Review article

ANTIHYPERTENSIVE DRUG THERAPY FOR HYPERTENSIVE DISORDERS IN PREGNANCY

Marko Folic[1], Nevena Folic[2], Mirjana Varjacic[3], Mihajlo Jakovljevic[4] and Slobodan Jankovic[1]

Hypertension in pregnancy is associated with increased maternal and fetal mortality and morbidity. About 8 % of all pregnancies are complicated with hypertensive disorders. There is concordance that severe hypertension should be treated without delay to reduce maternal risks of acute cerebrovascular complications. Intravenous labetalol and oral nifedipine are as effective as intravenous hydralazine in control of severe hypertension, with less adverse effects. Still, there is no consensus as to whether mild-to-moderate hypertension in pregnancy should be treated, considering that there are no definitive conclusions which can be made about the relative maternal or perinatal benefits/risks of antihypertensive treatment. Considering their safe usage during pregnancy, methyldopa, labetalol and nifedipine are commonly used blood-pressure lowering drugs for pregnant women with hypertension. The cardio-selective β- blocker atenolol should be avoided in pregnancy, because it has been associated with lower birth weights and fetal growth impairment. ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. *Acta Medica Medianae 2008;47(3):65-72.*

***Key words**: antihypertensive drugs, hypertensive disorders, pregnancy*

Department of Clinical and Experimental Pharmacology of Clinical Center in Kragujevac[1]
Health Care Center of Kragujevac [2]
Clinic for Gynecology and Obstetrics, Clinical Center Kragujevac[3]
Faculty of Medicine, University of Kragujevac[4]

Contact: Marko Folic
Department of Clinical and Experimental Pharmacology of Clinical Center
30 Zmaj Jovina Street
34000 Kragujevac, Serbia
Phone: 064 1963660
E-mail: markof@medf.kg.ac.yu

Hypertensive pregnancy disorders - definitions and classification

Hypertensive disorders are among the most common of all medical complications in pregnancy and are the leading cause of maternal and perinatal morbidity and mortality (1). Approximately, 8% of all pregnancies are complicated by hypertension (2). It was estimated that 192 women die every day because of complications of pregnancy hypertension (3).

Hypertension in pregnancy is defined by systolic blood pressure (sBP)≥140 mmHg and/or diastolic blood pressure (dBP)≥90 mmHg, or by increase in sBP≥30 mmHg, or in dBP≥15 mmHg, from preconception or first trimester blood pressure confirmed by two measuring, 6 hours apart.

There are four major hypertensive disorders in pregnancy, each with specific characteristics. In chronic hypertension, blood pressure (BP) is diagnosed before pregnancy in the first 20 weeks of gestation, or persists 42 days after delivery ≥140/90 mmHg. In transient (now gestational) hypertension blood pressure ≥140/90 mmHg was established after the 20th week of gestation, and is not associated with proteinuria.

Preeclampsia-eclampsia

Preeclampsia is generally regarded as very important complication of pregnancy which is more dangerous than gestational or chronic hypertension, and is characterised by hypertension, proteinuria (≥0.3 g/24 hours) and oedema after the 20th week of gestation. Eclampsia is described as the appearance of generalised convulsion(s) associated with the signs of preeclampsia, or their occurrance within 7 days of parturition, and not caused by epilepsy or other convulsive disorders. Preeclampsia superimposed on chronic hypertension is defined as a condition of hypertension (BP≥140/90 mmHg) with onset of proteinuria (4,5).

In compliance with the decision of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, the transient hypertension was renamed into gestational hypertension, and presents the condition of increased blood pressure during pregnancy with the absence of preeclampsia at the time of delivery and normalisation of BP during the following 12 weeks after delivery. Also, in the definition of preeclampsia, oedema has been removed as a diagnostic criterion, thus the preeclampsia includes hypertension and proteinuria (6,7).

Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) also presented their common attitude on hypertensive disorders

in pregnancy (8). In the ASSHP system, gestational hypertension is hypertension after the 20th week of gestation. Women with preelampsia, in addition to hypertension have one or more of several abnormalities like proteinuria, elevated liver enzymes, thrombocytopenia, or elevated values of uric acid, or neurological disease.

Dilemma related to the beginning of antihypertensive therapy

While severe hypertension (sBP≥170 mmHg and/or dBP≥110 mmHg) in pregnancy represents a very serious risk for maternal health (9), mild-to-moderate hypertension (BP from 140/90 to 169/109 mmHg) in pregnancy is associated with lower maternal risk.

The necessity for antihypertensive therapy and the selection of certain antihypertensive agents during pregnancy should be estimated upon of the relative risks and/or benefits for the individual pregnant women. Still, there is dilemma in clinical practice when to use antihypertensive medications or what level of BP to target during pregnancy.

There is no suspicion about usage of antihypertensive drugs in cases of severe hypertension. BP≥170/110 mmHg corresponds to the level standing for a high risk of cerebrovascular incident, because of which the majority of obstetricians regard antihypertensive treatment as crucial for the mother (9). Identification of this specific risk made the control of acutely raised blood pressure as central point for women with severe hypertension, particularly that of preeclampsia (10). Coagulation disorders associated with severe preeclampsia represent additional complications and also require adequate therapy (11,12,13).

In mild-to-moderate hypertension in pregnancy (BP from 140/90 to 169/109 mmHg), usage of antihypertensive drugs is still controversial. In those cases, when the situation is less certain, selection of patients, choice of drug and duration of pregnancy at the beginning of treatment may be of great importance. Sibai consider that women with mild, uncomplicated chronic hypertension will accomplish good perinatal outcome regardless of the use of antihypertensive therapy (14). Some consider there are little indications for drug treatment of mild-to-moderate hypertension (15). Withholding from the treatment of hypertension in pregnancy to the value of 100 mmHg is not associated with additional maternal or fetal risk (16).

Benefits and risks of antihypertensive treatment for mild-to-moderate hypertension are not completely defined in recent reviews, including a Cochrane meta-analysis (17,18). It appears that with the use of antihypertensive treatment, there is less risk of developing severe hypertension, but no difference in outcomes of preeclampsia, neonatal death, preterm birth, and small-for-gestational-age (SGA) infants. Some investigators concluded that women with mild hypertension do not need antihypertensive treatment if they are closely followed up during pregnancy and delivery, especially pregnant women without hypertension and proteinuria development before pregnancy (19).

Doubts concerning antihypertensive drugs use in pregnancy mostly refer to the effects they might have on the developing fetus. Generally, antihypertensive agents cross the placental barrier and are present in various concentrations in the fetal circulation. It was noticed that the incidence of SGA infants and reduction of birth weight were increased with higher antihypertensive-induced fall in mean arterial BP among women who took antihypertensives when BP reached 160/100 mmHg. Among women whose BP was normalized (dBP<90 mmHg), there was a decrease in the risk of severe hypertension, maternal hospitalization and "proteinuria at delivery", on the basis of which no definitive conclusions can be drawn about the relative maternal or fetal benefits/risks of antihypertensive treatment for mild-to-moderate pregnancy hypertension (20).

International societies have differed in their attitudes and recommendations for the BP which should initiate antihypertensive therapy. The U.S. professional bodies recommend starting with the therapy at BP≥160/105 mmHg, not defining the target values (6). The Canadian Hypertension Society recommends normalization of BP for most hypertensive pregnancy disorders with BP of 140-150/90-95 mmHg, targeting dBP of 80-89 mmHg (21). The Australasian professional bodies recommend initiation of antihypertensive therapy at BP≥160/90 mmHg and conducting the therapy to the BP value of 110-140/80-90 mmHg (8). It should be underlined that there are still no definitive and complete data about safe BP treatment targets for women with hypertension in pregnancy, however, guidelines and reviews generally recommend the introduction of antihypertensive treatment with the BP values of 140 - 155/90 -105 mmHg (22).

A wide choice of antihypertensive agents

In accordance with intensive development of pharmaceutical industry in few last decades, the appearance of several different medical forms of the same medical substances is not unusual on market. Different medical forms can be considered as alternatives, pursuant to the scope of indications only if they are therapeutically equivalent, or, in other words, the same two preparations from different pharmaceutical producers must give the same clinical outcome. Besides, in our market, there are many generic drug forms used in hypertension therapy. It is very important that their efficiency and safety are the same as of brand-name drugs, because of why consequent bioequivalence testing may be of great significance (23).

A wide spectrum of antihypertensive agents represents the key of successful pregnancy hypertension treatment and opportunity of choice, in accordance with indications and availability of drugs provided by drug tendering (24).

Centrally acting α2-adrenergic agonists

Methyldopa is the most frequently prescribed and the agent of first choice for treatment of hypertension in pregnancy (21), in accordance with the fact that there are extensive clinical experience with the drug and long-term follow-up data regarding children whose mothers received methyldopa during pregnancy with proven maternal and fetal safety (25,26). During the long- term utilization in chronic hypertension in pregnancy, methyldopa does not alter cardiac output or blood flow to the uterus or kidneys (9). This drug is also used to control hypertension in preeclampsia (27). Compared with the pretreatment values, the mean arterial blood pressure decreased significantly while, analysed by computed cardiotocography, fetal heart rate patterns were not significantly changed during the treatment with methyldopa (28). Based on the long history of use, methyldopa does not seem to be teratogenic (29). Mutch et al. reported that there are no significant differences between birth weight, neonatal complications and development during the first year in children exposed to methyldopa and placebo group (30). Except basic adverse effects which are directly related to its mechanism of action (fatigue, depression, poor sleep), elevated transaminases and a positive Coomb's test (which is occasionally associated with haemolytic anemia) are also annunciated (31).

Peripherally acting adrenergic-receptor antagonists

Labetalol blocks both α- and β-adrenoceptors and produces its hypotensive effects without compromising the maternal cardiovascular system, which is significant in maintaining of renal and uterine blood flow. The results from multicentre, randomised, double-blind study in 152 patients (20 to 38 weeks of gestation) with mild-to-moderate non-proteinuric hypertension demonstrated that labetalol, compared with placebo group, significantly reduces maternal blood pressure ($p<0.001$) without increase in intrauterine growth retardation and neonatal hypoglycaemia (32). In a trial which has included 263 women with mild-to-moderate hypertension at 6 to 13 weeks of gestation, patients were randomly separated in three groups: first group (87 pregnant women) received methyldopa, second, labetalol (86 pregnant women) and group with no treatmant (90 pregnant women). The results showed that patients with therapy had significantly lower maternal blood pressures ($p<0.0001$) compared to the nonmedication group and that there were no differences among the groups concerning gestational age at delivery, birth weight, incidence of fetal growth retardation, neonatal head circumference or uteroplacental circulation (33). Redman also considers that uteroplacental circulation is not affected by labetalol (34). In preeclamptic hypertension treatment, labetalol can be deemed as safe and effective medicament (35). Parenterally, it is used to treat severe hypertension. Clinical studies of acute severe hypertension in pregnancy exhibited that labetalol was connected with less maternal hypotension than hydralazine (36). Adverse effects may be predicted on behalf of β-receptor blockade. Although fatigue, lethargy, exercise intolerance, peripheral vasoconstriction, sleep disturbance and bronchoconstriction may appear, discontinuation of usage because of adverse effects is uncommon (17).

Although atenolol is commonly used cardioselective β blocker in non-pregnancy, it has been considered that in pregnancy, especially in early pregnancy, usage of atenolol should be avoided. Based upon results of placebo-controlled study, which have been showed that in women with chronic hypertension, atenolol usage in early pregnancy (mean 15.9 weeks of pregnancy) is associated with the significantly lower birth weight (2620 vs 3530 g) and significantly higher proportion of small-for-gestational-age infants compared to the placebo group, the investigators concluded that atenolol had an adverse effect on birth weight and fetal growth (37). Lip et al. (38) reported significantly lower weight of babies born to women taking atenolol ($p < 0.001$) compared to those taking other β-blockers, other antihypertensives, or no therapy during the first 20 weeks of pregnancy. Bayliss et al. expounded that low birth weight was associated with atenolol taken at the time of conception or during the first trimester of pregnancy (39). Lydakis et al. noticed and compared the differences between the mean birthweight at delivery depending on time when atenolol was given (40). When atenolol was given before the 20th week of gestation for a mean period of 23 to 26 weeks, the mean birthweight at delivery was 2010 g; when given between the 20th and 30th weeks of gestation for 12 weeks, it was 2402 g, and 2644 g when given at > 30 weeks of gestation for 3 to 5 weeks. In contrast to the adverse effects of reduced birthweight and SGA babies of early atenolol use in some trials, the study with atenolol in pregnancy-induced hypertension (41) failed to present any difference in average birthweight in mothers receiving β-blockers. This may be the result of the late starting with antihypertensive therapy. Atenolol should be avoided in early stages of pregnancy and given with caution at later stages, as it has been associated with fetal growth impairment and lower birth weights.

Generally, oral beta-blockers for mild-to-moderate hypertension during pregnancy have specifically been estimated in the Cochrane database (42). Oral beta-blockers (except atenonol) decrease the risk of severe hypertension. It has been estimated that beta-blockers appear to be associated with an increase in small-for-gestational-age infants and frequency of neonatal bradycardia. Also, the respiratory distress syndrome and maternal hospital admissions decrease. Beta-blockers treatment seems to be no more effective compared with methyldopa.

For severe hypertension, β blockers may be administered parenterally. As we have noted, intravenous labetalol has been, because of a lower incidence of maternal hypotension and other adverse effects, supplanted the usage of hydralazine, which was previously the most commonly used agent for the treatment of severe hypertension (36).

Calcium Channel Antagonists

Calcium antagonists produce direct arterial vasodilatation, by inhibiting entry of Ca^{2+} in smooth muscle. These agents have been used in pregnancy, because they do not appear to produce a major teratogenic risk. Sibai et al. (43) studied 200 preeclamptic patients at 26 to 36 weeks of gestation which were assigned randomly to treatment with bed rest alone or oral nifedipine plus bed rest. Blood pressures was significantly lower ($p<0.0001$) in patients who received nifedipine while severe hypertension was significantly more frequent ($p<0.05$) in the patient group with bed rest alone. The difference between the groups in regard to birthweight, incidence of small-for-gestational-age babies, preterm birth and the number of days spent in the special care unit was not detected. Nifedipine reduces maternal BP, however, in regard to the perinatal outcome or reduction in the number of days of maternal hospitalisation, this drug is not effective. Fenakel et al. (44) reported, based on the results of randomised clinical trial in which patients with severe preeclampsia between the 26th and 36th weeks of gestation received either nifedipine or hydralazine, the effective control of blood pressure was attained with nifedipine in 95.8% of patients and 68% of patients with hydralazine. Also, the average number of days spent in the neonatal intensive care unit was significantly lower in patients treated with nifedipine (15.1 vs 32.7 days; $p<0.005$). Magee et al. concluded that, in accordance with the results of a multicenter, cohort study which investigated the safety of calcium channel blockers in human pregnancy, nifedipine and verapamil, which have been best studied, did not seem to pose teratogenic risks to fetuses exposed in the first trimester (45).

Brown et al. compared efficacy and safety of 10 mg nifedipine tablets with rapid onset and short-acting 10 mg nifedipine capsules for the treatment of severe hypertension in the second half of pregnancy (46). There was a smaller number of hypotensive episodes in women who took tablets. Fetal distress was rare with capsules and tablets. Authors concluded that, although slower at the start, nifedipine tablets were as effective as capsules for the rapid treatment of severe hypertension. Some other studies reported that administration of short-acting nifedipine capsules has been associated with maternal hypotension and fetal distress (47,48), which suggested the usage of a long-acting preparation.

In addition, administration of $MgSO_4$ to pregnant women receiving calcium channel antagonists may result in severe hypotension (49) and neuromuscular blockade (50), so that the combination should be used carefully.

Direct vasodilators

Oral hydralazine has been widely used for chronic hypertension in the second and third trimesters, but its use has been supplanted by agents with more favorable adverse effects (51). Generally, hydralazine has been used in all trimesters of pregnancy and experiences with its usage have not shown an association with teratogenicity, although Widerlov et al. (52) reported neonatal thrombocytopenia and Yemini et al. (53) a case of maternal, and possibly neonatal, lupus after six days of parenteral hydralazine therapy for severe hypertension. Parenteral hydralazine was earlier considered to be the drug of choice for the treatment of acute severe hypertension in pregnancy, but a recent meta-analysis of intravenous hydralazine usage in severe hypertension in pregnancy concluded that parenteral labetalol or oral nifedipine were preferable first-line agents in accordance with association of intravenous hydralazine with more maternal and perinatal adverse effects than intravenous labetalol or oral nifedipine, such as maternal hypotension, maternal oliguria, caesarean sections, placental abruption, adverse effects on fetal heart rate and low Apgar scores at one minute (36).

Sodium nitroprusside is potent, rapid-acting and short-lasting drug which is used in pregnancy for the treatment of an acute hypertensive crisis not responding to other agents. Considering that utilization of this medicament may cause fetus cyanide poisoning, transient fetal bradycardia, metabolic acidosis, and maternal hypotension (54,55), it must be given under continuous surveillance and with caution. Also, it is recommended that when control of acute crisis is attained, the fetus should be delivered as soon as possible. Nitroprusside is a drug of last choice for the treatment of acute hypertension in pregnancy.

Diuretics

Diuretics are commonly orally administered antihypertensives in non-pregnant patients because of low cost and suitable impact on major cardiovascular events as shown in randomized controlled trials (56). Also, it has been claimed that diuretics prevent pre-eclampsia (57,58). Although diuretics reducing maternal plasma volume have been reported to be connected with poor perinatal outcome (59), negative affect on fetal growth has not been completely proven (60). Collins et al. concluded that there is no increment in neonatal thrombocytopenia or other adverse effects among diuretic-exposed newborns (61). Hydrochlorothiazide, triamterene

and amiloride are not considered teratogenic (62). The usage of spironolactone is not advised because of its antiandrogenic effects during fetal development (63). Even though it was proven that the adverse effects of diuretics such as hypokalaemia or impaired glucose tolerance (64) can be minimized by using low doses, diuretics are not used frequently in pregnancy.

Angiotensin-Converting-Enzyme Inhibitors and Angiotensin Receptor

Antagonists

Angiotensin-converting–enzyme (ACE) inhibitors are widely prescribed and well tolerated antihypertensives, but it is proved that their usage in the second and third trimesters of pregnancy may cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures and neonatal renal failure, hypotension, and death (65,66,67). A similar fetal anomalies have been reported after treatment of women in the second or third trimester of pregnancy with angiotensin II receptor antagonists (68).

Some studies have not reported fetopathy among women who took ACE inhibitors only during the first trimester of pregnancy. Lip et al. (69) reported no congenital abnormalities with any evident neonatal renal dysfunction in six women receiving ACE inhibitors in early pregnancy as a continuation of therapy for more than 12 weeks, including one who continued treatment until 25 weeks. Steffensen et al. (70) reported the outcome of 21 pregnant women who received ACE inhibitors during their first trimester (at 5 to 15 gestational weeks) between 1991 and 1996. There were no stillborn babies. There was a case of one pre-term infant delivered at the 27th gestation week and died at 1 week of age, but with no signs of neonatal renal failure and no congenital malformation on performed autopsy. A case of congestive cardiomyopathy without structural malformation was also reported. Except these two cases, there were no other reports of any congenital abnormalities or fetal or neonatal renal failure.

Although the above reports give supportive evidence for the safety of ACE inhibitors in early pregnancy, further clinical experience is warranted for risk assessment.

Cooper et al. conducted a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy and risk of congenital malformations. They followed 29.507 infants from Tennessee Medicaid files who were born between 1985 and 2000 and whose mothers had no evidence of diabetes. It was identified that, from all those babies, 209 babies were exposed to ACE inhibitors during the first trimester only, 202 were exposed to other antihypertensives during the first trimester only, and 29. 096 babies were not exposed to antihypertensive drugs. The risk of major congenital malformations was higher in infants who had been exposed to ACE inhibitors, compared with infants who had not been exposed to antihypertensives, while exposition to other antihypertensive medications did not increase the risk of major malformations. ACE inhibitors increased risk of malformations of the cardiovascular system and the central nervous system. The authors concluded that exposure to ACE inhibitors during the first trimester of pregnancy should be avoided because they cannot be considered safe (71).

Also, it has been suggested that this agents should be avoided by women who attempt to conceive (72).

Based upon the analyzed association between a child born with renal impairment following anhydramnios and maternal exposure to an angiotensin II receptor type 1 (AT1) antagonist, valsartan, and hydrochlorothiazide during the first 28 weeks of pregnancy, Bos-Thompson et al. concluded that AT1 antagonists should be avoided throughout pregnancy because they reduce fetal kidney perfusion that may result in oligoamnios and neonatal renal insufficiency (73).

Conclusion

All hypertensive disorders of pregnancy are associated with increased maternal and perinatal risks, but the relation between benefits and risks of using any antihypertensive agent in pregnancy have not been still completely defined. There is consensus that women with severe hypertension should receive antihypertensive treatment in order to decrease the risk of stroke eclampsia or death, but in cases of mild-to-moderate hypertension, the attitudes of antihypertensive therapy usage are still controversial.

From a wide palette of antihypertensives, the most acceptable agents are methyldopa, labetalol, and nifedipine, in standard doses. The usage of atenolol should be avoided in pregnancy, because it has been associated with lower birth weights and fetal growth impairment. ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy and they should be avoided in all trimesters of pregnancy. In control of severe hypertension, intravenous labetalol or oral nifedipine is as effective as intravenous hydralazine, with less adverse effects.

Although there are many antihypertensive agents, large randomized controlled studies are needed to establish BP levels for the beginning of drug treatment, define specific drugs, and finally, to solve whether antihypertensive therapy in mild-to-moderate hypertension in pregnancy have greater benefits than risks for mother and fetus.

References

1. Department of Health. Why mothers die. Report on confidential enquiries into maternal deaths in the United Kingdom. London: HMSO, 1998.
2. Roberts J, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working group on researche on hypertension during pregnancy. Hypertens 2003; 41:437-45.
3. Hill K, AbouZahr C, Wardlaw T. Estimates of maternal mortality for 1995. Bulletin of the World Health Organization 2001;182-93.
4. Helewa M, Burrows RF, Smith J et al. Report of the Canadian Hypertension Society Consensus Conference: Definitions, evaluations and classification of hypertension disorders in pregnancy. Canadian Medical Association Journal 1997; 57:715-25.
5. Maharaj B, Moodley J. Management of hypertension in pregnancy. Cont Med Educ 1991; 12: 1581-9.
6. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1–S22.
7. Churchill D. The new American guidelines on the hypertensive disorders of pregnancy. Journal of Human Hypertension 2001;15:583–5.
8. Brown MA et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust NZ J Obstet Gynaecol 2000;40:139– 55.
9. Khedun S, Maharaj B, Moodley J. Effects of Antihypertensive Drugs on the Unborn Child. Paediatr Drugs 2000;2(6):419-36.
10. Lewis G, Drife J, eds. Why mothers die 1997-1999. The confidential enquiries into maternal deaths in the UK. London: RCOG Press, 2001.
11. Tanjung MT, Siddik HD, Hariman H, Koh SC. Coagulation and fibrinolysis in preeclampsia and neonates. Clin Appl Thromb Hemost. 2005 Oct; 11(4):467-73.
12. Folić M. Noviji fibrinolitici u terapiji akutnog infarkta miokarda. ABC časopis urgentne medicine 2007; 7(1):18-24.
13. Terao T, Kobayashi T, Imai N, Oda H, Karasawa T. Pathological state of the coagulatory and fibrinolytic system in preeclampsia and the possibility of its treatment with AT III concentrate. Asia Oceania J Obstet Gynaecol. 1989 Mar;15(1):25-32.
14. Sibai BM. Chronic hypertension in pregnancy. Clin Perinatol 1991;18: 833-44.
15. Kyle P, Redman CWG. Comparative risk benefit assessment of drugs used in the management of hypertension in pregnancy. Drug Saf 1992;7:223-34.
16. Bott-Kanner G, Hirsch M, Friedman S. Antihypertensive therapy in the management of hypertension-a clinical double blind study of pindolol. Clin Exp Hypertens (B) 1992;11B:207-20.
17. Abalos E, Duley L, Steyn D, Henderson-Smart D. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2007;CD002252.
18. von Dadelszen P, Magee LA. Antihypertensive medications in management of gestational hypertension-preeclampsia. Clin Obstet Gynecol. 2005;48:441-59.
19. Hjertberg R, Belfrage P, Hanson U. Conservative treatment of mild and moderate hypertension in pregnancy. Acta Obstet Gynaecol Scand 1992; 71:439-46.
20. von Dadelszen P, Ornstein MP, Bull S et al. Fall inmean arterial pressure and fetal growth restriction in pregnancy hypertension. Lancet 2000; 355: 87-92 (commentary by Ray JG, ACP J Club 2000;133:2).
21. Rey E, LeLorier J, Burgess E et al. Report of the Canadian Hypertension Society consensus conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. Canadian Medical Association Journal 1997;157:1245-54.
22. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol. 2007;196:514 e511–e519.
23. Jakovljević M, Janković S. Studije bioekvivalencije. Acta Medica Medianae 2006;45(4):50-5.
24. Milovanović DR, Pavlović R, Folić M, Janković SM. Public drug procurement: the lessons from a drug tender in a teaching hospital of a transition country. Eur J Clin Pharmacol. 2004 May; 60(3):149-53.
25. Fidler J, Smith V, Fayers P. Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. BMJ 1983;286:1927-30.
26. Cockburn J, Moar VA, Qunsted M, et al. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1982; I: 647-9.
27. National High Blood Pressure Education Program Working Group Report on high blood pressure in pregnancy. Am J Obstet Gynaecol 1990;163:1689-712.
28. Wide-Swensson D, Montan S, Arulkumaran S, et al. Effect of methyldopa and isradipine on fetal heart rate pattern assessed by computerized cardiotocography in human pregnancy. Am J Obstet Gynaecol 1993;169:1581-5.
29. Gallery ED, Ross MR, Gyory AZ. Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. BMJ (Clin Res Ed). 1985;291:563-6.
30. Mutch LM, Moar VA, Ounsted MK, Redman CW. Hypertension during pregnancy, with and without specific hypotensive treatment. I. Perinatal factors and neonatal morbidity. Early Hum Dev. 1977;1:47–57.
31. Magee LA. Drugs in pregnancy. Antihypertensives. Best Pract Res Clin Obstet Gynaecol. 2001;15:827-45.
32. Pickles CJ, Broughton-Pipkin F, Symonds EM. A randomised placebo controlled trial of labetalol in treatment of mild to moderate pregnancy induced hypertension. Br J Obstet Gynaecol 1992; 99: 964-8
33. Sibai BA, Mabie WC, Shamsa F, et al. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynaecol 1990;162:960-7.
34. Redman CWG. Hypertension in pregnancy. In: deSwietM. editor. Medical disorders in obstetric practice. London: Blackwell Science, 1995:182-225.
35. Michael CA. The evaluation of labetalol in the treatment of hypertension complicating pregnancy. Br J Clin Pharmacol 1982; 3 Suppl.:127-36.
36. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: metaanalysis. BMJ. 2003;327:955–60.
37. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension in pregnancy. BMJ 1990;301:587-9.
38. Lip GYH, Beevers M, Churchill D, et al. Effect of atenolol on birth weight. Am J Cardiol 1997;79:1436-8.
39. Bayliss H, Churchill D, Beevers M, Beevers DG. Antihypertensive drugs in pregnancy and fetal growth: evidence for 'pharmacological programming' in the first trimester? Hypertens Pregnancy 2002;21:161-74.

40. Lydakis C, Lip GYH, Beevers M, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999;12:541-7.
41. Rubin PC, Butters L, Clark DM, et al. Placebo controlled trial of atenolol in the treatment of pregnancy-associated hypertension. Lancet 1983;I:431-4.
42. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertensionduring pregnancy. Cochrane Database Syst Rev. 2003;(3):CD002863.
43. Sibai BM, Barton JR, Sherif A, et al. A randomised prospective study of nifedipine and bedrest versus bed rest alone in the management of pre-eclampsia remote from term. AmJ Obstet Gynaecol 1992; 167:879-84.
44. Fenakel K, Fenakel G, Appelman Z, et al. Nifedipine in the treatment of severe pre-ecalmpsia.Obstet Gynaecol 1991;77:331-7.
45. Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, McElhatton PR, Schmidt MA, Koren G. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol. 1996;174:823–8.
46. Brown MA, Buddle ML, Farrel T, Davis GK. Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. Am J Obstet Gynecol 2002;187:1046–50.
47. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. Br J Obstet Gynaecol. 1993;100:959–61.
48. Puzey MS, Ackovic KL, Lindow SW, Gonin R. The effect of nifedipine on fetal umbilical artery Doppler waveforms in pregnancies complicated by hypertension. S Afr Med J. 1991;79:192–4.
49. WaismanG, Mayorga L, AmeraM.Magnesium plus nifedipine: potetiation of hypotensive effects in pre-eclampsia? AmJ Obstet Gynaecol 1989;159:308-9.
50. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. Am J Obstet Gynaecol 1989;161:35-6.
51. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J. 2003;24:761–81.
52. Widerlov E, Karlman I, Storsater J. Hydralazine-induced neonatal thrombocytopenia. N Engl J Med. 1980;303:1235.
53. Yemini M, Shoham (Schwartz) Z, Dgani R et al. Lupus-like syndrome in a mother and newborn following administration of hydralazine: a case report. European Journal of Obstetrics, Gynecology and Reproductive Biology 1989;30:193-7.
54. Shoemaker CT, Meyers M. Sodium nitroprusside for control of severe hypertensive disease of pregnancy. A case report and discussion of potential toxicity. Am J Obstet Gynaecol 1984;149:171-3
55. Godlin RC. Fetal and maternal effects of sodium nitroprusside. Am J Obstet Gynaecol 1983;146:350-1.
56. Joint National Committee on detection, evaluation, and treatment of high blood pressure. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI). Archives of Internal Medicine 1997;157:2413-46.
57. Henriksen T. Hypertension in pregnancy: use of antihypertensive drugs. Acta Obstet Gynaecol Scand 1997;76:96-106.
58. Redman CWG, Roberts JM. Management of pre-eclampsia. Lancet 1983;341:1451-4.
59. Sibai BM, Grossman RA, Grossman HG. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am J Obstet Gynaecol 1984;150:831-5.
60. Materson BJ, Reda DJ & Cushman WC (for the Department of Veterans A.airs Cooperative Study Group on Antihypertensive Agents). Single drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. New England Journal of Medicine 1993;328:914-21.
61. Collins R, Yusuf S & Peto R. Overview of randomised trails of diuretics in pregnancy. British Medical Journal 1985;290:17-23.
62. Psaty BM, Smith NL, Siscovick DS et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta analysis. JAMA 1997;277:739-45.
63. Groves TD, Corenblum B. Spironolactone therapy during humanpregnancy. Am J Obstet Gynecol. 1995;172:1655-6.
64. Gress TW, Nieto J, Shahar E et al for the Atherosclerosis Risk in Communities Study. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. New England Journal of Medicine 2000;342:905-12.
65. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. Early Hum Dev 2006;82:23-8.
66. Buttar HS. An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. Mol Cell Biochem 1997;176:61-71.
67. Barr M Jr. Teratogen update: angiotensin-converting enzyme inhibitors. Teratology 1994;50:399-409.
68. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res A Clin Mol Teratol 2005;73:123-30.
69. Lip GYH, Churchill D, Beevers M, et al. Angiotensin converting enzyme inhibitors in early pregnancy. Lancet 1997;350:1446-7.
70. Steffensen FH, Nielsen GL, Sorensen HT, et al. Pregnancy outcome with ACE-inhibitors use in early pregnancy (letter). Lancet 1998; 351 (9102):596.
71. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006;354:2443-51.
72. Podymow T, August P. Update on the Use of Antihypertensive Drugs in Pregnancy. Hypertension 2008;51:960-9.
73. Bos-Thompson MA, Hillaire-Buys D, Muller F, Dechaud H, Mazurier E, Boulot P, Morin D. Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up after birth. Ann Pharmacother. 2005 Jan; 39(1):157-61. Epub 2004 Dec 8. Review.

ANTIHIPERTENZIVNA TERAPIJA KOD HIPERTENZIVNIH POREMEĆAJA U TRUDNOĆI

Marko Folić, Nevena Folić, Mirjana Varjačić, Mihajlo Jakovljević i Slobodan Janković

Hipertenzija u trudnoći je udružena sa povišenim stepenom morbiditeta i mortaliteta majke i ploda. Oko 8% od ukupnog broja trudnoća komplikuje se hipertenzivnim poremećajima. Postoji opšta saglasnost o neophodnosti što hitnijeg lečenja budućih majki sa teškom hipertenzijom u cilju smanjenja rizika razvoja akutnih cerebrovaskularnih komplikacija. U kontroli teških oblika hipertenzije, intravenozno aplikovan labetalol ili oralno dat nifedipin su podjednako efikasni ali i udruženi sa manjim brojem neželjenih reakcija u odnosu na intravenozno ordiniran hidralazin. Opšteg stava u vezi sa potrebom lečenja blage do umerene hipertenzije u trudnoći još uvek nema, s obzirom da definitivni zaključci po pitanju odnosa potencijalnih koristi/rizika uzrokovanih primenom antihipertenzivne terapije u trudnoći još uvek ne postoje. S obzirom na bezbednu primenu u trudnoći, metildopa, labetalol i nifedipin su često korišćeni lekovi za regulaciju krvnog pritiska kod trudnica sa hipertenzijom. Kardioselektivni β blokator atenolol treba izbegavati u trudnoći jer dovodi do sniženja telesne težine na rođenju i smanjenja fetalnog rasta. Upotreba ACE inhibitora i blokatora angiotenzinskih receptora je kontraindikovana u trudnoći. *Acta Medica Medianae 2008;47(3):65-72.*

***Ključne reči**: antihipertenzivni lekovi, hipertenzivni poremećaji, trudnoća*