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Medical treatment of early-onset mild gestational hypertension reduces total peripheral vascular resistance and influences maternal and fetal complications

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KEYWORDS: echocardiography; hemodynamics; pre-eclampsia/pregnancy; therapy

ABSTRACT

Objective *Complications in early-onset mild gestational hypertension (GH) are better predicted by total peripheral vascular resistance (TPVR) > 1350 dyne than by blood pressure. We therefore aimed to assess the possible reduction of severe complications by lowering TPVR with nitric oxide (NO) donors, oral fluids and standard antihypertensive therapy in women with early-onset mild GH.*

Methods *A group of 400 patients with early-onset (20–27 weeks' gestation) mild GH (systolic and diastolic blood pressure < 170/110 mmHg) and TPVR > 1350 dyne were enrolled in a prospective non-randomized trial with sequential allocation: 100 patients were treated with nifedipine (Group A); 100 with nifedipine and NO donors (Group B); 100 with nifedipine and oral fluids (Group C); and 100 with nifedipine, NO donors and oral fluids (Group D). TPVR was checked 1 month after initiation of therapy, and the number of patients with severe maternal and fetal complications was recorded in each group. The relationship between reduction in TPVR and the frequency of severe complications was assessed.*

Results *Severe complications developed in 51% of patients in Group A, 48% in Group B, 53% in Group C and 35% in Group D, the frequency in Group D being significantly lower than that in the other treatment groups (*$P < 0.05$*). A reduction in TPVR of < 15% predicted the occurrence of severe complications with sensitivity 95.2% and specificity 88.3%. In Group D a reduction in TPVR of ≥ 15% was more probable (odds ratio* (OR) $= 2.03$*; 95% CI, 1.15–3.60;* $P < 0.015$*) and severe complications were less probable (*OR $= 0.52$*; 95% CI, 0.29–0.91;* $P < 0.023$*).*

Conclusion *In women with early-onset mild GH, combined treatment with NO donors, oral fluids and nifedipine optimally reduces TPVR and seems to reduce maternal and fetal complications. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

To date, the goal of pharmacological treatment for mild gestational hypertension (GH) has been the lowering of blood pressure (BP) to prevent or delay progression to more severe disease, and thereby improve outcome[1–3]. In particular, antihypertensive medication, such as beta-blockers, seems to be associated with a reduction in neonatal respiratory distress syndrome and in the progression to severe hypertension[1–3]. Although the observation of mildly elevated systolic and diastolic BP without proteinuria early in pregnancy is usually associated with a normal evolution of pregnancy, some patients with such characteristics do go on to develop complications[4–6]. Therefore, BP values alone appear to be insufficient to identify patients who will develop complications and those who will not[5–7].

Some researchers have used maternal hemodynamics as a target of therapy in GH[8–10], with promising results. In particular, Chaffin *et al.*[10] found that pharmacological modulation of maternal hemodynamics might improve pregnancy outcome, and that an elevated total peripheral vascular resistance (TPVR) is associated with worse

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outcomes compared with a hyperdynamic state. Several reports have shown that the observation of TPVR > 1350 dyne often precedes the development of complications both in normotensive and in hypertensive patients[5,6,11], suggesting a key role of this parameter in the early identification of high-risk patients[5,6,11].

Most studies on the administration of nitric oxide (NO) donors during pregnancy have focused on the effects of these drugs on BP without considering the effects on cardiac output (CO) and TPVR, making it difficult to evaluate its real benefit with respect to maternal hemodynamics[12]. Recently we noted that the addition of plasma volume expansion and NO donors to antihypertensive therapy in GH patients with severe fetal growth restriction could enhance maternal and fetal hemodynamics, improving pregnancy outcome[12].

From this experience, we hypothesized that modulation of TPVR might affect pregnancy outcomes more than lowering the BP alone, and that a combination of antihypertensive drugs, NO donors and fluid therapy might influence TPVR more than antihypertensive drugs alone. Based on this we developed a non-randomized trial to assess the possible reduction in the progression to severe complications that might be achieved by lowering TPVR through the addition of NO donors and oral fluids to standard antihypertensive therapy in women with early-onset (20–27 weeks' gestation) mild GH (systolic and diastolic BP < 170/110 mmHg).

PATIENTS AND METHODS

This was a prospective non-randomized trial with sequential allocation of 400 women with mild GH recruited between 20 and 27 weeks of gestation. Inclusion criteria were: normal estimated fetal weight (> 10th percentile), fetal anatomy and umbilical artery Doppler; normal BP values before 20 weeks' gestation and 6 months postpartum; mild GH[13] at enrolment; absence of proteinuria on routine urinalysis and normal renal function (blood urea nitrogen and creatinine); and TPVR > 1350 dyne at diagnosis, which is predictive for complications[5,6,11]. Exclusion criteria were: undetermined gestational age; tobacco use; twin pregnancies; maternal heart disease; pre-existing maternal chronic medical problems such as pre-existing hypertension, renal or liver diseases, or autoimmune diseases; and chromosomal and/or suspected fetal abnormalities on ultrasound.

Over a 6-year period (2005–2010) 1357 hypertensive pregnant women were referred to the obstetrics outpatient clinic of Tor Vergata University. Patients meeting the inclusion criteria were enrolled in the study. For each patient enrolled in the first 'standard treatment' group (Group A), the next three patients similar in gestational age (difference of no more than 7 days), maternal age (± 1 year) and body mass index (BMI) (± 1 kg/m^2), were included in the second (Group B), third (Group C) and fourth (Group D) treatment groups, respectively. The process continued until 100 patients had been recruited into each group: 257 patients (64.3%) were seen by our outpatient clinic from the start of the first trimester and 143 patients (35.8%) were referred by other centers. Patients enrolled in Group A were treated with nifedipine, patients enrolled in Group B were treated with nifedipine and NO donors, patients enrolled in Group C were treated with nifedipine and oral fluids, and patients enrolled in Group D were treated with nifedipine, NO donors and oral fluids. A group of 100 normotensive patients was also enrolled.

Nifedipine was given orally to achieve a diastolic BP between 85 and 105 mmHg according to international guidelines[14,15]. Based on previous studies in non-pregnant women demonstrating that increasing oral intake of fluid by 2 L or more a day in addition to normal intake could reduce TPVR and increase stroke volume[16,17], the patients in Groups C and D were instructed to consume 2.5–3 L of fluid per day in addition to their normal intake before diagnosis. If clinical signs of pulmonary edema or echocardiographic signs of ventricular dysfunction (defined as a reduction of the ejection fraction (EF) of ≥ 5% or a reduction of the absolute value of the EF to ≤ 50%) were observed then the fluid treatment was discontinued[12]. Therapy with NO donors consisted of the use of transdermal patches of glycerine trinitrate at a dosage of 10 mg/24 h, which were utilized for 12 h a day to avoid tolerance.

Based on our clinical experience and on the recommendations made by respected authorities regarding treatment to lower the risk of developing severe hypertension[1–3], it was decided that it would be inappropriate to leave early-onset mild GH untreated; therefore, we did not enrol a control non-treated group.

Approval by the local Ethics Committee was obtained, and written informed consent was collected from all patients. GH was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[18].

Fetal ultrasound examination

For the ultrasound examinations, a 3.5-MHz sector ultrasound transducer was used with the high-pass filter set at 100 Hz. Fetal biometry and estimated fetal weight were assessed according to local reference values[19].

Maternal echocardiographic evaluation

The M-mode, two-dimensional (2D) and Doppler ultrasound maternal echocardiographic evaluation was performed, by a researcher blinded to the treatment, within 24 h from the diagnosis of hypertension and before the initiation of treatment, and was repeated every 7–10 days throughout the duration of therapy to calculate TPVR. Variables were evaluated according to the recommendations of the American Society of Echocardiography[20]. Stroke volume (SV) and CO were calculated from the aortic valve area, flow-velocity time integral and heart rate, as previously described[5,6,11,21].

At the end of the maternal echocardiographic examination, systolic BP and diastolic BP were measured from the brachial artery with a manual cuff. TPVR was calculated in dynes×s/cm^5 according to the following formula: TPVR= (mean BP (mm Hg)/CO (L/min)) × 80, where mean BP was calculated as: diastolic BP + (systolic BP – diastolic BP)/3.

Outcomes

The pregnancy was followed until term by an investigator who was blinded to the results of maternal echocardiography and treatment. The pregnancy was considered as severely complicated if mild GH progressed to one or more of the following: early-onset pre-eclampsia (before 34 weeks)[22] or severe pre-eclampsia (associated with fetal growth restriction, proteinuria > 1g/24h, BP > 160/110 mmHg) according to Society for Maternal–Fetal Medicine (SMFM)[23]; severe GH resistant to therapy (rise of BP to > 170/110 mmHg during maximized therapy); placental abruption; HELLP syndrome; fetal growth restriction (defined as a birth weight below the 10th percentile with umbilical artery pulsatility index above the 95th percentile)[5]; severe respiratory distress syndrome; and perinatal death. When other neonatal complications (such as necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis or anemia) developed in patients with intrauterine growth restriction (IUGR) these were recorded but patients were classified as IUGR to avoid duplicate counting of complications. Mild pre-eclampsia and mild-to-moderate neonatal respiratory distress syndrome were also noted but were not included in the severe complications.

Statistical analysis

Values are expressed as mean ± SD or as median (range). Comparisons among groups were performed using one-way ANOVA with Student–Newman–Keuls correction for multiple comparisons, and intragroup comparison between variables at diagnosis and 4 weeks after pharmacological intervention was performed using ANOVA for repeated measurements. A receiver–operating characteristics (ROC) curve was generated to find the best cut-off value for the prediction of severe complications based on the percentage reduction in TPVR after 4 weeks of therapy. Binary logistic regression analysis was used to evaluate the probability of a reduction in TPVR beyond the cut-off value identified for treatment Groups B, C and D in comparison with treatment Group A. The same analysis was used to evaluate the probability of progression to severe complications during pregnancy for Groups B, C and D in comparison with Group A.

The interobserver and intraobserver variability in our clinic for the echocardiographic parameters evaluated have been previously reported[5,6,11].

RESULTS

Table 1 reports the demographic and pregnancy characteristics of the study groups. Estimated fetal weight

Table 1 Demographic and pregnancy characteristics of the five groups included in the study ($n = 100$ for each)

Characteristic	*Normotensive group*	*Group A (nifedipine)*	*Group B (nifedipine+NO)*	*Group C (nifedipine+OF)*	*Group D (nifedipine+NO+OF)*
Maternal (at enrolment)					
Age (years)	34 (21–45)	34 (22–44)	34 (21–43)	34 (22–44)	34 (21–44)
Gestational age (weeks)	25 + 3 (20 + 5 to 27 + 0)	25 + 3 (20 + 6 to 27 + 0)	25 + 3 (21 + 0 to 27 + 0)	25 + 3 (20 + 6 to 27 + 0)	25 + 3 (20 + 6 to 27 + 0)
Prepregnancy BMI (kg/m^2)	22.5 (15.0–45.0)	22.5 (15.0–45.0)	23.0 (15.0–44.5)	22.0 (15.6–44.8)	22.5 (15.2–44.0)
Nulliparous	34	35	32	35	36
Fetal/neonatal					
Estimated fetal weight percentile at enrolment	40 (15–85)	31.0 (11–55)*	28.0 (11–56)*	31.0 (11–57)*	31.0 (11–55)*
Birth weight percentile at delivery	39 (14–90)	19.5 (7–58)*	19.5 (6–55)*	19.0 (6–55)*	28 (6–58)*†‡§
Gestational age at delivery (weeks)	39 + 3 (37 + 0 to 41 + 6)	35 + 3 (27 + 5 to 40 + 0)*	35 + 2 (26 + 4 to 40 + 0)*	35 + 2 (26 + 2 to 40 + 0)*	37 + 2 (28 + 3 to 40 + 0)*†‡§

Values are expressed as median (range) or %. *$P < 0.05$ *vs* normotensive group. Intergroup comparison, $P < 0.05$: †*vs* Group A; ‡*vs* Group B; §*vs* Group C. BMI, body mass index; OF, oral fluids (increased fluid intake of about 2.5–3L per day); NO, nitric oxide donor patches administered for 12 h per day.

percentile at enrolment was similar in the four treatment groups and lower compared with the normotensive group. Birth-weight percentile was lower in the four treatment groups compared with the normotensive group, although Group D showed a higher birth-weight percentile and an older gestational age at delivery in comparison with Groups A, B and C.

The complications observed in each treatment group are summarized in Table 2. No complications were observed in the normotensive women. The percentage of patients with complications in Group D (41%) was lower *vs* the percentage of patients with complications in Group A (72%, $P < 0.001$), Group B (66%, $P < 0.001$) and Group C (72%, $P < 0.001$). The percentage of patients with maternal complications in Group D (29%) was lower *vs* the percentage of patients with maternal complications in Group A (46%, $P = 0.02$), Group B (45%, $P = 0.03$) and Group C (48%, $P = 0.01$). The percentage of patients with late-onset or mild pre-eclampsia in Group D (5%) was lower *vs* the percentage of patients with late-onset or mild pre-eclampsia in Group A (16%, $P = 0.02$), Group B (15%, $P < 0.03$) and Group C (15%, $P < 0.03$). When considering only severe complications, the percentage of patients in Group D (35%) was lower compared with the percentage of patients in the other groups (Group A, 51%, $P < 0.05$; Group B, 48%, $P < 0.05$; and Group C, 53%, $P < 0.05$).

Table 3 shows the hemodynamic parameters at enrolment and 4 weeks after initiation of therapy in each group. A 4-week cut-off was chosen arbitrarily for evaluating therapeutic effects and BP stabilization. If patients were

Table 2 Maternal and fetal/neonatal complications that developed in each treatment group

Complication	*All four groups*	*Group A (nifedipine)*	*Group B (nifedipine+NO)*	*Group C (nifedipine+OF)*	*Group D (nifedipine+NO+OF)*
Maternal	168	46	45	48	29
Late-onset or mild pre-eclampsia	51	16	15	15	5
Early-onset or severe pre-eclampsia	68	17	17	20	14
Severe gestational hypertension resistant to therapy	37	10	9	10	8
Placental abruption	8	2	2	2	2
HELLP syndrome	4	1	2	1	0
Fetal/neonatal	80	25	20	24	11
Fetal growth restriction	48	14	12	15	7
Severe respiratory distress syndrome	17	5	5	4	3
Mild and moderate respiratory distress syndrome	13	5	3	4	1
Perinatal death	2	1	0	1	0
Maternal and fetal/neonatal	3	1	1	0	1
HELLP syndrome and neonatal death	3	1	1	0	1
Total	251	72	66	72	41

Values are given as *n*. OF, oral fluids (increased fluid intake of about 2.5–3L per day); NO, nitric oxide donor patches given for 12 h per day.

Table 3 Hemodynamic data in normotensive controls and in the four treatment groups at enrolment and 4 weeks after initiation of therapy

Parameter	*Normotensive group*	*Group A (nifedipine)*	*Group B (nifedipine+NO)*	*Group C (nifedipine+OF)*	*Group D (nifedipine+NO+OF)*
At enrolment					
Heart rate (bpm)	80 ± 10	75 ± 10*	74 ± 10*	74 ± 10*	75 ± 10*
SV (mL)	84 ± 13	69 ± 11*	68 ± 11*	69 ± 11*	70 ± 13*
Systolic BP (mmHg)	114 ± 11	153 ± 9*	152 ± 9*	153 ± 9*	152 ± 9*
Diastolic BP (mmHg)	63 ± 11	94 ± 10*	94 ± 10*	93 ± 9*	95 ± 10*
Mean BP (mmHg)	80 ± 8	114 ± 5*	113 ± 5*	114 ± 5*	114 ± 5*
CO (L/min)	6.67 ± 1.02	5.11 ± 0.89*	5.06 ± 0.84*	5.09 ± 0.89*	5.20 ± 1.14*
TPVR (dynes × s/cm^5)	982 ± 188	1843 ± 350*	1852 ± 344*	1849 ± 349*	1842 ± 418*
4 weeks after initiation of therapy					
Heart rate (bpm)	81 ± 10	78 ± 12	79 ± 12†	77 ± 11*	83 ± 14†
SV (mL)	84 ± 13	70 ± 20*	68 ± 18*	69 ± 19*	77 ± 21*†‡
Systolic BP (mmHg)	115 ± 11	137 ± 11*†	137 ± 10*†	137 ± 11*†	138 ± 11*†
Diastolic BP (mmHg)	63 ± 10	86 ± 9*†	86 ± 10*†	85 ± 9*†	88 ± 9*†
Mean BP (mmHg)	80 ± 8	103 ± 8*†	103 ± 8*†	103 ± 8*†	104 ± 8*†
CO (L/min)	6.74 ± 1.1	5.45 ± 1.79*	5.34 ± 1.65*	5.36 ± 1.74*	6.42 ± 2.05†‡
TPVR (dynes × s/cm^5)	979 ± 190	1682 ± 548*†	1699 ± 528*†	1713 ± 568*†	1473 ± 566*†‡§¶

Values are given as mean ± SD. *$P < 0.05$ *vs* normotensive group. †$P < 0.05$, intragroup comparison. Intergroup comparison, $P < 0.05$: ‡*vs* Group A; §*vs* Group B; ¶*vs* Group C. BP, blood pressure; CO, cardiac output; OF, oral fluids (increased fluid intake of about 2.5–3L per day); NO, nitric oxide donor patches administered for 12 h per day; SV, stroke volume; TPVR, total peripheral vascular resistance.

not able to reach the 4-week cut-off and required intervention for early delivery, the last evaluation of TPVR before delivery was used. Intragroup comparisons in all groups showed significantly ($P < 0.001$) lower systolic BP, diastolic BP, mean BP and TPVR compared with enrolment. Only Group D showed a higher CO. The mean oral dose of nifedipine 4 weeks after initiation of therapy in Groups A, B, C and D was 45.2 ± 17, 44.7 ± 17, 44.9 ± 18.0 and 45.1 ± 18.1 mg/day, respectively (range, 40–80 mg/day) ($P =$ NS).

Intergroup comparison showed no differences at enrolment among the four treatment groups. After 4 weeks of therapy, higher values of HR, SV and CO, and lower values of TPVR, were observed in Group D compared with Groups A, B and C. The CO in Group D was not statistically different in comparison with the CO of the normotensive group, but TPVR was still higher and SV was slightly, but significantly, lower.

Figure 1 shows the ROC curve for reduction of TPVR during therapy in predicting severe complications. A reduction in TPVR of less than 15% during therapy was found to predict severe complications with a sensitivity of 95.2% and specificity of 88.3% in all 400 patients. Binary logistic regression analysis, with the standard treatment Group A as the baseline, showed that there was a higher probability in Group D of reducing TPVR by more than 15% (odds ratio (OR) = 2.03; 95% CI, 1.15–3.60; $P < 0.015$), whereas treatment Groups B and C did not show a significant difference compared with standard treatment (Group B *vs* Group A: OR = 0.96; 95% CI, 0.55–1.67 and Group C *vs* Group A: OR = 1.00; 95% CI, 0.57–1.72; $P =$ NS). Moreover, Group D showed a lower probability of progression to severe complications compared with standard treatment Group A (OR = 0.52; 95% CI, 0.29–0.91; $P < 0.023$), whereas treatment Groups B and C did not have a significant impact on the rate of progression to severe complications (Group B *vs* Group A: OR = 0.89; 95% CI, 0.51–1.54 and Group C *vs* Group A: OR = 1.08; 95% CI, 0.62–1.89; $P =$ NS).

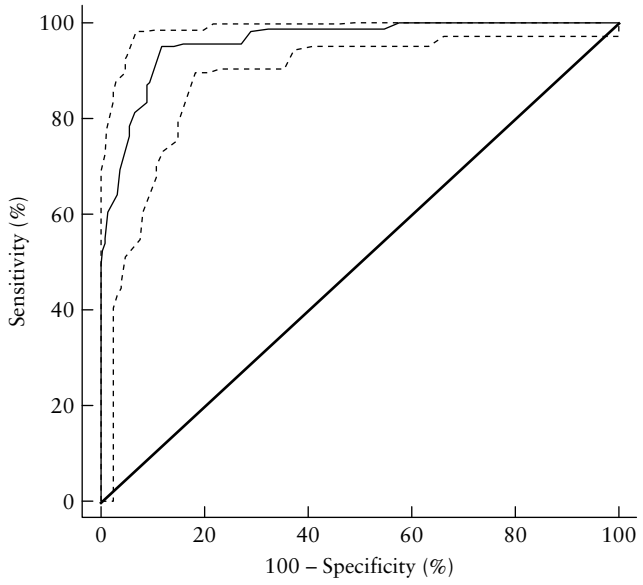

Figure 1 Receiver–operating characteristics curve (with 95% CI) for percentage reduction in total peripheral vascular resistance (TPVR) from enrolment to 4 weeks later in predicting severe pregnancy complications. A reduction in TPVR of < 15% was associated with the occurrence of severe complications with sensitivity 95.2% and specificity 88.3%.

Time from enrolment to delivery in patients with severe complications was 45 ± 24 days in Group A, 45 ± 22 days in Group B, 43 ± 23 days in Group C and 52 ± 19 days in Group D ($P < 0.05$ *vs* Groups A, B and C).

DISCUSSION

This study has found that a reduction in TPVR can be achieved through the addition of NO donors and fluid therapy to standard antihypertensive treatment in mild GH, leading to a reduction in the rate of progression to severe pregnancy complications. One of the most important findings of the study was that a cut-off in TPVR reduction could be identified beyond which there is a consistent reduction in severe complications.

In each of the four treatment groups there was a similar reduction of BP, but only the addition of both NO donors and oral fluids (Group D) was able to increase CO, therefore reducing TPVR, compared with the other three treatment groups. The question therefore arises as to why only the combined therapy has an effect on CO, which nifedipine, NO donors and hydration do not show when administered separately. In order to answer this, it should be noted that these patients with high TPVR have three simultaneous problems: (i) constriction of the resistance vessels (arteriolar compartment); (ii) low venous capacitance (venous compartment)[24]; and (iii) an underfilled vascular state. The venous compartment in the underfilled state is probably vasoconstricted in order to favor the venous return. Only by simultaneous action on these three aspects can we exert a truly positive effect on maternal hemodynamics. We therefore chose to act with nifedipine on the resistance vessels, with NO donors on the capacitance vessels and with hydration on the underfilled state. Nifedipine has an effect on the resistance vessels but not on the capacitance vessels, and the addition of fluid therapy cannot be effective if the venous compartment has a low capacitance. Therapy with NO donors produces a dilatation of the capacitance vessels, which increases venous pooling, acting on the problem of the low venous capacitance in these patients. If NO donors are used without the addition of fluid therapy, the overall result could be a decrease of the preload, which might already be deficient in high-risk GH patients[5,6,11,25,26]. To balance this potentially negative effect of treatment using NO donors and to increase the venous return (increasing SV and CO), an enhancement of maternal hydration was achieved through the administration of oral fluids; this therapeutic strategy allowed for an improvement in positive outcomes (reduction of the afterload) whilst avoiding the potential threats (reduction of the preload) of therapy with NO donors.

The confirmation of TPVR as a target for pharmacological treatment was another important result of this study; a reduction in TPVR of $> 15\%$, compared with pretreatment values, appeared to be associated with a lower probability of severe complications. The combination of treatment with NO donors, oral fluids and nifedipine demonstrated a greater ability to reduce TPVR by $> 15\%$ compared with the standard treatment and was associated with a lower probability for the development of severe complications (35% in Group D *vs* $\approx 50\%$ in Groups A, B and C). The explanation for the reduction in severe complications might be linked to the improvement in maternal hemodynamics which, as previously demonstrated[12], positively influences fetal hemodynamics, reducing fetal and neonatal complications. The higher birth-weight percentile found in Group D strengthens this hypothesis.

Another important result is the observation that we were able to sustain complicated pregnancies to term in Group D, suggesting that the additional treatment with NO donors and oral fluids might delay the onset of severe complications. To date there is no conclusive evidence that antihypertensive treatment is beneficial to the mother in mild GH[1]; however, a variable percentage of pregnant women receive an antihypertensive drug at some point during their pregnancy[15,25,26] in an attempt to control the progression toward severe hypertension[1], and a high percentage of patients with non-threatening GH develop maternal and fetal complications.

This study was designed with the aim of finding a pharmacological treatment strategy that would act on maternal hemodynamics (in particular on the equilibrium between CO and BP, i.e. TPVR) and not only on BP. Most of the previous studies of pharmacological treatments targeting maternal hemodynamics focused on CO[8,9] in patients with a hyperdynamic state (low TPVR and high CO) using beta-blockers[9]. Beta-blockers are known to reduce neonatal respiratory distress syndrome and the progression to severe hypertension, but are also suspected to be associated with an increase in small-for-gestational-age infants[3]. We selected patients with a hypovolemic state with high TPVR and low CO, usually associated with a worse outcome compared with a hyperdynamic state[10]. The hyperdynamic population is usually characterized by high BMI, and progresses to late forms of pre-eclampsia without fetal growth restriction[8,9], mainly linked to maternal risk factors rather than to placental insufficiency[27]. Women included in our series mainly showed normal BMI, a hypovolemic state[27–31] and early forms of pre-eclampsia often associated with fetal growth restriction, probably triggered by a defective trophoblast invasion and placental insufficiency[27]. The different pharmacological approach we used compared with that of Easterling *et al.*[8,9] and the different results obtained might therefore be a result of the different hemodynamics characterizing the populations selected.

The limitation of the current study is the non-randomized design, requiring a randomized controlled study to confirm the data. The absence of a non-treated control group might be considered as another weak point. However, if we compare this set of patients with another group of non-treated patients with mild GH studied previously[5] (with later (28–31 weeks) and milder (BP $< 160/100$ mmHg) forms of hypertension), redefining the outcomes according to the present study, we find that 63 (64.2%) of 98 patients of that historical series[5] would have been classified as having a severe complication, which is much more than the 35% observed in Group D.

This study underlines the importance of TPVR, more than the simple evaluation of BP, in characterizing hypertensive disease of pregnancy, suggesting its role in monitoring the effect of therapy. In particular, the combination of NO donors, oral fluids and standard antihypertensive therapy in patients with low CO and high TPVR is able to reduce TPVR and the frequency of severe complications in mild GH more than other treatments. Another important result of our study was the identification of non-responders (a reduction of TPVR of $\leq 15\%$) to pharmacological therapy at higher risk for progression to severe complications during pregnancy.

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REFERENCES

1. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007; **1**: CD002252.
2. Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, Rolnick SJ, Roblin D, Smith DH, Dal Pan GJ, Scott PE, Platt R. Outpatient use of cardiovascular drugs during pregnancy. *Pharmacoepidemiol Drug Saf* 2008; **17**: 240–247.
3. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2003; **3**: CD002863.
4. Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *Am J Obstet Gynecol* 2001; **184**: 979–983.
5. Vasapollo B, Novelli GP, Valensise H. Total vascular resistance and left ventricular morphology as screening tools for complications in pregnancy. *Hypertension* 2008; **51**: 1020–1026.
6. Valensise H, Vasapollo B, Novelli GP, Pasqualetti P, Galante A, Arduini D. Maternal total vascular resistance and concentric geometry: a key to identify uncomplicated gestational hypertension. *BJOG* 2006; **113**: 1044–1052.
7. Zhang J, Klebanoff MA, Roberts JM. Prediction of adverse outcomes by common definition of hypertension in pregnancy. *Obstet Gynecol* 2001; **97**: 261–267.
8. Easterling TR, Benedetti TJ, Schmucker BC, Carlson KL. Antihypertensive therapy in pregnancy directed by noninvasive hemodynamic monitoring. *Am J Perinatol* 1989; **6**: 86–89.
9. Easterling TR, Carr DB, Brateng D, Diederichs C, Schmucker B. Treatment of hypertension in pregnancy: effect of atenolol on maternal disease, preterm delivery, and fetal growth. *Obstet Gynecol* 2001; **98**: 427–433.

10. Chaffin DG, Webb DG. Outcomes of pregnancies at risk for hypertensive complications managed using impedance cardiography. *Am J Perinatol* 2009; **26**: 717–721.
11. Novelli GP, Valensise H, Vasapollo B, Larciprete G, Altomare F, Di Pierro G, Casalino B, Galante A, Arduini D. Left ventricular concentric geometry as a risk factor in gestational hypertension. *Hypertension* 2003; **41**: 469–475.
12. Valensise H, Vasapollo B, Novelli GP, Giorgi G, Verallo P, Galante A, Arduini D. Maternal and fetal hemodynamic effects induced by nitric oxide donors and plasma volume expansion in pregnancies with gestational hypertension complicated by intrauterine growth restriction with absent end-diastolic flow in the umbilical artery. *Ultrasound Obstet Gynecol* 2008; **31**: 55–64.
13. Lowe SA, Brown MA, Dekker GA, Gatt S, McLintock CK, McMahon LP, Mangos G, Moore MP, Muller P, Paech M, Walters B; Society of Obstetric Medicine of Australia and New Zealand. Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust N Z J Obstet Gynaecol* 2009; **49**: 242–246.
14. Rey E, LeLorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. *CMAJ* 1997; **157**: 1245–1254.
15. Visintin C, Mugglestone MA, Almerie MQ, Nherera LM, James D, Walkinshaw S; Guideline Development Group. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ* 2010; **341**: 499–502.
16. Rochette LM, Patterson SM. Hydration status and cardiovascular function: effects of hydration enhancement on cardiovascular function at rest and during psychological stress. *Int J Psychophysiol* 2005; **56**: 81–91.
17. Patterson SM, VanderKaay MM, Shanholtzer BA, Patterson CA. Influence of acute fluid loading on stress-induced hemoconcentration and cardiovascular reactivity. *J Behav Med* 2008; **31**: 319–330.
18. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988; **158**: 892–898.
19. Parazzini F, Cortinovis I, Bortolus R, Fedele L, Recarli A. Weight at birth by gestational age in Italy. *Hum Reprod* 1995; **10**: 1862–1863.
20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.
21. Valensise H, Novelli GP, Vasapollo B, Di Ruzza G, Romanini ME, Marchei M, Larciprete G, Manfellotto D, Romanini C, Galante A. Maternal diastolic dysfunction and left ventricular geometry in gestational hypertension. *Hypertension* 2001; **37**: 1209–1215.
22. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010; **376**: 631–644.
23. Publication Committee, Society for Maternal Fetal Medicine. Evaluation and management of severe preeclampsia before 34 weeks. *Am J Obstet Gynecol* 2011; **205**: 191–198.
24. Aardenburg R, Spaanderman ME, Courtar DA, van Eijndhoven HW, de Leeuw PW, Peeters LL. A subnormal plasma volume in formerly preeclamptic women is associated with a low venous capacitance. *J Soc Gynecol Investig* 2005; **12**: 107–111.
25. Anderson GD, Carr DB. Effect of pregnancy on the pharmacokinetics of antihypertensive drugs. *Clin Pharmacokinet* 2009; **48**: 159–168.
26. Magee LA, Helewa M, Moutquin JM, von Dadelszen P, for the Hypertension Guideline Committee. Diagnosis, evaluation and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can* 2008; **30**: S1–S48.
27. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 2008; **52**: 873–880.
28. Vasapollo B, Valensise H, Novelli GP, Altomare F, Galante A, Arduini D. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. *Ultrasound Obstet Gynecol* 2004; **24**: 23–29.
29. Valensise H, Vasapollo B, Novelli GP, Larciprete G, Romanini ME, Arduini D, Galante A, Romanini C. Maternal diastolic function in asymptomatic pregnant women with bilateral notching of the uterine artery waveform at 24 weeks' gestation: a pilot study. *Ultrasound Obstet Gynecol* 2001; **18**: 450–455.
30. Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. *Acta Obstet Gynecol Scand* 1995; **74**: 693–697.
31. Nisell H, Lunell NO, Linde B. Maternal hemodynamics and impaired fetal growth in pregnancy-induced hypertension. *Obstet Gynecol* 1988; **71**: 163–166.

