CHIPS data suggest that both labetalol and methyldopa are acceptable for management of non-severe pregnancy hypertension. These findings both challenge the assertion that methyldopa is either antiquated or inferior, and support systematic review of trials that did not demonstrate that methyldopa is associated with greater need to change drugs due to side effects [9].

6. Prediction & prognosis

Predictive modelling did not demonstrate that women destined to develop subsequent severe hypertension could be identified by clinical characteristics when a BP strategy was instituted at randomisation [22]. In this planned, secondary analysis, stepwise logistic regression was used to examine the impact of 19 candidate predictors on the probability of adverse perinatal or maternal outcomes, forcing into the model treatment group ('less tight' or 'tight' control), antihypertensive type at randomisation, and BP within one week before randomisation. Point estimates for area-under-the-receiver-operating curve (AUC ROC) were < 0.70 for all but severe hypertension (0.70, 95% CI 0.67–0.74) and delivery at < 34 weeks (0.71, 95% CI 0.66–0.75), suggesting that none were potentially useful clinically.

CHIPS results have confirmed that higher BP, regardless of target BP, is an adverse prognostic marker for mothers and babies. Using mixed effects logistic regression, adjusted for baseline characteristics (as in the main CHIPS analysis) and allocated group, higher BP level (regardless of 'less tight' or 'tight' control) was associated with more adverse maternal and perinatal outcomes (usually at $p < 0.001$), except for serious maternal complications (of which there were few events, N = 28) [23]. Additional analyses suggest that BP variability may have additional prognostic value [23].

7. Health system costs

The economic analysis of CHIPS was performed from the perspective of the health care system in each of three provinces in Canada, using data from the entire trial according to previously published methodology [24]. 'Tight' BP control was associated with no additional (and possibly lower) costs to the health care system, by almost CAD $6000 per woman ($p = 0.07$). 'Tight' control may be substantially less expensive due to a marked reduction in the costs of neonatal care.

8. Conclusion

CHIPS has provided evidence that use of a simple algorithm for 'tight' BP control, aiming for a diastolic BP of 85 mmHg, resulted in improved outcomes for the mother (namely decreased likelihood of severe hypertension and associated morbidities), without increasing risks to the fetus, newborn, or infant (Fig. 5). The intervention is acceptable to women and there are likely to be cost-savings. A research priority is the effective implementation of this fundamental change in the philosophy of pregnancy hypertension care. Other priorities include the incorporation of women's values into decision-making, and study of whether there is an antihypertensive agent that optimises outcomes, with specific consideration given to methyldopa given its low cost and high level of comfort among practitioners.

Fig. 5. CHIPS Infographic summarising the major CHIPS findings. CHIPS (Control of Hypertension In Pregnancy Study).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.08.166.

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