Effect of antihypertensive therapy with alpha-methyldopa on umbilical artery Doppler in pregnancies with hypertensive disorders

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ABSTRACT

Aim To clarify whether applying alpha-methyldopa treatment influences flow resistance in umbilical cord artery in pregnant women suffering from hypertensive disorder.

Methods In this prospective cross-sectional study a follow-up was done for 50 pregnant women with singleton pregnancies between 36 and 40 gestation weeks, who had been hospitalized at the Gynecology and Obstetrics Department of the Cantonal Hospital Zenica, Bosnia and Herzegovina from October 2009 to January 2012. Pregnant women were classified in two groups according to the level of using alpha-methyldopa in the treatment. For all expectant mothers, flow in umbilical cord artery was measured, Resistance Index (RI) was determined and values were compared accordingly.

Results There was a statistically significant difference in values of umbilical artery resistance index (UA RI) in terms mother’s hypertension (p<0.05). Therefore, mothers with chronic hypertension had the highest UA RI (0.885±0.4), as well as mothers with preeclampsia superimposed on chronic hypertension (0.785±0.7), while mothers with gestational hypertension had the lowest UA RI (0.6413±0.13) (p<0.05). In mothers using the methyldopa UA RI was lower (0.6875±0.14) in comparison to those who did not use it (0.6686±0.13) but with no statistical significance (p>0.05).

Conclusion There was no change in flow resistance in umbilical cord artery in pregnant women suffering from hypertensive disorder.

Key words: ultrasonography, umbilical artery, pregnancy-induced hypertension
INTRODUCTION

Hypertension in pregnancy is a very important problem in perinatology. About 8% of all pregnancies are affected by high blood pressure difficulties (1). Direct consequence of hypertension for the baby originate from changes in blood vessels of the placenta in terms of obliteration, hyalinization, placcental infarction and thrombosis whereby nutritional and oxidation function of the placenta is weakened (1). The disease is primarily related to damage of the endothelium of blood vessels and leads to misbalance between humoral vasodilators (endothelium relaxing factor, nitric oxide, prostacyclin) and vasoconstrictors (endothelin, thromboxane, angiotensin and lipid peroxides) in favor of factors of vasoconstriction (2). Reduced flow through the placenta affects the increase of resistance in the umbilical cord artery. Using color Doppler ultrasound it is possible to study precisely these hemodynamic changes in utero-placenta and fetal bloodstream (3).

For a long period of time, it seemed that the umbilical cord artery was most appropriate for detecting chronic placental insufficiency and projection of suspicious and pathological changes in cardiotocography (CTG) record during pregnancy and delivery (4). Bekedam et al. proved that the period from the occurrence of shortage of diastole flow through the umbilical cord until the occurrence of late decelerations in cardiograph record lasts for approximately 12 days with the span of 0-49 days (5).

Unfortunately, despite numerous efforts, the cause of preeclampsia is still unknown while existing theories only partially explain its formation and the present studies prove that presence of trophoblastic tissue in mother’s body makes a backbone of pathophysiological event (6).

Methyldopa is most frequently used hypertensive medicament during pregnancy. It belongs to the group of central hypertensive medicaments (7). It stimulates receptors in the brain that regulate decrease of tonus of sympathetic nervous system and thereby reduces increased blood pressure (7).

The aim of this study was to clarify whether applying alpha-methyldopa treatment influences flow resistance in navel cord artery in pregnant women suffering from hypertensive disorder.

PATIENTS AND METHODS

This prospective study monitored 50 pregnant women with hypertensive disorder with singleton pregnancies, between 36 and 40 gestation weeks, and pregnant women with intrauterine growth restriction (IUGR) hospitalized at the Gynecology and Obstetrics Department, Cantonal Hospital Zenica, Bosnia and Herzegovina, from October 2009 to January 2012. The approval of the Ethics Committee of the Cantonal Hospital Zenica was obtained prior to initiation of the study, and all patients signed informed consents.

A selection of patients was done based on parity and age and they were classified according to hypertension level into chronic hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension and gestational hypertension according to the criteria provided by the American Gynecological & Obstetrical Society (8,9). Pregnant women were classified in two groups according to hypertension therapy. The first group comprised the patients who had undergone methyldopa treatment. Criteria for applying methyldopa included blood pressure values of 140-155/90-105 mmHg measured twice in an interval of four to six hours. The second group comprised the patients with some level of clinical hypertension defined but for unknown reasons those women had not undergone the methyldopa treatment prior to hospitalization. It is important to note that the second group of pregnant women mostly came to the hospital for gynecological examination for the first time in their pregnancy. Pregnant women, who, in addition to methyldopa, took alternative hypertensive medicaments due to blood pressure deterioration, were excluded from the study. Umbilical cord flow was measured in all patients and Resistance Index (RI) was determined and values were compared. Hemodynamic examination was done by applying pulse color Doppler ultrasound with transabdominal probe of 5 Mhz (MEDISON SA-6000C Color Doppler Ultrasound, South Korea).

In statistical analysis, parameters of descriptive statistics were defined using an absolute number of cases, relative number of cases (percentages, arithmetic mean with standard deviation and standard error, as well as span of value). For examination of statistical significance, one-way analysis of variance (ANOVA) tests with the level p<0.05 was used.
RESULTS

Pregnancy was most often represented with the first pregnancy, in 34 (68%) cases, in 10 (20%) cases it was the second pregnancy. Most frequent hypertension type in pregnancy was gestational hypertension, 23(46%), followed by preeclampsia, 19 (38%). Mothers with preeclampsia were the oldest, 30.16 (±6.3) years of age, while the youngest were mothers with gestational hypertension, 26.3 (%±6.1) years of age. Concerning the hypertension therapy, 28 % of patients did not take therapy prior to the present hospitalization and their first gynecological examination was either because of complications and/or delivery. Mostly, those were patients from rural areas (Table 1).

Table 1. Index values according clinical hypertension type

<table>
<thead>
<tr>
<th>Umbilical artery resistance index</th>
<th>N</th>
<th>AM</th>
<th>SD</th>
<th>SEM</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>2</td>
<td>0.8550</td>
<td>0.03536</td>
<td>0.02500</td>
<td>0.36</td>
<td>0.91</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>19</td>
<td>0.6779</td>
<td>0.16568</td>
<td>0.03801</td>
<td>0.34</td>
<td>0.99</td>
</tr>
<tr>
<td>Preeclampsia SPH</td>
<td>6</td>
<td>0.7850</td>
<td>0.07148</td>
<td>0.02918</td>
<td>0.70</td>
<td>0.88</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>23</td>
<td>0.6413</td>
<td>0.12920</td>
<td>0.02694</td>
<td>0.46</td>
<td>0.97</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>0.6822</td>
<td>0.14796</td>
<td>0.02092</td>
<td>0.34</td>
<td>0.99</td>
</tr>
</tbody>
</table>

UA RI, umbilical artery resistance index; N, total number of samples; AM, arithmetic mean; SD, standard deviation; SEM, standard arithmetic mean error; Min, minimum; Max, maximum; Preeclampsia SPH, preeclampsia superimposed on chronic hypertension.

There was a statistically significant difference in RI UA (AU) values in terms of mother’s hypertension (p<0.05). Therefore, mothers with chronic hypertension had the highest RI UA values (0.885±0.4), as well as mothers with preeclampsia superimposed on chronic hypertension (0.785±0.7), while mothers with gestation hypertension had the lowest values (0.6413±0.13).

The mothers’ sonogram was subnormal in preeclampsia superposed on chronic hypertension, in five (83.3%), and abnormal in mothers with chronic hypertension, in one (out of two) woman (p<0.05) (Table 2).

Table 2. Sonogram of mothers with hypertension

<table>
<thead>
<tr>
<th>No (%) of women with hypertension type</th>
<th>Chronic hypertension</th>
<th>Preeclampsia</th>
<th>Preeclampsia SPH</th>
<th>Gestational hypertension</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>0 (52.6)</td>
<td>0</td>
<td>17 (73.9)</td>
<td>27 (54.0)</td>
<td></td>
</tr>
<tr>
<td>Sub abnormal</td>
<td>1 (26.3)</td>
<td>5 (83.3)</td>
<td>2 (8.7)</td>
<td>13 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>4 (21.1)</td>
<td>1 (16.7)</td>
<td>4 (17.4)</td>
<td>10 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2 (19)</td>
<td>6</td>
<td>23</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

preeclampsia SPH, preeclampsia superimposed on chronic hypertension;

Intrauterine growth restriction was present in 17 (34%) patients with hypertension, in all patients with severe clinical types of hypertension. Analysis of RI UA with regard to applying methyldopa was lower (0.6875±0.14) in mothers who took methyldopa in comparison to those who did not use it (0.6686±0.13) (p>0.05) (Table 3).

Table 3. Umbilical artery resistance index value according to applied therapy

<table>
<thead>
<tr>
<th>Umbilical artery resistance index</th>
<th>N</th>
<th>AM</th>
<th>SD</th>
<th>SEM</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No applied therapy</td>
<td>14</td>
<td>0.6686</td>
<td>0.13917</td>
<td>0.03719</td>
<td>0.46</td>
<td>0.87</td>
</tr>
<tr>
<td>Applied therapy</td>
<td>36</td>
<td>0.6875</td>
<td>0.15281</td>
<td>0.02547</td>
<td>0.34</td>
<td>0.99</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>0.6822</td>
<td>0.14796</td>
<td>0.02092</td>
<td>0.34</td>
<td>0.99</td>
</tr>
</tbody>
</table>

N, total number of samples; AM, arithmetic mean; SD, standard deviation; SEM, standard arithmetic mean error; Min, minimum; Max, maximum;

DISCUSSION

All hypertensive disorders in pregnancy are associated with increased risk for the mother’s health and baby’s growth, but specific conclusions related to parity of potential benefits/risks caused by applying antihypertensive therapy in pregnancy are still not completely defined (7). Methyldopa is the most frequently prescribed drug and the first-choice treatment of hypertension in pregnancy (l0). Mutch et al. declared no significant differences in terms of babies’ weight at birth, neonatal complications and development during the first year of life in children exposed to methyldopa treatment during mother’s pregnancy compared to a placebo group (11).

It is a common opinion that the age of a pregnant woman plays an important role in the occurrence of preeclampsia, although some studies reject such a relation. A study done in the USA showed that after the age of 34, the risk of preeclampsia increases for 30 % with each following year (12) The results of this study confirmed the results of some previous studies (13,14) that the age is an important factor for the appearance of gestosis. A study from Saudi Arabia showed a frequency of nulliparous women in the population of pregnant women with preeclampsia of 40.2 % (14). Prevalence of nulliparous women in our research was 68%, which is three times higher than with second pregnancies. This could be explained by the fact that an exposure of fetal trophoblast to mother’s immunology system and its unmatched response can partially influence the gestosis appearance (15).

The most common type of hypertension in this research was gestation hypertension (46%), followed by preeclampsia (38 %). This study has proved that the highest RI UA index values were
found in fetuses with IUGR, supporting the thesis that Color Doppler sonography could successfully differentiate fetoplacental insufficiency. Pregnant women with hypertension, without intrauterine growth retardation had physiological UA RI values. Similar results were presented by Stamenovic et al. and Radovic et al., as well as other authors (16-18).

The results of this study have shown that circulation in umbilical cord artery is a valuable parameter for an estimation of fetus condition in pregnant women with hypertension. There was some disagreement about the effect of anti-hypertensive therapy on uteroplacental circulation. Therefore, a study of Gunecet al. done in Turkey confirmed that in pregnancies with preeclampsia, application of methyldopa therapy starting with one gram/day had demonstrated significantly lower resistance in uterine artery, but it was not valid for umbilical cord artery and medium brain artery. It is confirmed that not only does the methyldopa therapy improve the flow in umbilical cord artery, it also treats hypertension and prevents its complications (19).

With severe preeclampsia, therapy of MgSO4 of 6 gr. i.v. reduces the RI in uterine umbilical and medium brain arteries (20). Rytlewski et al. study proved that following a three-week oral use of 3g L-arginine as a supplement to standard therapy, a RI decreased in umbilical circulation and increased in cerebral circulation of the fetus in patients with preeclampsia (21). Preliminary researches show that substitution therapy with amino acid aimed at fixing the placenta perfusion before ending pregnancy of women suffering from preeclampsia would have a lot of significance (21). Khalil et al. study proved that resistance in uterine artery did not change if a woman was on methyldopa therapy in case of hypertensive illness in pregnancy (22). Some authors have noted that folic acid as a supplement can improve utero-placenta flow to a small extent in case of hypertension in pregnancy (23).

In conclusion, there were no significant changes of resistance through the placenta in patients who had used methyldopa therapy. The therapy treatment of the mother is not beneficial only for the fetus but also reduces complications of mother’s hypertension. The inclusion of substitution therapy that would possibly reduce oxidative stress of the placenta should be considered, as well as a check-up of any hemodynamic changes in placental circulation.

FUNDING
No specific funding was received for this study.

TRANSPARENCY DECLARATION
Competing interests: non to declare.

REFERENCES
Utjecaj primjene metildope na protok u pupčanoj arteriji ploda kod hipertenzivne bolesti trudnice

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SAŽETAK

Cilj Utvrditi utjecaj primjene metildope na otpor protoka krvi u pupčanoj arteriji kod hipertenzivne bolesti trudnice.


Rezultati Ustanovljena je statistički značajna razlika u vrijednosti indeksa resistencije pupčane arterije (RI AU) prema tipu hipertenzije majke (p<0,05). Tako su majke s hroničnom hipertenzijom u prosjeku imale najviše vrijednosti RI AU (0,885±0,4), kao i majke s preeklampsijom superponiranoj na hroničnu hipertenziju (0,785±0,7), dok su majke s gestacijom hipertenzijom imale najniže vrijednosti (0,6413±0,13) (p<0,05). Analiza RI AU-a prema uzimanju metildope pokazala je da je, u prosjeku, ako su majke uzimale metildopu, RI AU bio niži (0,6875±0,14) u odnosu na one koje nisu uzimali (0,6686±0,13), ali bez statistički značajne razlike (p>0,05).

Zaključak U studiji nije ustanovljena promjena otpora protoka krvi u pupčanoj arteriji ploda kod hipertenzivne bolesti trudnice liječenjem metildopom.

Ključne riječi: ultrasonografija, umbilikalna arterija, hipertenzija indukovana trudnoćom