A randomized trial of plasma volume expansion in hypertensive disorders of pregnancy: influence on the pulsatility indices of the fetal umbilical artery and middle cerebral artery


*WG and AR are co-first authors, as they contributed equally to this work
Summary

OBJECTIVE: The purpose of this study was to investigate the effect of plasma volume expansion on pulsatility indices of the fetal umbilical and middle cerebral arteries.

STUDY DESIGN: Two hundred sixteen patients with severe preeclampsia, HELLP (hemolysis elevated liver enzymes low platelet count) syndrome, eclampsia, hypertension-related fetal growth restriction, and gestational ages between 24 and 34 completed weeks were assigned randomly for temporizing treatment with plasma volume expansion (n = 111 patients; 250 mL hydroxyethylstarch 6% twice daily in 4 hours, and NaCl 0.9% between doses of hydroxyethylstarch and with intravenous medication) or without plasma volume expansion (n = 105 patients; only NaCl 0.9% when necessary with medication). Measurements of the pulsatility index of the umbilical and middle cerebral arteries were performed at admission, after 16 to 48 hours, 60 to 120 hours and 7 to 11 days.

RESULTS: Median gestational age was 30 weeks in both groups. Infused volumes of plasma volume expansion in the treatment group (total median 813 mL/day) were associated with a significant decrease of hemoglobin concentration. Changes from baseline measurements of the umbilical and middle cerebral arteries were not different between the groups nor within subgroups during the first 7 to 11 days.

CONCLUSIONS: Plasma volume expansion did not influence the pulsatility indices of the umbilical and middle cerebral arteries.
Introduction

Temporizing management in pregnancies that are complicated by hypertensive disorders (preeclampsia, HELLP [hemolysis elevated liver enzymes low platelet count] syndrome, pregnancy induced hypertension and associated fetal growth restriction) remote from term might benefit neonatal outcome,\textsuperscript{1,2} without increasing maternal risk for adverse outcome.\textsuperscript{3-5} Several aspects of temporizing management remain subject to debate. Whether or not to correct the observed hypovolemia with plasma volume expansion (PVE) is 1 of the topics.\textsuperscript{6-8} It is suggested that PVE improves hemodynamic characteristics and organ function and benefits neonatal outcome,\textsuperscript{9-11} although adverse maternal effects (eg, pulmonary edema) have been described.\textsuperscript{8}

Doppler blood flow velocity measurements of the fetal umbilical artery and middle cerebral artery are parameters that are used to assess fetal well-being. Absent or reversed end-diastolic flow (EDF) in the umbilical artery is usually progressive, with the reduction, loss, and eventually reversal of EDF,\textsuperscript{12} and is significantly associated with increased perinatal mortality and morbidity rates.\textsuperscript{13,14} A few studies observed improvement of fetal Doppler blood flow velocimetry of the umbilical artery after PVE, although these studies lacked a properly selected control group.\textsuperscript{9,11} The brain-sparing effect, described by the ratio between blood flow velocity of the umbilical artery and of the middle cerebral artery (U/C-ratio) reflects a change in cerebral hemodynamics to prevent fetal cerebral hypoxia.\textsuperscript{15} No studies to date have focused on the effect of PVE on the middle cerebral artery. We report changes in the pulsatility index (PI) of the umbilical and middle cerebral arteries during PVE in a randomized clinical trial.

Methods

All consecutive women presenting at a gestational age between 24 and 34 completed weeks who were referred to the Departments of Obstetrics of the Academic Medical Center and the VU University Medical Center between April 1, 2000 and May 31, 2003, were invited to participate in the trial if they met the inclusion criteria (Table I).\textsuperscript{16-18} Both university hospitals are located in Amsterdam, The Netherlands and serve as tertiary care centers for a community of approximately 2.5 million inhabitants. All patients who were included fit at least one of the diagnostic criteria. Patients with eclamptic convulsions were only assigned randomly if a stable situation could be maintained and if further prolongation of pregnancy was attempted.

We excluded patients from being assigned randomly if they refused to participate, if there were signs of fetal distress at admission, if a diagnosis of lethal fetal congenital abnormalities had already been made at admission, or if language difficulties prohibited
informed consent. Antihypertensive or magnesium sulphate treatment was allowed before assignment, but we excluded women who had been given PVE. Excluded patients received no PVE.

**Table I. Criteria for inclusion into the trial**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Explanation</th>
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<tr>
<td>HELLP syndrome&lt;sup&gt;17&lt;/sup&gt;</td>
<td>platelet count &lt;100 X 10&lt;sup&gt;9&lt;/sup&gt;/L and aspartate aminotransferase ≥70 U/L and/or lactic dehydrogenase ≥600 U/L</td>
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<tr>
<td>Fetal growth restriction and pregnancy induced hypertension&lt;sup&gt;16,18&lt;/sup&gt;</td>
<td>abdominal circumference &lt;5th percentile for gestational age or estimated fetal weight &lt;10th percentile for gestational age (ultrasound) and diastolic blood pressure ≥90 mm Hg</td>
</tr>
<tr>
<td>Severe preeclampsia&lt;sup&gt;16&lt;/sup&gt;</td>
<td>diastolic blood pressure ≥110 mm Hg and proteinuria (≥0.3 g/24 hr)</td>
</tr>
<tr>
<td>Eclampsia&lt;sup&gt;16&lt;/sup&gt;</td>
<td>generalized convulsions in pregnancy that were not caused by epilepsy</td>
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Gestational age was determined by the first day of the last period, which was verified in almost all cases by a first-trimester ultrasound dating scan. At all hours, 1 of the authors (WG or AR) assessed eligibility, sought informed consent and randomly assigned patients on a designated palmtop computer with random number generation software, within two strata of gestational age (between 24 weeks and 29<sup>6/7</sup> of gestation, between 30 weeks and 33<sup>6/7</sup> of gestation). The medical ethics committees of both hospitals approved the study. Maternal and perinatal outcomes of the study are reported separately. A specific objective was to report on the effect of PVE on the pulsatility indices of the umbilical and middle cerebral artery.

**Treatment procedures**

In both groups, magnesium sulphate therapy was used for prevention or treatment of eclampsia. One course of corticosteroid therapy with intramuscular betamethasone was given when delivery was considered imminent. In the management with PVE (treatment group) a dose of 250 mL hydroxyethylstarch 6% (200/0.5) was given twice daily in two periods of 4 hours (8:00 until 12:00 AM and PM). NaCl 0.9% was infused in-between doses of hydroxyethylstarch and with intravenous medication. A subgroup of 9 patients with severe preeclampsia and gestational age of <30 completed weeks was treated with PVE under invasive hemodynamic monitoring. Antihypertensive treatment was used to achieve a target diastolic blood pressure between 85 and 95 mm Hg. The drug of first choice was ketanserin intravenously. Additional medication (oral labetalol, α-methyldopa, and nifedipine; incidentally intravenous dihydralazine) was used when necessary. In the treatment without PVE (control group) antihypertensive treatment was targeted to achieve a diastolic blood pressure between 95 and 105
mm Hg as target. The drug of first choice was α-methyldopa. Additional medication (oral labetalol, nifedipine, and intravenous ketanserin) was used when necessary. Restricted amounts of NaCl 0.9% were infused with intravenous medication. The different blood pressure target ranges and choice of medication between groups reflect the hypothesized mode of action of PVE. According to this theory, PVE allows more aggressive antihypertensive treatment, which may reduce the risk of maternal eclampsia or HELLP syndrome, without increasing the risk for hypotensive episodes, which might induce fetal distress. In treatment without PVE, higher blood pressures have to be accepted necessarily, and treatment is instituted more gradually to prevent hypotension by overshoot of antihypertensive medication. In practice, diastolic blood pressure after stabilization in both types of management is 95 mm Hg on average, and combination therapy is frequent.

Fetal heart rate tracings were performed twice daily. Fetal indications for delivery were repeated decelerations or prolonged poor variability on fetal heart rate tracings. Absent or reversed EDF in the umbilical artery was sometimes the indication to start corticosteroid treatment but was never the sole indication for delivery. The measurements of the middle cerebral artery were solely descriptive of nature and did not influence timing of delivery.

**Study procedures**

Ultrasonographic assessment was performed at inclusion in the study and was repeated after 16 to 48 hours, 60 to 120 hours, and 7 to 11 days after randomization and subsequently twice weekly. Different available machines (ATL 3000, ATL 5000 Philips Medical Systems, Best, The Netherlands), ALOKA 1700; Zug, Switzerland) with pulsed and color Doppler blood flow technology were used. They were operated principally by 2 of the authors (WG and AR) but, for logistic reasons, other operators performed the procedure in some cases. At all sessions, Doppler blood flow velocity waveforms were recorded in the umbilical artery in a free-floating loop of the mid section of the umbilical cord and of the middle cerebral artery just past the level of the bifurcation of the internal carotid artery (Circle of Willis) into the anterior and middle cerebral artery. The PI was calculated from a series of uniform blood flow velocity waveforms with a high signal-to-noise ratio. The presence, absence or reversal of EDF in the umbilical artery was recorded. The umbilical/cerebral ratio was calculated as the ratio of the umbilical artery PI divided by the middle cerebral artery PI. Fetal biometry was measured once a week. The Hadlock IV formula was used to estimate fetal weight. The estimated fetal weight-ratio was calculated as the ratio of the estimated fetal weight divided by the expected fetal weight for gestational age, adjusted for maternal weight, height,
ethnic group and parity (the Gardosi customized growth chart p50-value).\textsuperscript{18} Amniotic fluid index was measured by dividing the abdomen in 4 quadrants and assessing the largest vertical diameter in each. If the cord was visible, the largest vertical diameter to the cord was taken.\textsuperscript{23} The hemoglobin concentration was determined twice a week.

Because the normal distribution of the PIs of the umbilical artery and middle cerebral artery change with gestational age, measurements at baseline were normalized by expressing them as a ratio of the measured value divided by the mean value for gestational age.\textsuperscript{24,25} To compare changes over time, we calculated the individual absolute differences between later measurements and the measurements at admission. Statistical analysis was performed by non-parametric Mann-Whitney tests with SPSS software (version 11.0; SPSS Inc, Chicago Illinois). Differences were considered statistically significant at probability values \( P < .05 \). The null-hypothesis was that no differences in umbilical artery or middle cerebral artery PI would be detected between the 2 groups. To identify subgroups that would specifically benefit from PVE, post-hoc subgroup analysis was planned for patients included before or after 30 weeks of gestational age or with an initial diagnosis of HELLP syndrome enzymes, severe preeclampsia, or fetal growth restriction. An additional subgroup analysis was performed on groups with PIs of the umbilical artery higher than the 95th percentile for gestational age and on groups with the lowest and highest one-third hemoglobin concentrations on admission.

\section*{Results}

During the study period, 216 patients were assigned randomly; 111 patients were assigned to the treatment group, and 105 patients were assigned to the control group. We excluded 2 cases (1 case from each randomization group) because of unanticipated significant congenital malformations at birth. One infant had trisomy 13 and died 1 day after birth. The other infant had numerous dysmorphic features (no specific diagnosis made) and died 59 days after birth from pulmonary disease. At 16 to 48 hours, 100 patients in the control group were undelivered and measured \textit{versus} 102 in the treatment group; at 60 to 120 hours the groups numbered 80 \textit{versus} 81, and at 7 to 11 days the groups numbered 64 \textit{versus} 55 patients, respectively.

All baseline characteristics were comparable between both randomization groups (Table II), although there was a small, nonsignificant imbalance at baseline in the umbilical artery PI (median normalized value, 1.2 in the control group \textit{versus} 1.3 in the treatment group) and in estimated fetal weight (median, 1146 \textit{versus} 1076 g). After 60 to 120 hours and 7 to 11 days, the hemoglobin concentration was reduced
significantly in the treatment group in comparison with the control group (median -0.6 mmol/L versus -0.2 mmol/L at 7 to 11 days; P < .01, Figure 1, A). This correlated with the difference in infused volumes (median, 813 mL/d; range, 0-2143 mL/d versus 13 mL/d; range, 0-1404 mL/d, respectively).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group</th>
<th>Treatment group</th>
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<tbody>
<tr>
<td>Maternal age (y)*</td>
<td>30.9 (20-41)</td>
<td>28.9 (18-41)</td>
</tr>
<tr>
<td>Nulliparity (n)</td>
<td>69 (66%)</td>
<td>80 (73%)</td>
</tr>
<tr>
<td>Non-white (n)</td>
<td>28 (27%)</td>
<td>31 (28%)</td>
</tr>
<tr>
<td>Chronic hypertension (n)†</td>
<td>32 (31%)</td>
<td>37 (34%)</td>
</tr>
<tr>
<td>Gestational age at inclusion (wk)*</td>
<td>30.0 (24.1-33.9)</td>
<td>29.9 (24.3-33.7)</td>
</tr>
<tr>
<td>Severe PE at inclusion (n)‡</td>
<td>43 (41%)</td>
<td>52 (47%)</td>
</tr>
<tr>
<td>HELLP at inclusion (n)‡</td>
<td>27 (26%)</td>
<td>27 (25%)</td>
</tr>
<tr>
<td>FGR at inclusion (n)‡</td>
<td>56 (54%)</td>
<td>67 (61%)</td>
</tr>
<tr>
<td>Eclampsia at inclusion (n)‡</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hemoglobin concentration at inclusion (mmol/L)</td>
<td>7.7 (6.2-9.4)</td>
<td>7.8 (6.0-9.9)</td>
</tr>
<tr>
<td>Umbilical artery at inclusion (Pl)*§</td>
<td>1.19 (0.64-3.40)</td>
<td>1.31 (0.63-4.48)</td>
</tr>
<tr>
<td>Positive EDF (n)</td>
<td>84 (81%)</td>
<td>80 (73%)</td>
</tr>
<tr>
<td>Absent EDF (n)</td>
<td>16 (15%)</td>
<td>24 (22%)</td>
</tr>
<tr>
<td>Reversed EDF (n)</td>
<td>4 (4%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Middle cerebral artery (Pl)*§</td>
<td>0.79 (0.48-1.30)</td>
<td>0.73 (0.45-1.28)</td>
</tr>
<tr>
<td>Umbilical/cerebral ratio*</td>
<td>0.87 (0.30-3.60)</td>
<td>1.04 (0.45-5.03)</td>
</tr>
<tr>
<td>Estimated fetal weight (g)*</td>
<td>1146 (453-2401)</td>
<td>1076 (298-2257)</td>
</tr>
<tr>
<td>Estimated fetal weight ratio*</td>
<td>0.72 (0.48-1.02)</td>
<td>0.70 (0.32-1.17)</td>
</tr>
<tr>
<td>Amniotic fluid index*</td>
<td>9.6 (2.5-20.5)</td>
<td>9.3 (0.0-16.7)</td>
</tr>
</tbody>
</table>

* Values are expressed as median (range).
† Antihypertensive medication and/or persistent systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg at 3 months after term age.
‡ Some patients match more than one inclusion diagnosis.
§ Normalized value for gestational age.24,25

There were no statistically significant differences between the groups in the changes in measurement results of the umbilical artery PI and middle cerebral artery PI, amniotic fluid index, and estimated fetal weight during the first 7 to 11 days (Figure 1, B-E). Subgroup analysis revealed no differences between control and treatment group in
Figure 1. Box plot of changes from baseline in measurements of the hemoglobin concentration (A), the PI of the umbilical artery (B), the PI of the middle cerebral artery (C), the estimated fetal weight (D), and the amniotic fluid index (E) in the control group (white box plots) and the treatment group (gray box plots) at 16 to 48 hours (100 versus 102 patients), 60 to 120 hours (80 versus 81 patients), and 7 to 11 days (64 versus 55 patients). The asterisk denotes statistical significance at a probability value of <.05.
subgroups of gestational age below or above 30 weeks at enrollment or with an initial diagnosis of HELLP syndrome, severe preeclampsia or fetal growth restriction. Also, within the subgroup with a high PI of the umbilical artery at entry of the study, changes from baseline value were not influenced by PVE (Figure 2). Both patients with the highest one-third hemoglobin concentration and patients with the lowest one-third hemoglobin concentration had a significant reduction in hemoglobin concentration after 60 to 120 hours and after 7 to 11 days in the treatment group than in the control group; this effect was greater in patients with the highest concentrations at baseline evaluation. Within these groups, all other measurement results, however, were comparable between treatment and control groups. Among patients with positive EDF at baseline in the treatment group, 17% of patients (14/80) developed absent or reversed EDF before delivery versus 14% of patients (12/84) in the control group. Among patients with absent or reversed EDF at baseline in the treatment group, positive EDF was seen at later measurements in 30% of patients (9/30) versus 45% of patients (9/20) in the control group. This changed back before delivery to absent or reversed EDF in 44% of patients (4/9) in the treatment group and in 56% of patients (5/9) in the control group.

**Comment**

This randomized clinical trial has been the largest trial on PVE for hypertensive disorders of pregnancy so far. All studied effect parameters were equal in both groups and within subgroups during the first 11 days.
Although Doppler parameters were never the sole indication for delivery, patients with worse Doppler parameters may have been delivered earlier. This could have lead to improved average values in the remaining group. To address this type of selection bias and to address the observed slight random imbalance at admission, we presented intra-individual changes, using each patient as her own control.

Our findings disagree with the results of Karsdorp et al.\textsuperscript{11} who reported the reappearance of end-diastolic velocities, and a decrease in the PI of 0.5 in the umbilical artery and an improvement in the survival rate in a historical comparison on a group of 14 patients after maternal PVE (250-1500 mL polygeline initially, subsequently 750 mL daily). With our sample size, we could have detected a difference of 0.25 (\(\beta = .8; \alpha = .05\)). Our findings also contradict the results of Hubner and Sander,\textsuperscript{9} who treated a cohort of 48 patients with PVE (500 mL hydroxyethyl starch [200/0.5] 10\% combined with 500 mL Ringer’s lactate daily) and demonstrated a correlation between a decrease of hematocrit level and normalization of Doppler results (Figure 2). Moreover, we could not confirm earlier observations that PVE improves fetal growth.\textsuperscript{9,26}

In other studies, comparable amounts of infused volumes were given.\textsuperscript{9,11} We observed a concomitant significant decrease in the hemoglobin concentration that was also comparable to other studies.\textsuperscript{9,26} We opted for hemoglobin concentration as a proxy for volume expansion because it is easy to obtain, even outside office hours. Other noninvasive parameters are doubtfully better at reflecting intravascular volume, and not as readily available. Because benefits of invasive hemodynamic monitoring are currently under scrutiny, and with potential medical disadvantages in mind, we limited invasive hemodynamic management to 9 patients with low gestational ages and severe maternal disease.\textsuperscript{27} Hence, in most cases, we administered fixed volumes daily. Insufficient PVE in individual patients may have contributed to our results, but, as we observed, a significant average decrease in hemoglobin concentration occurred with this strategy. Therefore, we assume that, on average, a concomitant relevant increase in plasma volume was effected. The slightly different antihypertensive management between the groups reflects the hypothesized mode of action of PVE, and this trial should be considered to compare an entire management strategy with and without PVE.

Patients with different characteristics (fetal growth restriction, HELLP syndrome, preeclampsia) might differentially benefit from PVE, because pathophysiologic conditions might be different. Even within each category, causal pathways may be heterogeneous, and overlap within patients is frequent. To optimize generalizability of the study, we chose to include women across the spectrum of preeclampsia and opted for a PVE protocol that could be easily implemented in clinical practice. Subgroup
analysis identified no subgroup that might have changes differentially in the umbilical or middle cerebral artery, that were induced by PVE.

Benefits of treatment with PVE may not be reflected by changes in flow characteristics of the umbilical artery and middle cerebral artery, which are parameters associated with fetal condition. Long-term neonatal neurological development may better testify to the quality of fetomaternal transfer of nutrients, oxygen and waste products in the placenta.

In this randomized clinical trial, PVE decreased hemoglobin concentration but had no effect on Doppler blood flow velocimetry of the umbilical and middle cerebral arteries, amniotic fluid index, or fetal growth.
Reference List


