

# FALL IN MEAN ARTERIAL PRESSURE AND FETAL GROWTH RESTRICTION IN PREGNANCY HYPERTENSION: AN UPDATED METAREGRESSION ANALYSIS

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## Abstract

**Objective:** To update our previous analysis of randomized controlled trials in pregnancy hypertension, which discerned that greater treatment-induced decreases in maternal mean arterial pressure (MAP) appear to adversely affect fetal growth.

**Methods:** We conducted an English-language computer search of MEDLINE, *Hypertension in Pregnancy*, the relevant Cochrane reviews, and the bibliographies of retrieved papers, review articles, and standard obstetric and toxicology texts. Metaregression analysis was used to compare the change in MAP from enrolment to delivery with birth weight.

**Results:** Seven new trials with 335 women were added to the 27 trials with 2305 women previously reported. No new trials reported on the frequency of small for gestational age infants. Treatment-induced mean difference in MAP was associated with lower mean birth weight (slope:  $-17.55$  [SD 6.67],  $r^2 = 0.19$ , Spearman's non-parametric  $p = 0.031$ , Pearson's parametric  $p = 0.013$ ). Therefore, over the range of reported mean differences in MAP, a 10 mm Hg fall in MAP was associated with a 176 g decrease in birth weight, and 19% of the birth weight difference between trials could be explained by differential blood pressure control.

**Conclusion:** These results strengthen the association between blood pressure control and restricted fetal growth, and reinforce the need for new data to elucidate optimal antihypertensive use for mild to moderate pregnancy hypertension.

## Résumé

**Objectif :** Mettre à jour notre analyse précédente sur les essais randomisés et contrôlés, portant sur l'hypertension de grossesse, qui indiquaient que de plus fortes réductions de la pression artérielle moyenne (PAM) maternelle, provoquées par le traitement, semblaient avoir un effet indésirable sur la croissance fœtale.

**Méthodes :** Nous avons mené, en anglais, une recherche sur MEDLINE, *Hypertension in Pregnancy*, les revues pertinentes de

## Key Words

Pregnancy hypertension, antihypertensive, fetal growth, birth weight, meta-analysis

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Cochrane et les bibliographies des articles relevés, les articles de revue et les manuels habituels d'obstétrique et de toxicologie. Nous avons utilisé l'analyse de méta-régression pour comparer les changements de PAM, du début du traitement jusqu'à l'accouchement, avec le poids de naissance.

**Résultats :** On a ajouté sept nouveaux essais, auxquels ont participé 335 femmes, aux 27 essais, comportant 2305 femmes, sur lesquels portait le rapport précédent. Aucun nouvel essai n'a rapporté de données sur la fréquence des nouveau-nés jugés petits pour l'âge gestationnel. La différence moyenne de la PAM, provoquée par le traitement, a été liée à un poids de naissance moyen inférieur (pente :  $-17,55$  [ÉT 6,67],  $r^2 = 0,19$ , test de Spearman non paramétrique  $p = 0,031$ , test paramétrique de Pearson  $p = 0,013$ ). Ainsi donc, pour le champ de différences de PAM moyennes rapportées, une chute de 10 mm Hg de la PAM a été liée à une baisse de 176 g du poids de naissance et 19 % des différences de poids de naissance d'un essai à l'autre pouvaient s'expliquer par les différentes méthodes de contrôle de la pression artérielle.

**Conclusion :** Ces résultats renforcent le lien entre la réduction de la pression artérielle et une croissance fœtale restreinte et ils confirment le besoin d'obtenir de nouveaux résultats pour élucider la question de déterminer le traitement antihypertensif optimum pour le traitement de l'hypertension de grossesse légère ou modérée.

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## INTRODUCTION

In 1999, we undertook a meta-analysis of randomized controlled trials (RCTs) of antihypertensive therapy for mild to moderate hypertension in pregnancy.<sup>1</sup> In that study, we found that there was a heterogeneous trend toward an increase in small for gestational age (SGA) infants. The definition of SGA was accepted as defined within each trial, but generally as birth weight less than the 10th percentile for gestational age and gender, associated with the use of antihypertensive agents compared with placebo or no therapy (odds ratio 1.31; 95% CI 0.98-1.75).

To explain the heterogeneity of effect identified in the meta-analysis of 1999, we conducted a metaregression analysis that compared change in group mean arterial pressure

(MAP) from enrolment to delivery with indicators of fetoplacental growth.<sup>2</sup> *A priori*, data from a paper that was regarded as a statistical outlier<sup>3</sup> were excluded from the primary analyses. In our previous study,<sup>2</sup> greater mean difference in MAP with antihypertensive therapy was associated with the birth of a higher proportion of SGA infants (slope: 0.09 [SD 0.03],  $r^2 = 0.48$ ,  $p = 0.006$ , 14 trials) and significant lower mean birth weight (the latter only after exclusion of data from another paper regarded as an extreme statistical outlier;<sup>4</sup> slope:  $-14.49$  [SD 6.98],  $r^2 = 0.16$ ,  $p = 0.049$ , 27 trials). No relationship with mean placental weight was seen (slope:  $-2.01$  [SD 1.62],  $r^2 = 0.15$ ,  $p = 0.25$ , 11 trials).

Given knowledge of recent relevant publications,<sup>5-9</sup> and the identification of a trial of differential blood pressure control<sup>10</sup> that was not eligible for the initial meta-analysis, we have updated our previous metaregression analysis.

## METHODS

We conducted an English-language computer search of MEDLINE, *Hypertension in Pregnancy*, the relevant Cochrane reviews, and the bibliographies of retrieved papers, review articles, and standard obstetric and toxicology texts. Both authors abstracted data pertaining to blood pressure changes in pregnancy and birth weight, and disagreement was resolved by consensus.

For each trial, the change in MAP, defined as {diastolic blood pressure + pulse pressure/3}, from trial entry to the last record in the pregnancy was calculated from treatment values; this defined the mean differences in MAP ( $\Delta$ MAP) for each trial, for both the treatment and control arms of the trial. Therefore, a greater difference in MAP reflected a greater fall in MAP in the treatment group than in the control group.

The weighted mean difference in birth weight was determined for each trial using the Review Manager 3.01 software (Update Software, UK). The metaregression was done by weighted least-squares regression and then determining the line of best fit. The relationship between difference in MAP and birth weight was estimated by Pearson's  $r^2$ , and Spearman's non-parametric  $p < 0.05$  was considered statistically significant. We weighted each data point by multiplying both the independent (i.e., difference in MAP) and the dependent (i.e., birth weight) variables by the square root of the weight assigned by the Review Manager software.

*A priori*, and to be conservative,<sup>11</sup> we omitted the data of Butters *et al.*<sup>3</sup> and Jannet *et al.*<sup>4</sup> from the primary analysis, as they had been found to be significant outliers in our previous analysis. The Butters trial was identified to be a statistical outlier (by our work and by others). However, there are no methodological problems in the trial of Jannet *et al.* (women randomly assigned metoprolol or nicardipine) that could explain the marked disparity in their results. Jannet *et al.* found a much greater difference in both fall in MAP and birth weight

between groups, for reasons that were unexplained by trial design or type of antihypertensive (i.e., nicardipine vs. metoprolol).<sup>4</sup> However, in this study, we also did a sensitivity analysis that included data from the papers of Butters *et al.* and Jannet *et al.*, applying both non-parametric (Spearman's) and parametric (Pearson's  $r^2$ ) methods.

## RESULTS

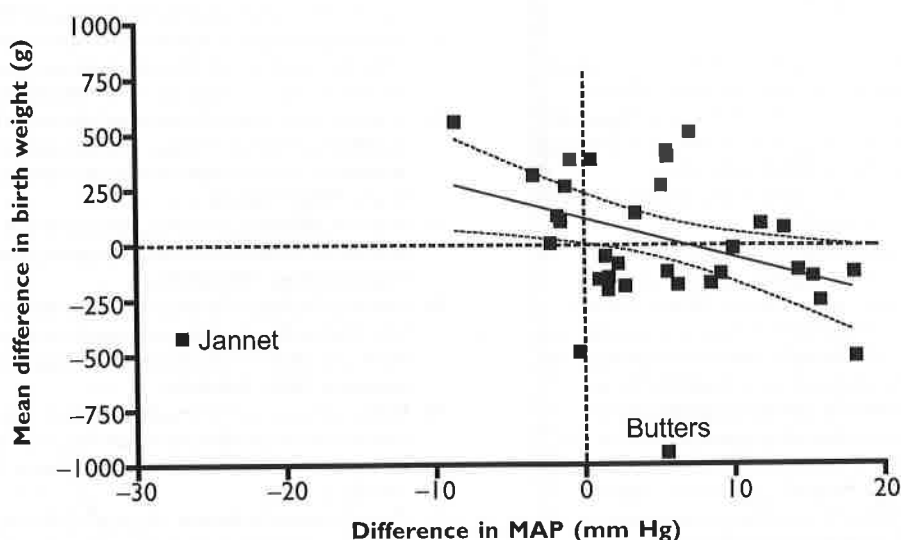
In addition to the 27 RCTs (25 publications<sup>3,4,12-34</sup>) previously analysed,<sup>2</sup> 7 new RCTs (6 publications<sup>5-10</sup>) enrolling 335 women were identified for inclusion in this update. No new trials were identified that had reported SGA as an outcome.

The trial of Blake and Macdonald<sup>10</sup> reported the incidence of birth weights less than the 50th centile for gender and gestational age. They found an excess of babies smaller than the 50th centile in the group of women whose blood pressure had been more tightly controlled (15/17 ["tight" control] vs. 10/19 ["less tight" control]). However, this definition of "poor fetal growth" was considered insufficiently robust for inclusion in an update of the relationship between MAP and the incidence of SGA at delivery, although its inclusion would have strengthened the association.

In total, 34 RCTs (31 publications<sup>3-10,12-34</sup>) were identified that randomly allocated 2640 women with mild to moderate pregnancy hypertension to oral antihypertensive treatment or either placebo or no therapy, or other antihypertensive therapy, and reported both blood pressure change and birth weight. Five trials (4 publications)<sup>3,12,29,31</sup> randomized women with chronic hypertension to therapy or to placebo or no therapy, 8 trials (8 publications)<sup>8,23,24,26,28,30,32,33</sup> randomized women with late-onset hypertension to therapy or to placebo or no therapy, and 22 trials (20 publications)<sup>4-10,13-22,25,27,34</sup> randomized women with late-onset hypertension to alternative drug therapies.

The treatment-induced mean difference in MAP was associated with lower mean birth weight (slope:  $-17.55$  [SD 6.67],  $r^2 = 0.19$ , Spearman's non-parametric  $p = 0.031$ , Pearson's parametric  $p = 0.013$ ). Therefore, over the range of reported mean differences in MAP, a 10 mm Hg fall in MAP was associated with a 176 g decrease in birth weight, and 19% of the birth weight difference between trials could be explained by differential blood pressure control (Figure). Inclusion of the trial by Butters *et al.*<sup>3</sup> (excluding that of Jannet *et al.*<sup>4</sup>) did not alter the results (slope:  $-17.8$  [SD 8.00],  $r^2 = 0.14$ , Spearman's non-parametric  $p = 0.038$ , Pearson's parametric  $p = 0.033$ ). However, there was a loss of the association with inclusion of the trial by Jannet *et al.*<sup>4</sup> (excluding that of Butters *et al.*<sup>3</sup> slope:  $-8.9$ , Spearman's  $p = 0.11$ ) and inclusion of both the Jannet and Butters trials<sup>3,4</sup> (slope:  $-8.8$ , Spearman's  $p = 0.13$ ).

## RELATIONSHIP BETWEEN FALL IN MEAN ARTERIAL PRESSURE AND LOW BIRTH WEIGHT\*



\*MAP: mean arterial pressure (diastolic blood pressure + pulse pressure/3). Excluding Butters *et al.*<sup>3</sup> and Jannet *et al.*,<sup>4</sup> treatment-induced mean difference in MAP was associated with lower mean birth weight (slope:  $-17.55$  [SD 6.67],  $r^2 = 0.19$ , Spearman's non-parametric  $p = 0.031$ , Pearson's parametric  $p = 0.013$ ).

### DISCUSSION

In our previous study,<sup>2</sup> we found that a 10 mm Hg fall in MAP was associated with a 145 g difference in birth weight, or 16% of the change in birth weight being attributable to differential blood pressure control. The inclusion of additional trials has increased the significance of the association between blood pressure control and birth weight (176 g birth weight difference or 19% attributable to  $\Delta$ MAP). This relationship was not recognized prior to the publication of our previous analysis.<sup>2</sup> Given the pivotal role of gestational age on birth weight, we were not surprised that  $\Delta$ MAP contributes to only 19% of the variation in birth weight, compared with the 48% attributable odds for being delivered SGA. However, it must be noted that the results of this metaregression analysis remain dependent on the exclusion of the trial by Jannet *et al.*<sup>4</sup> Also, the analysis is both observational and retrospective, and should be considered only as hypothesis generating.

We remain concerned that normalization of mild to moderate maternal hypertension in pregnancy may have an adverse effect on fetal growth. This has potential perinatal,<sup>35</sup> paediatric,<sup>35-37</sup> and long-term neurodevelopmental<sup>36,38</sup> and adult<sup>39</sup> consequences. There is increasing evidence to support the conjecture that some hypertension in pregnancy is protective of fetal and neonatal outcomes.<sup>40-42</sup> Preeclampsia may reflect a species-specific adaptation under circumstances where fetoplacental

demands exceed maternal supply.<sup>40-42</sup> Therefore, the advisability of lowering blood pressure beyond levels required for acute maternal cerebrovascular safety ( $< 160-170/110$  mm Hg)<sup>43</sup> remains unproven, as minimal (if any) maternal advantage will be proffered, and adverse fetal effects may ensue. Different blood pressure goals in pregnancy are recommended by different international bodies.<sup>45-47</sup>

The current Canadian guidelines for the management of hypertension<sup>44</sup> outside pregnancy advise that non-pharmacological therapies such as weight loss, dietary modification, and exercise are appropriate for women with mild to moderate hypertension (diastolic blood pressure  $< 100$  mm Hg), while normalization of blood pressure is mandatory for women with target organ damage or those with non-gestational diabetes mellitus.<sup>44,45</sup> As there is no evidence that blood pressure control alters the evolution of the preeclampsia process,<sup>41</sup> the placenta does not appear to be an organ vulnerable to increased blood pressure.

### SUMMARY

These results strengthen the hypotheses of our previous report<sup>2</sup> and the need for new data to determine the optimal blood pressure target for antihypertensive use in mild to moderate pregnancy hypertension.<sup>41,46,48</sup> This target should be defined against adverse maternal and perinatal outcomes in an appropriately

powered clinical trial. Until new data become available, international guidelines that are based largely on expert opinion will continue to recommend different diastolic blood pressure goals.

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