Prehypertension and hypertension in pregnancy

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Department of Medicine II, Charles University Medical School
Prague, Czech Republic
Hypertension in pregnancy

- Most common medical problem in pregnancy

- Complicates 5 - 10% of pregnancies:
  - 1-5% of preexisting hypertension
  - 5-6% of gestational hypertension
  - 1-4% of preeclampsia
Hypertensive disorders in pregnancy: a major cause of
- maternal
- fetal
- neonatal morbidity and mortality
Prehypertension prior to or during early pregnancy is associated with increased risk for hypertensive disorders in pregnancy and gestational diabetes

Mary Helen Black\textsuperscript{a}, Hui Zhou\textsuperscript{a}, David A. Sacks\textsuperscript{a}, Sascha Dublin\textsuperscript{b}, Jean M. Lawrence\textsuperscript{a}, Teresa N. Harrison\textsuperscript{a}, and Kristi Reynolds\textsuperscript{a}

**Kaiser Permanente Bellflower Med Center, CA, USA**

- 7802 women with at least 2 BP measurements prior to or in early pregnancy
- 653 (8.4\%) developed HT in pregnancy
  - OR 2.65 (95\% CI 2.22–3.16) hypertensive disorders
  - OR 2.17 (95\% CI 1.72–2.73) PE/E
  - OR 1.20 (95\% CI 1.09–1.33) GDM

*J Hypertens 2015;33:1860-1867*
Blood pressure measurements within the JNC7 pre-hypertensive range after 32 weeks of gestation are a risk factor for decreased fetal growth

Kyushu University Hospital, Japan

- Japanese women < 20 w of gestation delivery after 34 w of gestation

<table>
<thead>
<tr>
<th></th>
<th>NT</th>
<th>Pre-HT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>15 (3.7%)</td>
<td>8 (11.3%)</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

167,695 term pregnancies
11% prehypertension in late pregnancy

- OR 1.69 (95% CI 1.51–1.90) SGA births
- OR 1.70 (95% CI 1.16–2.49) stillbirths

Risk of an SGA birth in term pregnancy increased by 2% per each mmHg rise in DBP from early to late pregnancy.

Hypertension 2016;67:640–646
Prehypertension identified by DBP trajectories throughout pregnancy is an independent risk factor for predicting postpartum metabolic syndrome in normotensive pregnant women

*Hypertension* 2016;68:455–463
Early pregnancy prehypertension maternal outcomes

Early pregnancy prehypertension neonatal outcomes

NY University Langone Medical Center

Women with persistent hypertension had an SGA rate 2–3 times higher and preeclampsia rate higher than normotensive ones.

Women with elevated enrolment BP did not have an increased SGA rate if their BP improved throughout pregnancy.
Why it is difficult to treat hypertension in pregnancy
1. There is general consensus severe hypertension in pregnancy (≥ 160/110 mmHg) should be treated by antihypertensive drugs

2. However, there is no evidence drug treatment of mild-to-moderate hypertension in pregnancy is beneficial (no difference in outcome of preeclampsia, neonatal death, pre-term birth, small-for-gestational-age babies)

3. Limitations in study design (small number of participants, no longitudinal outcome)
## Pregnancy complications

**Swedish Medical Birth Register, 1992-1998**

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th></th>
<th>Chronic hypertension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>per 1000</td>
<td>n</td>
<td>per 1000</td>
</tr>
<tr>
<td>Pre-eclampsia, total</td>
<td>18 573</td>
<td>27.4</td>
<td>393</td>
<td>116.5</td>
</tr>
<tr>
<td>Pre-eclampsia, mild</td>
<td>13 060</td>
<td>19.3</td>
<td>247</td>
<td>73.2</td>
</tr>
<tr>
<td>Pre-eclampsia, severe</td>
<td>5 555</td>
<td>8.2</td>
<td>146</td>
<td>43.3</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5 328</td>
<td>7.9</td>
<td>79</td>
<td>23.4</td>
</tr>
<tr>
<td>Abruptio placentae</td>
<td>3 331</td>
<td>4.9</td>
<td>38</td>
<td>11.3</td>
</tr>
</tbody>
</table>

*Acta Obstet Gynecol Scand 2005;84:419-424*
Treatment-induced falls in maternal BP may adversely affect fetal growth. *Given the small maternal benefits that are likely to be derived from therapy, new data are urgently needed to elucidate the relative maternal and fetal benefits and risks of oral antihypertensive drug treatment of mild-to-moderate pregnancy hypertension.*

*Lancet 2000;355:87-92*
Emergency management of hypertension in pregnancy

- SBP ≥ 170 or DBP ≥ 110 mmHg
- hydralazine, labetalol, methyldopa or nifedipine
- nicardipine, sodium nitroprusside (risk of fatal cyanide poisoning with prolonged treatment), nitroglycerin
Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis
Laura A Magee, Chris Cham, Elizabeth J Waterman, Arne Ohlsson, Peter von Dadelszen

Abstract

Objective To review outcomes in randomised controlled trials comparing hydralazine against other antihypertensives for severe hypertension in pregnancy.
Study design Meta-analysis of randomised controlled trials (published between 1966 and September 2002) of short acting antihypertensives for severe hypertension in pregnancy. Independent data abstraction by two reviewers. Data were entered into RevMan software for analysis (fixed effects model, relative risk and 95% confidence interval); in a secondary analysis, risk difference was also calculated.

Results Of 21 trials (893 women), eight compared hydralazine with nifedipine and five with labetalol. Hydralazine was associated with a trend towards less persistent severe hypertension than labetalol (relative risk 0.29 (95% confidence interval 0.08 to 1.04); two trials), but more severe hypertension than nifedipine or isradipine (1.41 (0.95 to 2.09); four trials); there was significant heterogeneity in outcome between trials and differences in methodological quality. Hydralazine was associated with more maternal hypotension (3.29 (1.50 to 7.13); 13 trials); more caesarean sections (1.30 (1.08 to 1.59); 14 trials); more placental abruption (4.17 (1.19 to 14.28); five trials); more maternal oliguria (4.00 (1.22 to 12.50); three trials); more adverse effects on fetal heart rate (2.04
Nifedipine versus expectant management in mild to moderate hypertension in pregnancy

*Gruppo di Studio Ipertensione in Gravidanza

*The complete list of the names of those involved in this study can be found on page 722 of this report

Objective  To compare the effect of routine treatment with the calcium channel blocker nifedipine in mild to moderate hypertension in pregnancy.

Design  Randomised clinical trial.

Setting  General and University hospitals.

Participants  Pregnant women, between 12 and 34 weeks of gestation, with chronic, pregnancy-induced or unclassifiable hypertension and diastolic pressure between 90 and 110 mmHg.

Methods  Eligible women were randomly assigned treatment with slow-release nifedipine, 10 mg twice daily until delivery, or no treatment. In the no treatment group nifedipine was given if the diastolic pressure exceeded 110 mmHg. A total of 145 women were assigned nifedipine and 138 no treatment.

Results  In the nifedipine group 45·0% of women were delivered before term, compared with 37·0% in the no treatment group; the difference was not significant. In all, 56·3% of women allocated nifedipine and 62·1% allocated no treatment underwent caesarean section: the difference was not statistically different (OR 0·79, 95% CI 0·4·1·1). There was no significant difference between the two groups in the percentage of babies weighing less than the 10th centile (OR 0·8; 95% CI 0·4·1·4) or in the mean birthweight. The frequency of admission of infants to the neonatal intensive care unit was not affected by treatment.

Conclusions  This trial found no benefit on pregnancy outcome of routine treatment with nifedipine. In clinical practice, the treatment of hypertension in pregnancy may be delayed until the hypertension becomes severe.
Less-tight vs tight control of hypertension in pregnancy

Design

- Open, international, multicenter trial

Primary outcome

- Composite of pregnancy loss (miscarriage, ectopic pregnancy, pregnancy termination, still-birth, or neonatal death) or

- high-level neonatal care (defined as greater-than-normal newborn care) for more than 48 hours until 24 days of life or until discharge home, whichever was later

NEJM 2015;372:407-417
Less-tight vs tight control of hypertension in pregnancy

Secondary outcome

- **Serious maternal complications** (death, stroke, eclampsia, blindness, uncontrolled hypertension, use of inotropic agents, pulmonary edema, respiratory failure, myocardial ischemia or infarction, hepatic dysfunction, hepatic hematoma or rupture, renal failure or transfusion) up to 6 weeks postpartum or until hospital discharge, whichever was later

*NEJM 2015;372:407-417*
Less-tight vs tight control of hypertension in pregnancy

Inclusion criteria

- Non-proteinuric pre-existing hypertension or gestational hypertension
- Office DBP 90–105 mmHg or 85–105 mmHg if on antihypertensive medication
- 14 weeks to 33 weeks of gestation

NEJM 2015;372:407-417
n = 1030
95 sites, 16 countries

Less-tight control
n=519
22 excluded
Less-tight control
n=497
1 IC withdrawal
2 lost FU
Final analysis
n=493

Tight control
n=511
21 excluded
1 IC withdrawal

Tight control
n=489
1 lost FU
Final analysis
n=488

NEJM 2015;372:407-417
# Less-tight vs tight control of hypertension in pregnancy

## Baseline characteristics at enrolment

<table>
<thead>
<tr>
<th></th>
<th>Less-tight control</th>
<th>Tight control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age at delivery, yrs</strong></td>
<td>34.0 ± 5.7</td>
<td>33.7 ± 5.8</td>
</tr>
<tr>
<td><strong>Cigarette smoking during this pregnancy, n (%)</strong></td>
<td>35 (7.0)</td>
<td>28 (5.7)</td>
</tr>
<tr>
<td><strong>Nulliparity, n (%)</strong></td>
<td>161 (32.4)</td>
<td>168 (34.3)</td>
</tr>
<tr>
<td><strong>Weeks of gestation</strong></td>
<td>23.7 ± 6.3</td>
<td>24.2 ± 6.3</td>
</tr>
<tr>
<td><strong>Type of hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pre-existing</td>
<td>371 (74.6)</td>
<td>365 (74.5)</td>
</tr>
<tr>
<td>- gestational</td>
<td>126 (25.4)</td>
<td>125 (25.5)</td>
</tr>
<tr>
<td><strong>Antihypertensive medication at enrolment</strong></td>
<td>276 (56.1)</td>
<td>287 (58.6)</td>
</tr>
<tr>
<td><strong>BP within 1 week before randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- SBP, mmHg</td>
<td>140.4 ± 9.7</td>
<td>139.7 ± 9.8</td>
</tr>
<tr>
<td>- DBP, mmHg</td>
<td>92.6 ± 4.8</td>
<td>92.2 ± 5.2</td>
</tr>
</tbody>
</table>

*NEJM 2015;372:407-417*
Less-tight vs tight control of hypertension in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Less-tight control n = 493</th>
<th>Tight control n = 488</th>
<th>Adj. OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>155 (31.4%)</td>
<td>150 (30.7%)</td>
<td>1.02 (0.77–1.35)</td>
</tr>
<tr>
<td>Secondary and other maternal outcome</td>
<td>18 (3.7%)</td>
<td>10 (2.0%)</td>
<td>1.74 (0.79–3.84)</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>200 (40.6%)</td>
<td>134 (27.5%)</td>
<td>1.80 (1.34–2.38)</td>
</tr>
</tbody>
</table>

*NEJM 2015;372:407-417*
Less-tight vs tight control of hypertension in pregnancy

● **Conclusions**

No significant between-group differences in the risk of pregnancy loss, high-level neonatal care or overall maternal complications, although less-tight control was associated with a significantly higher frequency of severe maternal hypertension

*NEJM 2015;372:407-417*
Classification of hypertension in pregnancy

- pre-existing hypertension
- gestational hypertension
- pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- antenatally unclassifiable hypertension
Pre-eclampsia

Gestational hypertension associated with significant proteinuria

- 300 mg/l or
- 500 mg/24 h or
- dipstick 2+ or more
- albumin/creatinin > 30 mg/mmol in spot urine sample

Poorest organ perfusion
Queensland Clinical Guidelines
Translating evidence into best clinical practice

Maternity and Neonatal Clinical Guideline

Hypertensive disorders of pregnancy
## Risk factors for preeclampsia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibodies (APLS)</td>
<td>9.72 [4.34–21.75]</td>
</tr>
<tr>
<td>Previous history of preeclampsia</td>
<td>7.19 [5.85–8.83]</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td>3.56 [2.54–4.99]</td>
</tr>
<tr>
<td>Twin pregnancy (increased risk with multiples)</td>
<td>2.93 [2.04–4.21]</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2.91 [1.28–6.61]</td>
</tr>
<tr>
<td>Family history of preeclampsia</td>
<td>2.90 [1.70–4.93]</td>
</tr>
<tr>
<td>Raised BMI before pregnancy</td>
<td>2.47 [1.66–3.67]</td>
</tr>
<tr>
<td>Raised BMI at booking</td>
<td>1.55 [1.28–1.88]</td>
</tr>
<tr>
<td>Maternal age ≥ 40 years (primipara)</td>
<td>1.68 [1.23–2.29]</td>
</tr>
<tr>
<td>Maternal age ≥ 40 years (multipara)</td>
<td>1.96 [1.34–2.87]</td>
</tr>
<tr>
<td>SBP ≥ 130 mmHg at booking</td>
<td>2.37 [1.78–3.15]</td>
</tr>
<tr>
<td>DBP ≥ 80 mmHg at booking</td>
<td>1.38 [1.01–1.87]</td>
</tr>
<tr>
<td>Inter-pregnancy interval &gt; 10 years</td>
<td>1.12 [1.11–1.13]</td>
</tr>
</tbody>
</table>

*Adapted from Queensland Clin Guidelines, 2015*
## Risk of pre-eclampsia determined by 16 weeks’ gestation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No of women/No of studies</th>
<th>i²</th>
<th>Pooled unadjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior IUGR</td>
<td>55,542/1</td>
<td>N/A</td>
<td>1.4 (0.6 to 3.0)</td>
</tr>
<tr>
<td>SLE</td>
<td>2,413,908/2</td>
<td>71</td>
<td>2.5 (1.0 to 6.3)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2,975,158/25</td>
<td>90</td>
<td>2.1 (1.9 to 2.4)</td>
</tr>
<tr>
<td>Maternal age &gt;35</td>
<td>5,244,543/22</td>
<td>92</td>
<td>1.2 (1.1 to 1.3)</td>
</tr>
<tr>
<td>Maternal age &gt;40</td>
<td>4,260,202/16</td>
<td>95</td>
<td>1.5 (1.2 to 2.0)</td>
</tr>
<tr>
<td>Prior stillbirth</td>
<td>63,814/2</td>
<td>0</td>
<td>2.4 (1.7 to 3.4)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>966,505/5</td>
<td>44</td>
<td>1.8 (1.5 to 2.1)</td>
</tr>
<tr>
<td>ART</td>
<td>1,463,529/20</td>
<td>79</td>
<td>1.8 (1.6 to 2.1)</td>
</tr>
<tr>
<td>Prepregnancy BMI &gt;25</td>
<td>3,644,747/38</td>
<td>89</td>
<td>2.1 (2.0 to 2.2)</td>
</tr>
<tr>
<td>Prepregnancy BMI &gt;30</td>
<td>5,921,559/40</td>
<td>98</td>
<td>2.8 (2.6 to 3.1)</td>
</tr>
<tr>
<td>Multifetal pregnancy</td>
<td>7,309,227/8</td>
<td>67</td>
<td>2.9 (2.6 to 3.1)</td>
</tr>
<tr>
<td>Prior placental abruption</td>
<td>291,134/3</td>
<td>61</td>
<td>2.0 (1.4 to 2.7)</td>
</tr>
<tr>
<td>Pregestational diabetes</td>
<td>2,553,117/19</td>
<td>79</td>
<td>3.7 (3.1 to 4.3)</td>
</tr>
<tr>
<td>Prior pre-eclampsia</td>
<td>3,720,885/20</td>
<td>96</td>
<td>8.4 (7.1 to 9.9)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>6,589,661/20</td>
<td>98</td>
<td>5.1 (4.0 to 6.5)</td>
</tr>
<tr>
<td>aPL</td>
<td>220,156/3</td>
<td>0</td>
<td>2.8 (1.8 to 4.3)</td>
</tr>
</tbody>
</table>

*BMJ 2016; 353: i1753*
Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review

Lelia Duley, David Henderson-Smart, Marian Knight, James King

39 trials; 30 563 women

- 15% RR of pre-eclampsia
- 8% RR preterm birth
- 14% RR fetal or neonatal death

BMJ 2001;322:329-33
Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy
A Meta-Analysis

Emmanuel Bujold, MD, MSc, Stéphanie Roberge, MSc, Yves Lacasse, MD, MSc, Marc Bureau, MD, François Audibert, MD, MSc, Sylvie Marcoux, MD, PhD, Jean-Claude Forest, MD, PhD, and Yves Giguère, MD, PhD

27 studies; 11 348 women

● 53% RR of pre-eclampsia
● 56% RR IUGR

Obstet Gynecol 2010;116:402-14
Antiplatelet agents

Advise women at high risk of pre-eclampsia and those with ≥ 1 moderate risk factor for pre-eclampsia to take 75 mg of ASA daily from 12 weeks until the birth of the baby.

High risk

- Hypertensive disease during a previous pregnancy
- CKD
- Autoimmune disease such as SLE or antiphospholipid syndrome
- Type 1 or Type 2 diabetes
- Chronic hypertension
Antiplatelet agents

Advise women at high risk of pre-eclampsia and those with \( \geq 1 \) moderate risk factor for pre-eclampsia to take 75 mg of ASA daily from 12 weeks until the birth of the baby.

Moderate risk

- First pregnancy
- Age \( \geq 40 \) years
- Pregnancy interval of more than 10 years
- BMI \( \geq 35 \) kg/m\( ^2 \)
- Family history of pre-eclampsia
- Multiple pregnancy
multicenter, double-blind, placebo-controlled trial
1776 women, singleton pregnancies at high risk for preterm preeclampsia
ASA 150 mg vs. placebo
Conclusions

Treatment with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo.
Conclusion: Changes in circulating concentrations of PI GF, sFlt-1, and in the sFlt-1/PI GF ratio precede the onset of preeclampsia. The risk profile of circulating angiogenic factors for developing preeclampsia distinctly evolves depending on whether this condition is manifested at preterm or term.
Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Mats Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Holger Stepan, M.D., Deirdre Allegranza, B.A., Peter Dilba, M.Sc., Maria Schoedl, Ph.D., Martin Hund, Ph.D., and Stefan Verlohren, M.D., Ph.D.

Conclusions
An sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically. (funded by Roche Diagnostics)
sFlt-1/PIGF

Development Cohort

Validation Cohort

Ratio of sFlt-1 to PIGF

No preeclampsia (N=466)  Preeclampsia (N=34)  No Preeclampsia (N=535)  Preeclampsia (N=15)

Diagnosis within 1 Wk

NEJM 2016;374:13-22
Cutoff point validation for sFlt-1/PIGF in predicting preeclampsia

<table>
<thead>
<tr>
<th>Preeclampsia</th>
<th>Development Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent (95% CI)</td>
<td>percent (95% CI)</td>
</tr>
<tr>
<td>Within 1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value: rule out</td>
<td>98.9 (97.3–99.7)</td>
<td>99.3 (97.9–99.9)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88.2 (72.5–96.7)</td>
<td>80.0 (51.9–95.7)</td>
</tr>
<tr>
<td>Specificity</td>
<td>80.0 (76.1–83.6)</td>
<td>78.3 (74.6–81.7)</td>
</tr>
<tr>
<td>Within 4 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value: rule in</td>
<td>40.7 (31.9–49.9)</td>
<td>36.7 (28.4–45.7)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74.6 (62.5–84.5)</td>
<td>66.2 (54.0–77.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>83.1 (79.3–86.5)</td>
<td>83.1 (79.4–86.3)</td>
</tr>
</tbody>
</table>
Classification of hypertension in pregnancy

- pre-existing hypertension
- gestational hypertension
- pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- antenatally unclassifiable hypertension
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Δ</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>↓4-6 mmHg</td>
<td>All bottom at 20-24 wks, then rise gradually to pre-pregnancy values at term</td>
</tr>
<tr>
<td>DBP</td>
<td>↓8-15 mmHg</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>↓6-10 mmHg</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>↑12-18 BPM</td>
<td>Early 2nd trimester, then stable</td>
</tr>
<tr>
<td>SV</td>
<td>↑10-30%</td>
<td>Early 2nd trimester, then stable</td>
</tr>
<tr>
<td>CO</td>
<td>↑33-45%</td>
<td>Peaks in early 2nd trimester, then until term</td>
</tr>
</tbody>
</table>

*Main DM, Main EK: Obstetrics and Gynecology, 1984*
Antenatally unclassifiable hypertension

Hypertension with or without systemic manifestation

BP *first recorded after 20 weeks’ gestation*, re-assessment necessary at or after 42 days post partum
Management of hypertension in pregnancy depends on

- BP levels
- gestational age
- associated maternal and fetal risk factors
Non-pharmacologic management

- SBP 140-149 mmHg or DBP 90-99 mmHg
- ↓ activity, bed rest (left lateral position)

**AVOID**: weight reduction and salt restriction
Principles for treatment of mild-to-moderate hypertension in pregnancy

The benefits of antihypertensive therapy for mild-to-moderately elevated BP in pregnancy (≤ 160/110 mmHg), either chronic or pregnancy-induced, have not been demonstrated in clinical trials.

- Less risk of developing severe hypertension
- No difference in outcome of preeclampsia, neonatal death, pre-term birth
- No difference in small-for-gestational-age babies

_Cochrane Database Syst Review 2007;CD002252_
Thresholds for drug treatment initiation

**BP > 140/90 mmHg in women**
- with gestational hypertension without proteinuria or
- pre-existing hypertension before 28 weeks' gestation or
- gestational hypertension and proteinuria or symptoms at any time or
- pre-existing hypertension and TOD or
- pre-existing hypertension and superimposed gestational hypertension

**BP > 150/95 mmHg**
- In all other circumstances
  - methyldopa, labetalol, calcium antagonists, and beta-blockers

**AVOID: ACE inhibitors, AIIA, diuretics**

**Magnesium sulfate:** eclampsia, treatment and prevention of seizures
Antihypertensive drugs used in pregnancy

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors, AIIA and direct renin inhibitors.
Why is RAS important in pregnancy?

- Regulation of renal hemodynamics
  (by maintaining GFR and urine production under conditions of low renal perfusion pressure, which are characteristic of the fetal and neonatal periods)

- Regulation of umbilical and placental circulation

- Regulation of fetal BP

- Kidney development (growth factors)

- Angiogenesis (angiotensin II)

- Regulation of fetal renal growth, function and development (ACE gene)
Administration of AT$_1$-blockers in pregnancy

- Fetal arterial hypotension
- Decreased glomerular perfusion pressure
- Impaired renal tubular development
- Reduced fetal urine output, oligohydramnios
  
  Sequelae: limb contractures
  
  pulmonary hypoplasia
  
  cranio-facial deformation and neonatal anuria
- Decreased placental and umbilical perfusion:
  
  intrauterine growth restriction
- Action on skull bones angiogenesis:
  
  impaired ossification processes

*Critical period: second trimester* !!
Maternal exposure to AT$_1$-blockers

**Critical period: second trimester**

5 cases of fetal death and 1 case of neonatal death on Day 4 postpartum, with persisting anuria; exposure in early pregnancy, oligohydramnion.

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors


RESULTS

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02).
**Antihypertensive drugs used in pregnancy**

<table>
<thead>
<tr>
<th>Central alfa agonists</th>
<th>Methyldopa is the drug of choice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Atenolol and metoprolol appear to be safe and effective in late pregnancy.</td>
</tr>
<tr>
<td>Alfa-/beta-blockers</td>
<td>Labetalol has comparable efficacy with methyldopa, in case of severe hypertension, it could be given intravenously.</td>
</tr>
</tbody>
</table>
Atenolol in essential hypertension during pregnancy

Lucy Butters, Susan Kennedy, Peter C Rubin

Abstract

Objective—To determine the effect of atenolol on the outcome of pregnancy in women with essential hypertension.

Design—Prospective, randomised, double blind, placebo controlled study.

Setting—Hospital clinic.

Patients—33 Women with mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart) consecutively referred to two obstetric medical clinics. Four patients in the placebo group were withdrawn from the study: control of blood pressure was inadequate in two, one developed breathlessness, and one changed her mind about participating. The mean gestation in the 29 remaining women on entry to the study was 15·9 weeks.

Main outcome measures—Blood pressure and birth weight.

Intervention—14 Women received placebo. 15 Women received atenolol 50 mg daily initially, increasing until either the blood pressure was <140/90 mm Hg or a dose of 200 μg daily was reached.

Results—The mean blood pressure on entry was 148/86 mm Hg in the group given atenolol and 144/86 mm Hg in the group given placebo. During treatment the mean diastolic pressure was significantly reduced by atenolol compared with placebo (to 74 v 81 mm Hg; difference in means (95% confidence interval) 7·0 (2·9 to 10·0) mm Hg) but the effect on systolic pressure was marginal (132 v 136 mm Hg; 4·0 (−1·4 to 8·6) mm Hg). Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2620 g v 3530 g; 910 (440 to 1380) g).

Conclusion—Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation. When taken in conjunction with the results of a previous study in which methyldopa was given these findings indicate that benefit is unlikely to result from treating mild essential hypertension in pregnancy.
Birth weights of babies in atenolol and placebo groups

Mean 3,470 g

Mean 2,670 g

n = 14  n = 15

BMJ 1990;301:587-9
Effect of Atenolol on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

A previous small, prospective study from Glasgow reported that babies born to women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group. 1 Beta blockers, while safe in the third trimester of pregnancy, are also considered to cause significant growth restriction when used for longer periods. 2 An antenatal hypertension clinic has been in operation at City Hospital, Birmingham since 1980, where pregnant women with hypertension undergo careful follow-up jointly by an obstetrician and a physician with a special interest in hypertension. Patients were referred to the clinic by obstetricians and general practitioners on the basis of previous hypertension, or raised blood pressures detected for the first time in pregnancy. In many, the blood pressure decreased with no therapy, and where possible antihypertensive drugs were discontinued. After the Glasgow study, 1 the use of atenolol in early pregnancy was discontinued and an audit was conducted of birth weights in relation to drug therapy.

We conducted an analysis of our own prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. Information on demographic data, presenting blood pressures, drug therapies, pregnancy complications, and pregnancy outcome were recorded. The mean

termine significant predictors for birth weights. A p value < 0.05 was considered statistically significant.

We reviewed data from the antenatal records of 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 ± 6 years) attending our antenatal hypertension clinic between 1980 and 1995. Two hundred thirty-five women were not taking any therapy during the first 20 weeks of pregnancy, whereas atenolol was taken by 76 women, labetolol by 7, other β blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations.

Blood pressures during antihypertensive therapy are summarized in Table I. When compared with untreated cases, there was a trend toward higher mean systolic (1-way ANOVA, p = 0.064) and diastolic blood pressures (p < 0.001) in the first 20 weeks of pregnancy among women who were taking antihypertensive drugs (Table I). There were no significant differences in mean gestation period for each patient subgroup of treated and untreated women (1-way ANOVA, p = NS).

Mean birth weights, median placental weights, and ponderal index are also summarized in Table I. Babies born to women taking atenolol were significantly lighter (1-way ANOVA, F = 5.3, p < 0.001) than those born to women not taking any β blocker.
In conclusion, this survey suggests that atenolol use may be detrimental in early pregnancy and provides confirmatory data with previous small prospective randomized trials. Our findings suggest that atenolol should be avoided in women who are trying to conceive or who are in the early stages of pregnancy.
Antihypertensive drugs used in pregnancy

**Diuretics**
Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia.

**Direct vasodilators**
Hydralazine is no longer the parenteral drug of choice; perinatal adverse effects.
Antihypertensive drugs used in pregnancy

**Calcium-channel blockers**

Oral nifedipine or i.v. isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulfate may induce hypotension.

**ACE inhibitors, AIIA, direct renin inhibitors**

Fetal abnormalities including death can be caused and these drugs should not be used in pregnancy.
Breast-feeding

- Does not increase BP in nursing mothers

- All antihypertensive agents taken by the nursing mother are excreted into breast milk; however, most of them are present at very low concentrations, except for propranolol and nifedipine concentrations, which are similar to maternal plasma
Maternal antihypertensive medications usually compatible with breastfeeding

- Captopril
- Diltiazem
- Enalapril
- Hydralazine
- Hydrochlorothiazide
- Labetalol
- Methyldopa
- Minoxidil
- Nadolol
- Nifedipine
- Oxprenolol
- Propranolol
- Spironolactone
- Timolol
- Verapamil

*Pediatrics 2001;108:776-789*
Maternal antihypertensive medications usually compatible with breastfeeding

- Diuretics (furosemide, hydrochlorothiazide, and spironolactone) may reduce milk production.

- Metoprolol is classified as compatible with breastfeeding, although it is concentrated in human milk.

- Acebutolol and atenolol should not be used in nursing mothers.

*Pediatrics 2001;108:776-789*
Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks’ gestation (HYPITAT): a multicentre, open-label randomised controlled trial


- Multicentre, parallel, open-label randomised controlled trial in six academic and 32 non-academic hospitals in the Netherlands, 2005–8
- 756 patients
- **Induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks’ gestation.**

*Lancet 2009; 374 (9694): 979–988*
Conclusions

- Hypertensive disorders in pregnancy are associated with an increased risk of maternal, fetal and neonatal morbidity and mortality.

- There is growing evidence that prehypertension, particularly in the first half of pregnancy, increases the likelihood of adverse outcomes.
Significant proteinuria: albumin/creatinine > 30 mg/mmol

s Flt-1/PlGF < 38 can be used to exclude the development of preeclampsia in the next week when suspected clinically

Conclusions
Conclusions

- There is no clear benefit from less or more aggressive treatment of hypertension in pregnancy.
- Less tight control of BP was associated with higher frequency of severe maternal hypertension.
- There is no evidence that drug treatment of mild to moderate hypertension in pregnancy is beneficial (except for less development of severe hypertension).
ASA in the prevention of pre-eclampsia

- ASA (100-150 mg daily) is recommended in the prevention of pre-eclampsia in women at high or moderate risk of pre-eclampsia from 12 weeks of gestation until week 36
Conclusions

- In non-severe hypertension, oral methyldopa, labetalol, calcium antagonists, and (less frequently) beta-blockers are drugs of choice.

- In pre-eclampsia with pulmonary edema, nitroglycerin is the drug of choice, diuretic therapy is inappropriate because plasma volume is reduced.

- As emergency, intravenous labetalol, oral methyldopa, and oral nifedipine are indicated. Intravenous hydralazine is no longer the drug of choice because of an excess of perinatal adverse effects.
Conclusions

- *I.v. infusion of sodium nitroprusside* is useful in *hypertensive crisis*, but prolonged administration should be avoided.

- Calcium supplementation, fish oil, and low-dose aspirin are not recommended. However, *low-dose aspirin may be used prophylactically in women with a history of an early onset of pre-eclampsia*.
Hypertensive encephalopathy

1-2% of untreated essential hypertension
SBP > 250 or DBP > 150 mmHg

Treatment

- ↓Mean BP by no more than 15-25% towards DBP 100-110 mmHg
- Drug of choice: sodium nitroprusside
- Other drugs: nitroglycerin, nifedipine, labetalol
Conclusions

- **Korotkoff Phase V** is now recommended for the measurement of DBP in pregnancy with Phase IV being indicated only if Korotkoff sounds persist at cuff pressures approaching 0 mmHg.

- **Non-pharmacological management** should be considered for pregnant women with SBP 140-149 mmHg or DBP 90-95 mmHg.

- In *gestational hypertension* with or without proteinuria, *drug treatment* is indicated at BP levels $\geq 140/90$ mmHg.
24h ABPM values by gestational age

<table>
<thead>
<tr>
<th>Gestational week</th>
<th>SBP mmHg</th>
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<tbody>
<tr>
<td>9 – 17</td>
<td></td>
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<tr>
<td>18 – 22</td>
<td></td>
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<tr>
<td>26 – 30</td>
<td></td>
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<tr>
<td>31 – 40</td>
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</table>

Mean ±2 SD

Upper range

Lower range

Am J Obstet Gynecol 1998;178:836-42
24h ABPM values by gestational age

<table>
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<tr>
<th>Gestational week</th>
<th>Mean +2 SD</th>
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DBP mmHg

Am J Obstet Gynecol 1998;178:836-42
Guideline

European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring


Ambulatory blood pressure monitoring (ABPM) is being used increasingly in both clinical practice and hypertension research. Although there are many guidelines that emphasize the indications for ABPM, there is no comprehensive guideline dealing with all aspects of the technique. It was agreed at a consensus meeting on ABPM

Keywords: ambulatory blood pressure monitoring, clinic blood pressure measurement, clinical indications, guidelines, home blood pressure measurement, recommendations, research application

J Hypertens 2013; 31: 1731-1738
Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks’ gestation (HYPITAT): a multicentre, open-label randomised controlled trial


- **Multicentre, parallel, open-label randomised controlled trial in six academic and 32 non-academic hospitals in the Netherlands, 2005–8**
- **756 patients**
- **Induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks’ gestation.**

*Lancet 2009; 374 (9694): 979–988*
Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial


- open-label, randomised controlled trial, in seven academic hospitals and 44 non-academic hospitals in the Netherlands.
- 703 were enrolled and randomly assigned to immediate delivery or expectant monitoring

Lancet 2015; 385 (9986): 2492 – 2501
For women with non-severe hypertensive disorders at 34–37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it significantly increases the risk of neonatal respiratory distress syndrome. Therefore, routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered.
Prehypertension prior to or during early pregnancy is associated with increased risk for hypertensive disorders in pregnancy and gestational diabetes

Mary Helen Black\textsuperscript{a}, Hui Zhou\textsuperscript{a}, David A. Sacks\textsuperscript{a}, Sascha Dublin\textsuperscript{b}, Jean M. Lawrence\textsuperscript{a}, Teresa N. Harrison\textsuperscript{a}, and Kristi Reynolds\textsuperscript{a}

**Kaiser Permanente Bellflower Med Center, CA, USA**

- 7802 women with at least 2 BP measurements prior to or in early pregnancy
- 653 (8.4\%) developed HT in pregnancy
  - OR 2.65 (95\% CI 2.22–3.16) hypertensive disorders
  - OR 2.17 (95\% CI 1.72–2.73) PE/E
  - OR 1.20 (95\% CI 1.09–1.33) GDM

*J Hypertens 2015;33:1860-1867*
Blood pressure measurements within the JNC7 pre-hypertensive range after 32 weeks of gestation are a risk factor for decreased fetal growth.

Kyushu University Hospital, Japan

- Japanese women < 20 w of gestation delivery after 34 w of gestation

<table>
<thead>
<tr>
<th></th>
<th>NT n = 403</th>
<th>Pre-HT n = 79</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>SGA</td>
<td>15 (3.7%)</td>
<td>8 (11.3%)</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

167,695 term pregnancies
11% prehypertension in late pregnancy

- OR 1.69 (95% CI 1.51–1.90) SGA births
- OR 1.70 (95% CI 1.16–2.49) stillbirths

Risk of an SGA birth in term pregnancy increased by 2% per each mmHg rise in DBP from early to late pregnancy.

*Hypertension* 2016;67:640–646
Prehypertension identified by DBP trajectories throughout pregnancy is an independent risk factor for predicting postpartum metabolic syndrome in normotensive pregnant women.

Hypertension 2016;68:455–463
NY University Langone Medical Center

Early pregnancy prehypertension maternal outcomes
Early pregnancy prehypertension neonatal outcomes
Women with persistent hypertension had an SGA rate 2–3 times higher and preeclampsia rate higher than normotensive ones.

Women with elevated enrolment BP did not have an increased SGA rate if their BP improved throughout pregnancy.

*Hypertens Pregnancy 2016;35:350–360*
Conclusions

- Hypertensive disorders in pregnancy are associated with an increased risk of maternal, fetal and neonatal morbidity and mortality.

- There is growing evidence that prehypertension, particularly in the first half of pregnancy, increases the likelihood of adverse outcomes.
Conclusions

- Significant proteinuria: albumin/creatinine > 30 mg/mmol

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