WHO recommendation on choice and route of administration of antihypertensive drugs for women with severe hypertension during pregnancy

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Recommendation

The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability.

(very low-quality evidence, weak recommendation)

Publication history

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Updated: prioritized for updating

Assessed as up-to-date: October 2011

Remarks

- In terms of the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, the guideline development group noted that not only is the evidence base for this recommendation limited, but also some antihypertensive drugs may not be feasible options in many settings.
- The group acknowledged that hydralazine, alpha methyldopa, beta blockers (including labetalol) and nifedipine have been extensively used, and therefore, these agents would seem to be reasonable choices until further evidence becomes available.
- The group noted that there was no evidence to suggest that nifedipine interacts adversely with magnesium sulfate. In addition, the group considered that the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sodium nitroprusside should be avoided due to safety concerns.

Background

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths, whereas in Latin America and the Caribbean, they contribute to approximately 22% of all maternal
Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications.

A range of drug options are used for treatment of hypertension, such as thiazide diuretics, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers and beta blockers. Many antihypertensive medications have been tested in pregnant women with varying levels of hypertension (mild, moderate and severe).

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(2, 3) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of pre-eclampsia eclampsia (2011).(4)

Three Cochrane systematic review were conducted, on the effects of antihypertensive drug therapies for the treatment of mild to moderate and severe hypertension in pregnancy, as well as the use of diuretics for preventing pre-eclampsia. (5, 6) In the reviews, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations for prevention and treatment of pre-eclampsia or eclampsia in April 2011, where this recommendation was developed. The GDG comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Recommendation question

For this recommendation, we aimed to answer the following question/s:

- in women with severe hypertension (P), does treatment with antihypertensive drugs (I) compared to placebo or no treatment (C), improve maternal and perinatal outcomes (O)?
- If so, which drug/s and route of administration optimizes outcomes?

Evidence Summary

**Antihypertensive drug treatment for mild to moderate hypertension during pregnancy**

A Cochrane systematic review of 46 RCTs involving a total of 4282 women evaluated the potential benefits, risks and side-effects of antihypertensive drug treatment for women with mild to moderate hypertension in pregnancy.(5) The trials compared antihypertensive drugs with placebo (28 trials, 3200 women) or another
antihypertensive drug (19 trials, 1282 women). Thirty four of these trials (3480 women) were conducted in high-income countries and the others in low and middle-income countries. The trials were generally small, with the largest recruiting 300 women. The class of antihypertensive drugs evaluated included alpha agonists, beta blockers, calcium channel blockers, vasodilators, ketanserin and glyceryl trinitrate. All but glyceryl trinitrate were administered orally in the trials. In most trials, mild to moderate hypertension was defined as a diastolic blood pressure of 90 mm Hg or more, but not exceeding 110 mm Hg.

**Any antihypertensive drug versus placebo or no antihypertensive**

Comparison of any antihypertensive drug with placebo or no antihypertensive drug showed no statistically significant differences in the overall risk ratio for critical (and proxy) outcomes of pre-eclampsia (22 trials, 2702 women; RR 0.97, 95% CI 0.83–1.13), severe pre-eclampsia (two trials, 267 women; RR 0.61, 95% CI 0.25–1.48), eclampsia (five trials, 578 women; RR 0.34, 95% CI 0.01–8.15), HELLP syndrome (one trial, 197 women; RR 2.02, 95% CI 0.38–10.78), pulmonary oedema (one trial, 176 women; RR 5.23, 95% CI 0.25–107.39), maternal death (four trials, 376 women; RR 2.85, 95% CI 0.30–27.00), perinatal death (20 trials, 2382 women; RR 0.96, 95% CI 0.60–1.54) and admission to special care baby unit (eight trials, 1321 women; RR 1.11, 95% CI 0.93–1.32). Maternal adverse events as reflected by stopping or changing drugs due to side-effects were, however, significantly more common among women treated with an antihypertensive drug compared with those who received placebo (15 trials, 1403 women; RR 2.59, 95% CI 1.33–5.04) (EB Table 14).

For critical outcomes of pre-eclampsia, the lack of benefits with the use of antihypertensive drug over placebo was consistent across types of hypertensive disorders (hypertension alone, hypertension plus proteinuria or chronic hypertension). Four small trials involving 725 women given calcium channel blockers showed an increase in the risk ratio for pre-eclampsia (RR 1.40, 95% CI 1.06–1.86) while eight trials involving 883 women treated with beta blockers showed statistically significant decrease in the risk ratio for pre-eclampsia (RR 0.73, 95% CI 0.57–0.94). For the proxy outcome of total fetal or neonatal death (including miscarriage), the similarity between the two comparison groups was consistent across the types of hypertensive disorders and gestational age at trial entry (EB Table 15).

**Any antihypertensive drug versus methyldopa**

When any antihypertensive drug (essentially beta blockers, calcium channel blockers and/or ketanserin) was compared with methyldopa, no statistically significant differences were observed for the critical (or proxy) outcomes addressed: pre-eclampsia (nine trials, 804 women; RR 0.81, 95% CI 0.57–1.16); total fetal or neonatal death (17 trials, 1130 women; RR 0.67, 95% CI 0.37–1.21); admission to special care baby unit (three trials, 379 women; RR 0.94, 95% CI 0.68–1.29); and maternal adverse events (four trials, 272 women; RR 2.80, 95% CI 0.12–67.91) (EB Table 16).

**Any antihypertensive drug versus calcium channel blockers**

Comparison of any antihypertensive drug (essentially beta blockers and glyceryl trinitrate) with calcium channel blockers showed similarity in the overall risks for the critical (or proxy) outcomes addressed: pre-eclampsia (two trials, 128 women; RR 2.15, 95% CI 0.73–6.38); HELLP syndrome (one trial, 100 women; RR 1.50, 95% CI 0.26–8.60); total fetal or neonatal death including miscarriage (two trials, 136 women; RR 1.00, 95% CI 0.06–15.55); admission to special care baby unit (one trial, 99 women; RR 1.47, 95% CI 0.44–4.89); and maternal adverse events (two trials, 136 women; RR 2.60, 95% CI 0.13–50.25) (EB Table 17).

**Antihypertensive drug treatment for severe hypertension during pregnancy**

Evidence related to the differential effects of various antihypertensive drugs when used for the treatment of very high blood pressure in pregnancy came from an updated Cochrane systematic review of 29 RCTs involving 3351 women.(6) Most of the trials were relatively small and only five of them recruited more than
100 women. Most of the trials participants recruited had diastolic blood pressure of 100 mmHg or higher at trial entry. The antihypertensive drugs investigated in these trials were hydralazine, calcium channel blockers (nifedipine, nimodipine, nicardipine and isradipine), labetalol, methyldopa, diazoxide, prostacyclin, ketanserin, urapidil, magnesium sulfate, prazosin and isosorbide. Hydralazine was compared with another drug in 5 out of the 13 comparisons in the review. There were considerable variations between the studies regarding antihypertensive drug dosages.

**Labetalol versus hydralazine**

When labetalol was compared with hydralazine in women with very high blood pressure, no statistically significant differences were observed for any of the critical (or proxy) outcomes addressed in the trials: persistent high blood pressure (two trials, 217 women; RR 1.58, 95% CI 0.66–3.77); maternal pulmonary oedema (one trial, 197 women; RR 3.03, 95% CI 0.12–73.49); HELLP syndrome (one trial, 197 women; RR 1.01, 95% CI 0.15–7.03); oliguria (one trial, 197 women; RR 0.51, 95% CI 0.09–2.69); fetal or neonatal death (four trials, 274 women; RR 0.75, 95% CI 0.17–3.21); Apgar score <7 at 5 minutes (two trials, 224 women; RR 0.81, 95% CI 0.25–2.61); and hypotension (three trials, 247 women; RR 0.20, 95% CI 0.10–4.15). No events were recorded in both arms of the studies that reported eclampsia, maternal death and disseminated intravascular coagulation. The trials providing these results had moderate risk of bias, relatively small sample sizes and very sparse events, thus generating generally very-low-quality of evidence for the critical outcomes (EB Table 18).

**Calcium channel blockers versus hydralazine**

Compared with hydralazine, calcium channel blockers (nifedipine and isradipine) showed a statistically significant reduction in the risk of persistent high blood pressure (five trials, 263 women; RR 0.33, 95% CI 0.15–0.70). No statistically significant differences were observed for any other critical (or proxy) outcomes addressed: further episode(s) of very high blood pressure (two trials, 163 women; RR 0.85, 95% CI 0.65–1.11); fetal or neonatal death (four trials, 161 women; RR 1.36, 95% CI 0.42–4.41); low blood pressure for the woman (three trials, 199 women; RR 2.83, 95% CI 0.12–64.89); and side effects for the woman (four trials, 236 women; RR 0.79, 95% CI 0.50–1.24). Most of the trials providing these critical outcomes were small and at moderate or high risk of bias, thus generating very-low-quality evidence for the outcomes (EB Table 19).

**Prostacyclin versus hydralazine**

One trial (47 women) comparing prostacyclin with hydralazine showed no statistically significant differences between the comparison groups for the critical outcomes addressed: persistent high blood pressure (RR 0.23, 95% CI 0.01–4.47); neonatal death (RR 1.14, 95% CI 0.08–17.11); and side-effects for the woman (RR 1.14, 95% CI 0.08–17.11). This trial had moderate risk of bias and yielded generally imprecise estimates due to the very small sample size and few events (EB Table 20).

**Ketanserin versus hydralazine**

Compared with hydralazine, ketanserin was more likely to be associated with persistent high blood pressure (three trials, 180 women; RR 4.79, 95% CI 1.95–11.73), but fewer side-effects for the women (three trials, 120 women; RR 0.32, 95% CI 0.19–0.53). No statistically significant differences were observed in the effects of the two drugs for other critical (or proxy) outcomes addressed: eclampsia (two trials, 64 women; RR 0.60, 95% CI 0.08–4.24); severe maternal morbidity (one trial, 56 women; RR 0.32, 95% CI 0.09–1.12); maternal death (two trials, 124 women; RR 0.32, 95% CI 0.03–2.96); perinatal death (two trials, 116 women; RR 0.27, 95% CI 0.05–1.64); and hypotension (two trials, 76 women; RR 0.26, 95% CI 0.07–1.03) (EB Table 21).

**Uradipil versus hydralazine**

Two small trials (59 women) compared urapidil with hydralazine. There were no differences between the
comparison groups for the critical outcomes addressed: persistent high blood pressure (two trials, 59 women; RR 1.38, 95% CI 0.06–31.14); neonatal death (two trials, 59 women; RR 0.66, 95% CI 0.08–5.25); hypotension (one trial, 33 women; RR 0.22, 95% CI 0.02–2.13); and side-effects for the women (two trials, 59 women; RR 0.59, 95% CI 0.10–3.58). No case of eclampsia or stillbirth was recorded in either arm of both trials. The moderate risk of bias in the trials providing these results, in addition to the very small sample size and few events, generated evidence of very-low-quality for the critical outcomes (EB Table 22).

**Labetalol versus calcium channel blockers**

Two small trials (80 women) that compared labetalol with calcium channel blockers showed no statistical differences between the two drugs for any of the critical outcomes: eclampsia (one trial, 20 women, RR 0.20, 95% CI 0.01–3.70); persistent high blood pressure (one trial, 60 women; RR 1.22, 95% CI 0.59–2.51); and specific side-effects such as nausea and/or vomiting (one trial, 60 women; RR 1.00, 95% CI 0.07–15.26); and palpitations (one trial, 60 women; RR 0.14, 95% CI 0.01–2.65). No case of hypotension was recorded in either of the two arms of the trials (EB Table 23).

**Labetalol versus methyldopa**

One small trial (72 women) comparing labetalol with methyldopa showed no statistical differences between the two drugs for any of the critical outcomes addressed: persistent high blood pressure (RR 1.19, 95% CI 0.74–1.94); neonatal death (RR 4.49, 95% CI 0.22–90.30); total stillbirths and neonatal deaths (RR 4.49, 95% CI 0.22–90.30); admission to special care baby unit (RR 1.06, 95% CI 0.66–1.71); and side-effects resulting in changing of drugs (RR 8.08, 95% CI 0.45–144.73). The trial providing these results had moderate risk of bias and few events, thus yielding generally very-low-quality evidence for the reported critical outcomes (EB Table 24).

**Labetalol versus diazoxide**

One small trial (90 women) showed that labetalol was less likely to cause hypotension requiring treatment compared with diazoxide, although the confidence interval was borderline for statistical significance (RR 0.06, 95% CI 0.00–0.99). There were no statistical differences observed for the other critical outcomes addressed: persistent high blood pressure (RR 0.50, 95% CI 0.13–1.88); and perinatal deaths (RR 0.14, 95% CI 0.01–2.69) (EB Table 25).

**Nitrates versus magnesium sulfate**

A small trial (36 women) comparing isosorbide with magnesium sulfate reported no case of eclampsia in association with either drug and showed no statistically significant differences between them for the proxy outcome of persistent high blood pressure (RR 0.14, 95% CI 0.01–2.58) (EB Table 26).

**Nimodipine versus magnesium sulfate**

Compared with magnesium sulfate, nimodipine was statistically significantly more likely to be associated with eclampsia (two trials, 1683 women; RR 2.24, 95% CI 1.06–4.73), but there was less risk of persistent high blood pressure (one trial, 1650 women; RR 0.84, 95% CI 0.76–0.93) and flushing as a side-effect (one trial, 1650 women; RR 0.22, 95% CI 0.12–0.40). No statistical differences were observed for any other critical (or proxy) outcomes addressed: coagulopathy (one trial, 1650 women; RR 1.69, 95% CI 0.41–7.05); oliguria (one trial, 1650 women; RR 0.87, 95% CI 0.59–1.26); and hypotension (one trial 1650 women; RR 0.72, 95% CI 0.23–2.27). The quality of evidence for these outcomes ranges between very-low- to low quality, mainly because the principal study (1650 women) was at high risk of bias (EB Table 27).

**Nifedipine versus chlorpromazine**

One small trial (60 women) comparing nifedipine with chlorpromazine showed no statistically significant differences for the critical (and proxy) outcomes addressed: eclampsia (55 women; RR 2.52, 95% CI
0.11–59.18), persistent high blood pressure (60 women; RR 0.09, 95% CI 0.01–1.57) (EB Table 28).

**Nifedipine versus prasozin**

One trial (150 women) comparing nifedipine with prasozin showed no statistically significant differences for any of the critical (or proxy) outcomes addressed: HELLP syndrome (one trial, 145 women; RR 1.15, 95% CI 0.37–3.60); renal failure (one trial, 145 women; RR 0.48, 95% 0.04–5.17); pulmonary oedema (one trial, 145 women; RR 0.19, 95% CI 0.02–1.60); admission to intensive care (one trial, 145 women; RR 0.32, 95% CI 0.01–7.73); maternal death (one trial, 145 women; RR 0.32, 95% CI 0.01–7.73); stillbirth (one trial, 149 women; RR 0.46, 95% CI 0.18–1.13); and admission to special care baby unit (one trial, 130 women; RR 0.78, 95% CI 0.49–1.23). No case of eclampsia was recorded in either arms of the trial. This trial had moderate risk of bias, few events in addition to its small sample size and thus yielded generally very-low-quality evidence for the critical (and proxy) outcomes (EB Table 29).

**Nitroglycerine versus nifedipine**

One small trial (32 women) compared nitroglycerine administered as an infusion with sublingual nifedipine. The risk of critical (and proxy) outcomes addressed were similar for both drugs: Apgar <8 at 5 minutes (RR 3.00, 95% CI 0.13–68.57); and specific side-effects such as flushing (RR 0.67, 95% CI 0.23–1.92), headache (RR 1.50, 95% CI 0.29–7.81) and palpitations (RR 0.33, 95% CI 0.01–7.62). No case of maternal or perinatal death was recorded in the trial. Although this trial had little or no risk of bias, the very small sample size and few events resulted in generally low-quality evidence for the reported critical outcomes (EB Table 30).

In summary, the analysis of the evidence related to the multiple comparisons of antihypertensive drugs for very high hypertension during pregnancy is complicated by its low quality which is due primarily to the small samples used in the trials, rare events as outcomes and variations in the administered drug regimens. Hydralazine is the most studied drug, though in the comparison with calcium channel blockers (nifedipine and isradipine) the latter have been associated with a greater reduction in the risk of persistent high blood pressure.

**Diuretics for preventing pre-eclampsia**

Evidence related to the effects of diuretics on the prevention of pre-eclampsia came from a Cochrane systematic review of five RCTs involving 1836 women in the USA.(7) Both primiparous and multiparous women with gestations from first to the third trimester were recruited into the trials. Two trials (347 women) recruited only women with normal blood pressure, one trial (20 women) recruited only those with chronic hypertension while the other two trials (1658 women) did not report on blood pressure status at trial entry. In all trials thiazide diuretics were compared with placebo or no treatment.

When diuretics were compared with placebo or no treatment, there were no statistically significant differences in the critical (or proxy) outcomes: new or worsening hypertension (two trials, 1475 women; RR 0.85, 95% CI 0.68–1.08), pre-eclampsia (four trials, 1391 women; RR 0.68, 95% CI 0.45–1.03), severe pre-eclampsia (two trials, 1297 women; RR 1.56, 95% CI 0.26–9.17), use of antihypertensive drugs (one trial, 20 women; RR 2.00, 95% CI 0.21–18.69), adverse events (two trials, 1217 women; RR 1.85, 95% CI 0.81–4.22), perinatal death (five trials, 1836 women; RR 0.72, 95% CI 0.40–1.27) and 5-minute Apgar score less than seven (one trial, 20 women; RR 3.00, 95% CI 0.14–65.90). There was no case of eclampsia in both the intervention and control arms of one trial that reported it as an outcome measure. All the trials providing this evidence had moderate risk of bias, relatively small sample sizes and sparse events resulting in generally low overall quality of evidence for the critical outcomes (EB Table 31).

**Implementation considerations**
The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation. The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner. A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of low-dose aspirin in antenatal care settings), and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice. In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The 2011 GDG identified that further research on the following high-priority questions is needed:

- For mild to moderate high blood pressure, there is a need to determine whether treatment is better than no treatment.
- Further research is needed on the relative effectiveness of available drugs for severe acute hypertension.

Related Links

WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (2011) - full document and evidence tables (EB Tables 14 – 31)

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Supporting systematic review/s:


References

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