Maternal venous Doppler characteristics are abnormal in pre-eclampsia but not in gestational hypertension

Peer-reviewed author version

GYSELAERS, Wilfried; STAELENS, Anneleen; Mesens, Tinne; TOMSIN, Kathleen; OBEN, Jolien; VONCK, Sharona; VERRESEN, Luc & MOLENBERGHS, Geert
(2015) Maternal venous Doppler characteristics are abnormal in pre-eclampsia but not in gestational hypertension. In: ULTRASOUND IN OBSTETRICS & GYNECOLOGY, 45 (4), p. 421-426.

DOI: 10.1002/uog.13427
Handle: http://hdl.handle.net/1942/18858

Reference (Published version):
Gyselaers, Wilfried; Staelens, Anneleen; Mesens, Tinne; Tomsin, Kathleen; Oben, Jolien; Vonck, Sharona; Verresen, Luc & Molenberghs, Geert(2015) Maternal venous Doppler characteristics are abnormal in pre-eclampsia but not in gestational hypertension. In: ULTRASOUND IN OBSTETRICS & GYNECOLOGY, 45 (4), p. 421-426

DOI: 10.1002/uog.13427
Handle: http://hdl.handle.net/1942/18858

Maternal venous Doppler characteristics are abnormal in preeclampsia but not in gestational hypertension.

Wilfried GYSELAERS [a,b], Anneleen STAELENS [a,c], Tinne MESENS [a], Kathleen TOMSIN [a,c], Jolien OBEN [a,c], Sharona VONCK [a,c] , Luc VERRESEN [b,d] , Geert MOLENBERGHS [e].

[a] Dept. Obstetrics & Gynaecology, Ziekenhuis Oost Limburg, Genk, Belgium

[b] Dept. of Physiology, Hasselt University, Hasselt, Belgium

[c] Dept. Medicine and Life Sciences, Hasselt University, Hasselt, Belgium

[d] Dept. Nephrology, Ziekenhuis Oost Limburg, Genk, Belgium

[e] Centre for Medical Statistics, Hasselt University, Hasselt, Belgium

Correspondence: Wilfried Gyselaers MD PhD

Department of Obstetrics and Gynaecology

Ziekenhuis Oost-Limburg

Schiepse Bos 6, 3600 Genk, Belgium

Telephone: (032)89 32 75 24

Fax: (032)89 57 98 68

wilfried.gyselaers@zol.be

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.13427

Abstract

Aims: To compare functional characteristics of thoraco-abdominal arteries and veins in proteinuric and non-proteinuric hypertension in pregnancy.

Material and methods: This retrospective study includes singleton pregnancies of women during uncomplicated third trimester (UP), with non-proteinuric gestational hypertension (GH), with early-onset preeclampsia (PE) diagnosed < 34 weeks (EPE) or with late-onset PE ≥ 34 weeks (LPE). Demographic maternal and neonatal data were recorded together with maternal serum and urine analytes. All women had standardised automated blood pressure measurement, together with non-invasive Impedance Cardiography (ICG) for measurement of cardiac output (CO), aorta flow velocity (VI) and acceleration (ACI). A standardised combined Doppler – ECG assessment of maternal venous hemodynamics was done for measurement of Renal Interlobar Vein Impedance Index (RIVI), Hepatic Vein Impedance Index (HVI) and venous pulse transit time (VPTT) in liver and kidneys. Finally, resistivity index (RI), pulsatility index (PI) and arterial pulse transit time (APTT) were measured at the uterine arcuate arteries. SPSS software Version 20.0 was used for statistical comparison at nominal level $\alpha = 0.05$, using a non-parametric Mann-Whitney U-tests for intergroup comparison of continuous data and Fisher's exact tests for categorical data. Significant linear dependence between clinical, laboratory, ICG and Doppler-ECG variables was identified using Pearson's correlation coefficient (PCC) at nominal level $\alpha=0.05$ (two-tailed), and coefficient of determination R^2 and corresponding p-value were calculated.

Results: A total of 150 pregnancies were evaluated: 22 UP, 41 GH, 31 EPE and 56 LPE. Aorta VI and ACI were lower in GH, EPE and LPE than in UP. Both EPE and LPE differed from GH by shorter APTT at uterine arcuate arteries and higher RIVI and HVI.

Hemodynamic abnormalities were most pronounced in EPE, where uterine arcuate artery RI was higher and VPTT in kidneys and liver were shorter than in LPE. There was a relevant coefficient of determination between degree of proteinuria and RIVI for left ($R^2 = 0.145$) and right kidney ($R^2 = 0.120$) in LPE, which was not true for EPE.

Conclusion: There is a gradual aggravation of arterial and venous hemodynamic abnormalities from GH to LPE and finally EPE. Venous hemodynamic abnormalities are only present in preeclampsia, with a linear correlation between proteinuria and RIVI in LPE. The role of the maternal venous compartment in the pathophysiology and etiology of PE-related symptoms may be much more important than considered today.

Introduction

Normal circulation of the blood requires the coordinated activity of several systems in the cardiovascular circuit: the heart, the arterial compartment, the microcirculation, the venous compartment and the blood. Cardiovascular profiling is defined as the evaluation of the functionality of these systems for categorisation of the cardiovascular system into functional subtypes [1,2]. For this, invasive and non-invasive methods can be used [3,4]. Cardiovascular profiling in pregnant women can be performed non-invasively using standardized combined Doppler-electrocardiography (D-ECG) assessment [5] and Impedance Cardiography (ICG) [6,7].

Cardiovascular dysfunction has been reported as less severe in gestational hypertension than in preeclampsia [8-10] and pharmacologic response was found to differ between both entities [8]. Similarly, cardiac, arterial and venous hemodynamic dysfunction was found to present less severe in late-onset than in early-onset preeclampsia [11-13], and maternal serum concentrations

of angiogenic factor differed between both entities [14]. Micro-circulatory changes were also reported to differ between preeclampsia and HELLP-syndrome [15].

In this paper, we report our observations on the non-invasive maternal cardiovascular profile with D-ECG and ICG in women with different clinical types of hypertension in pregnancy, relative to the findings in uncomplicated pregnancies (UP): gestational hypertension (GH), early-onset preeclampsia (EPE) and late-onset preeclampsia (LPE).

Materials and methods

Approval of the ethical committee was obtained before study onset (MEC ZOL reference: 08/049, 09/050 and 10/065).

Women, admitted between 1/10/2009 and 31/12/2013 to the Fetal Maternal Medicine Unit of Ziekenhuis Oost Limburg Genk Belgium for hypertension in pregnancy were included. Exclusions were women with multiple gestation, essential hypertension with or without superimposed preeclampsia, renal disease with or without proteinuria, history of organ transplantation, women with concomitant diseases as diabetes, thyroid dysfunction, auto-immune disease, cholestasis or liver disease, women with HELLP syndrome, women with thrombocytopenia or with non-hypertensive proteinuria and IUGR without associated maternal symptoms. Included were only those women without known diseases and new onset hypertension > 20 weeks (Fig 1). In addition to this, a group of women with normal maternal and neonatal outcome at birth, who were admitted to the antenatal unit for presumed hypertension in the third trimester of pregnancy, were used as a control group. PE was defined as new onset gestational hypertension (≥ 140/90mmHg on at least 2 occasions at least 6 hours apart) with de novo proteinuria (≥ 300mg/24hours) without thrombocytopenia or liver dysfunction, according to the criteria of the National High Blood Pressure Education Program Working Group [16,17]. New onset hypertension > 20 weeks with proteinuria < 300

mg/24h is defined as gestational hypertension (GH). PE < 34 weeks is defined as early onset preeclampsia (EPE), whereas PE ≥ 34 weeks is defined as late onset preeclampsia (LPE). As such, there were 4 categories eligible for retrospective analysis: uncomplicated pregnancies (UP), gestational hypertension without proteinuria (GH), early onset preeclampsia (EP) and late onset preeclampsia (LP).

For each woman, data on demographics and perinatal outcome were recorded, together with results from serum and urine biochemistry, ICG-measurements and maternal Doppler-ECG parameters. Maternal demographic data include age (years), body mass index (BMI) at first visit as recorded from the records, gestational age at assessment (weeks), parity and use of antihypertensive medication. Data on perinatal outcome comprise gestational age at delivery (weeks), birth weight (BW in g) and customized birth weight percentile (BW% in %). Serum parameters include thrombocytes (1000/μL), creatinine (μmol/L), aspartate aminotransferase (ASAT in U/L), alanine aminotransferase (ALAT in U/L), and uric acid (μmol/L). Parameters evaluated in 24 hour urine collections at the time of diagnosis of PE were creatinine clearance (mL/min), and proteinuria over 24 hours (mg).

At the same time point, all women had an Impedance Cardiography (ICG-) assessment together with a combined Doppler-ECG (D-ECG-) evaluation at different sites of the circulation, as illustrated in Figure 2. None of the subjects were in labour at the time of the investigations.

ICG- examinations were performed in standing position using the Non-Invasive Continuous Cardiac Output Monitor (NICCOMO©, Software version 2.0, Medis Medizinische Messtechnik GmbH, Ilmenau Germany) according to the reported methodology and protocol with known repeatability [6]. This impedance technique is a non-invasive method of evaluating haemodynamic parameters, based on thoracic resistance changes of a high frequent, low

powered electrical current, measured during each heart cycle using a set of 4 skin-electrodes [18,19]. Blood pressures were measured standardised using the automated device of the NICCOMO-monitor. Pressure parameters were systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP = SBP – DBP) and mean blood pressure (MBP = DBP + PP/3), all expressed in mmHg. ICG-parameters were left ventricular output parameters, aortic flow parameters, and thoracic fluid content (TFC in 1/kOhm) [6,18]. Left ventricular output parameters were stroke volume (SV) in mL, heart rate (HR) in beats/min and cardiac output in mL/min (CO = HR x SV). Aortic flow parameters were velocity index (VI in 1/1000/s) which is equivalent to the amplitude of the systolic wave and acceleration index (ACI in 1/100/s²) which stands for the maximum acceleration of blood flow in the aorta [6,18]. Thoracic fluid content is measured directly from the electrical conductivity of the chest and reflects the total of intracellular, interstitial and circulation fluid volumes in the thorax [6,18].

All Doppler-ECG examinations were done by 5 sonographers (WG, TM, AS, KT and SV) according to the protocol reported elsewhere [20,21], with known intra - and interobserver correlation [22]. All women had ECG-D investigations in supine position at the level of hepatic veins (HV), renal interlobar veins (RIV) of both kidneys, and left and right arcuate uterine arteries as reported [20]. Uterine arcuate arteries were preferred over uterine arteries for their intra-parenchymatous localization, comparable with the localization of hepatic and renal interlobar veins [23], and were performed within a maximum of 2 cm distance from the bifurcation at the uterine artery. Arterial pulsatility and resistivity index were measured, defined as [(maximum velocity (MxV) – minimum velocity (MnV)]/mean velocity and [MxV – MnV]/MxV respectively. Doppler parameters measured at the level of HV and RIV were MxV and MnV. From this, Hepatic Vein velocity index (HVI) and Renal Interlobar Vein Impedance Index (RIVI) were calculated as [(MxV-MnV)/MxV] [20,24]. Pulse transit times were measured as the time interval between corresponding characteristics of the cardiac

cycle of the ECG-signal and Doppler wave. Arterial pulse transit time (APTT) was defined as the time interval (ms) between the maternal ECG Q-wave and start of Doppler systole, corrected for the duration of the corresponding cardiac cycle [23]. Venous pulse transit times (VPTT) were defined as the time interval (ms) between the maternal ECG P-wave and corresponding Doppler A-wave, again corrected for the duration of the corresponding cardiac cycle [25].

Data are presented as medians with first and third quartiles, or as percentages. SPSS software Version 20.0 was used for statistical comparison at nominal level $\alpha = 0.05$, using a non-parametric Mann-Whitney U-tests for intergroup comparison of continuous data and Fisher's exact tests for categorical data. Significant linear dependence between clinical, laboratory, ICG and ECG-Doppler variables was identified using Pearson's correlation coefficient (PCC) at nominal level $\alpha=0.05$ (two-tailed), and goodness-of-fit of the resulting linear regression model with heteroskedastic variance was reported by coefficient of determination R^2 and corresponding p-value (SAS software V9.2).

Results

A total of 150 women were included: 22 had UP, 41 had GH, 31 had EPE and 56 had LPE. Inclusions and exclusions in this study from the total cohort of women, admitted to the hospital for hypertension in pregnancy during the study period, are presented in Figure 1.

Demographic data are presented in Table 1, together with results from maternal serum and urine laboratory tests.

Table 2 shows the blood pressure values and ICG measurements of cardiac output, aortic flow velocities and thoracic fluid content. As is shown, HR, SV or CO were not different between groups. For GH, LPE and EPE, aortic flow VI and ACI were lower than in UP.

Table 3 presents the D-ECG results as measured at the level of hepatic veins, renal interlobar veins and uterine arcuate arteries. Only in preeclampsia, venous impedance index and arterial pulse transit times were different from UP. Arterial resistivity and pulsatility index and venous pulse transit times were different from UP only in EPE. Interestingly in late-onset preeclampsia, left and right kidney RIVI correlated with degree of proteinuria: PCC for the left kidney was 0.381 ($p=0.004$, $R^2 = 0.145$) and PCC for the right kidney was 0.347 ($p=0.010$, $R^2 = 0.120$). These correlations correspond to regression-based predictions as proteinuria = 9E2+5.29E3 x Left RIVI and Proteinuria = 4.58E2+4.41E3 x Right RIVI. No correlation was found between proteinuria and RIVI in early-onset preeclampsia: PCC for the left kidney was 0.073 ($p=0.696$, $R^2 = 0.005$) and PCC for the right kidney was 0.234 ($p=0.214$, $R^2 = 0.055$).

The most important findings of Tables 2 and 3 are summarized in Table 4. As compared to UP, hemodynamic dysfunction aggravates from GH to LPE and finally EPE.

Discussion

The data presented in this report support the view that (1) central arterial hemodynamic dysfunction is present in both gestational hypertension and preeclampsia, and (2) preeclampsia presents with signs of venous hemodynamic dysfunction, which is not true for gestation induced hypertension.

Our study is original because it evaluates aspects of hemodynamics at different sites of the maternal circulation: central and peripheral arterial hemodynamics together with venous hemodynamics. The strengths of our study are that every woman is examined according to a standard protocol using non-invasive assessment techniques with known inter- and intra-observer correlation [6,18,22]. Next to this, the patients included in each group strictly comply with all reported criteria for each disorder, and are free of interfering maternal or gestational

diseases known at time of inclusion. The lack of a physiologic explanation for the true nature of the venous impedance index as a venous Doppler flow characteristic, as well as the lack of associative data on experimental measurements of central venous pressure and venous vascular tone in preeclampsia, are a limitation to our study. Next to this, our observational study is retrospective in nature, which does not allow drawing conclusions on cause and effect relationships or on the individual role of heart, arteries and veins in the development or the clinical presentation of PE. For this, a prospective clinical study in a large group of women and experimental data are needed.

Our data are consistent with the observations from others, reporting a gradation in hemodynamic dysfunction and severity of clinical presentation between subtypes of gestational hypertensive diseases, with EPE as the most severe subtype [8-11]. Next to this, our observations are also in line with the ICG-measurements in pregnant hypertensive women as reported by Parrish et al [26], illustrating central arterial hemodynamic dysfunction and increased thoracic fluid content in the most severe subtypes of PE.

Next to this, our data in Table 3 illustrate that maternal venous hemodynamic dysfunction is a feature of both early- and late-onset preeclampsia, but not GH. Venous hemodynamic dysfunction in PE was reported for the first time by Bateman et al [27]. In former publications, we have reported that RIVI is higher in EPE than in LPE [13] and that HVI is also increased in PE, as compared to UP [21]. The higher values of RIVI in EPE than in LPE were linked to the presence of the so-called Doppler wave venous pre-acceleration nadir (VPAN) [5,13]. VPAN results from the retrograde intravenous rebound of right atrial contraction, which in PE presents up to the level of the kidneys resulting in a more pronounced deceleration of blood flow and higher RIVI-values. It is unclear whether this rebound in PE relates to increased cardiac diastolic dysfunction [2] or to reduced venous distensibility [28]. Pulse transit time is considered a measure for vascular stiffness: in conditions of increased vascular tone or

stiffness, the propulsion wave is transported faster through the circulation than in conditions of low vascular tone, and this is responsible for a shorter time interval between ECG and pulse or Doppler wave [29-31]. During PE, shorter pulse transit times have been measured at both the arterial [32] and venous sites of the circulation [23]. It is likely that increased venous tone in PE is associated with a faster and more distant rebound of atrial contraction throughout the venous circulation, up to the level of the kidneys. As such, increased RIVI, with or without VPAN, can be considered a reflection of pulsatile counteraction of forward venous flow from the kidneys, which intermittently counteracts renal outflow during each atrial contraction [33]. Our observations of increased Doppler Impedance Index and shortened venous pulse transit times in intrarenal veins are compatible with a state of increased intravenous or intravenular hydrostatic pressure. Therefore, we propose renal venous congestion as an additional explanation for some of the clinical manifestations of PE. A decrease of venous outflow from the kidneys will result in a decrease of glomerular plasma flow and glomerular filtration rate. In order to maintain the glomerular filtration rate, local renin angiotensin aldosteron system (RAAS) will be activated by stimulation of the juxtaglomerular apparatus [34]. This intrarenal production of angiotensin II (Ang II) will result in proteinuria [35] and increased salt sensitivity with subsequent edema and hypertension [36]. In PE circulating RAAS remains suppressed or unchanged [37]. Upregulation of Ang II Receptor-1 and increase of Ang II Receptor-1 Auto-Antibody in PE might further enhance the Ang II sensitivity [38]. Raised Ang II levels can cause proteinuria by several mechanisms: increased glomerular pressure, endothelial cell dysfunction, contraction of the podocytes and reduced expression of nephrin [39]. Experimentally induced increase of intravenous pressure in the renal veins [40] or subobstruction to venous drainage from the kidneys has been shown to result in overt proteinuria, partially reversible by Ang II antagonism [35]. Proteinuria due to renal congestion has also been described in the nutcracker syndrome where the left renal vein is narrowed in

the angle between the aorta abdominalis and the arteria mesenterica superior, leading to orthostatic proteinuria mainly in young adults. The improvement of this type of proteinuria by ACE inhibition demonstrates an etiologic role for Ang II [41]. The correlation we found between RIVI and degree of proteinuria in LPE suggests a possible underrecognised role for venous hemodynamics in the pathophysiology of PE, and invites for more research into the pathophysiology of PE-related proteinuria.

Conclusion

The combination of our observations allow describing the cardiovascular profile for different types of hypertensive disease in pregnancy : (1) gestational hypertension combines increased blood pressures with central hemodynamic dysfunction, and (2) preeclampsia presents as gestational hypertension with venous hemodynamic dysfunction.

Acknowledgements

This study is part of the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost Limburg and Jessa Ziekenhuis.

Disclosure of Interests

The authors report no conflict of interest.

Table 1: Maternal demographics, neonatal outcome and laboratory results.

	UP n=22	GH n=41	LPE n=56	EPE n=31
Maternal age (y)	29.00 (24.75;31.25)	30.00 (26.00;32.50)	28.00 (25.25;30.75)	29.00 (26.00;30.00)
Start BMI	25.06 (20.11;28.48)	25.90 (22.72;30.02)	25.08 (23.22;28.64)	24.48 (21.80;28.81)
Nulliparity n (%)	11 (50%) $	28 (68.3%) Q	47 (83.9%) *	22 (71.0%) °
Medication n (%)	0 (0%)	3 (7.3%)	5 (8.93%)	3 (9.68%)
GA examination (w)	36.79 (34.11;39.46) Q	38.00 (36.65;39.21) Q	37.50 (36.00;38.39) Q	31.28 (27.28;32.72) $°*
GA birth (w)	39.72 (37.14;40.43) $Q	39.14 (37.93;39.93) $Q	37.65 (36.32;38.72) °Q*	31.72 (27.86;33.14) $°*
Birth weight (g)	3465 (2923.75;3695.0) $Q	3080.0 (2710.0;3552.5) Q	2850 (2465;3260) Q*	1425.0 (992.0;1730.0) $°*
Birth weight %	50.00 (21.25;75.00) Q	25.00 (10.00;62.50)	25.00 (10.00-68.75)	25.00 (10.00,25.00) *
Hemoglobin (g%)	12.35 (11.53;12.80)	12.10 (11.75;12.90)	11.95 (10.90;12.88)	12.10 (11.40;13.10)
Thromb (x1000/mm³)	207.50 (168.25;235.50)	208.00 (166.50;241.00)	182 (152;229)	176.00 (150.0;209)
ASAT (U/L)	17.00 (15.00;19.25)	18.00 (15.00;22.50)	18.00 (15.00;24.00)	19.00 (16.00;25.50)
ALAT (U/L)	11.00 (9.00;12.25) Q	12.00 (9.00;14.50)	12.00 (9.00;17.25)	16.00 (10.00;23.00) *
Uric Acid (µmol/L)	4.65 (3.88;5.70) $°Q	5.48 (4.67;6.49) $Q*	5.95 (5.03;6.98) *°	6.60 (5.40;7.70) °*
ProtU24h (mg)	144.50 (112.75;174.50) $Q	164.0 (111.5;204.0) $Q	786 (434;1639) Q°*	2543 (838.0;7322.0) $°*
Creat Clear (ml/min)	131.07 (106.14;154.04)	125.73 (104.16;157.73)	121.94 (94.96;151.62)	116.72 (93.27;141.85)

* Significantly different from Uncomplicated Pregnancy (UP)

° Significantly different from Gestational Hypertension (GH)

$ Significantly different from Late-onset Preeclampsia (LPE)

Q Significantly different from Early-onset Preeclampsia (EPE)

BMI : Body Mass Index at first antenatal visit

GA: gestational age (w)

Thromb: thrombocytes (x 1000/mm³)

ASAT: Aspartate Aminotransferase (U/L)

ALAT: Alanine Aminotransferase (U/L)

ProtU24h: 24 hour proteinuria (mg)

CreatClear: creatinine clearance (mL/min)

Table 2: Blood pressure values and impedance cardiography measurements

	UP n=22	GH n=41	LPE n=56	EPE n=31
SBP (mm Hg)	137.50 (122.00;147.00) $°Q	149.0 (141.50;159.50) *	149.0 (135.25;163.75) *	153.00 (141.00;166.00) *
DBP (mm Hg)	87.50 (82.50;99.75) $°Q	98.0 (94.50;104.0) *	98.00 (93.0;103.0) *	102.0 (96.0;108.0) *
MAP (mm Hg)	99.50 (93.75;111.50) $°Q	112.0(107.0;118.0) *	110.0 (103.0;117.75) *	113.0(108.0;122.0) *
Heart rate (bpm)	97.0 (84.50;106.50)	94.0 (89.0;105.5) $	90.0 (82.0;102.5) °	94.0 (86.0;105.0)
Stroke volume (ml)	77.50 (67.00;93.25)	82.0(64.0;94.5)	85.00 (61.00;99.00)	75.00 (67.00;90.0)
Card output (L/min)	7.30 (6.55;8.10)	7.50 (6.25;8.80)	7.70 (6.10;9.08)	7.10 (6.20;8.10)
VI (1/1000/s)	59.50 (50.75;65.25) $°Q	46.00 (39.50,58.00) *	45.00 (38.25;55.75) *	45.00 (35.00;56.00) *
ACI (1/100/s²)	111.50 (86.5;147.0) $°Q	76.00 (59.00;102.50) *	84.00 (6.50;98.25) *	80.00 (58.00;108.75) *
TFC (1/kOhm)	27.05 (24.85;29.60) $Q	24.75 (24.75;29.45) $Q	30.60 (27.85;34.85) Q°*	34.10 (29.20;39.00) $°*

* Significantly different from Uncomplicated Pregnancy (UP)

° Significantly different from Gestational Hypertension (GH)

$ Significantly different from Late-onset Preeclampsia (LPE)

Q Significantly different from Early-onset Preeclampsia (EPE)

SBP: Systolic blood pressure (mm Hg)

DBP: Diastolic blood pressure (mm Hg)

MAP : Mean arterial pressure (mm Hg)

Card Output: Cardiac output (L/min)

VI : Aorta flow velocity index (1/1000/s)

ACI : Aorta flow acceleration index (1/100/s²)

TFC: thoracic Fluid Content (1/kOhm)

Table 3: Doppler-ECG measurements

	UP n=22	GH n=41	LPE n=56	EPE n=31
LK RIVI	0.330 (0.295;0.420) $Q	0.360 (0.32 ;0.428) Q	0.40 (0.34;0.45) *	0.427 (0.37 ;0.510) °*
RK RIVI	0.308 (0.27;0.35) $Q	0.33 (0.282;0.389) $Q	0.38 (0.33;0.44) Q°*	0.439 (0.367;0.544) $°*
HVI	0.220 (0.146;0.430) $Q	0.270 (0.165;0.784) Q	0.52 (0.20;1.10) Q*	0.920 (0.427;1.573) $°*
LK VPTT (sec)	0.437 (0.325;0.528) Q	0.410 (0.345;0.467) Q	0.37 (0.33;0.44) Q	0.327 (0.270;0.393) $°*
RK VPTT (sec)	0.40 (0.340;0.475) Q	0.40 (0.355;0.477) $Q	0.38 (0.32;0.42) °	0.335 (0.289;0.404) °*
L VPTT (sec)	0.320 (0.265;0.395) Q	0.300 (0.227;0.377)	0.300 (0.205;0.410)	0.247 (0.170;0.343) *
L Aut RI	0.520 (0.415;0.607) Q	0.550 (0.440;0.707) Q	0.549 (0.468;0.680) Q	0.707 (0.587;0.772) $°*
L Aut PI	0.710 (0.530;0.865) Q	0.750 (0.570;1.097) Q	0.755 (0.618;1.028) Q	1.095 (0.833;1.261) $°*
R Aut RI	0.457 (0.409;0.647) Q	0.460 (0.390;0.647) Q	0.515 (0.430;0.618) Q	0.717 (0.560;0.770) $°*
R Aut PI	0.570 (0.515;0.947) Q	0.610 (0.490;0.953) Q	0.702 (0.553;0.890) Q	1.112 (0.780;1.248) $°*
L Aut APTT (sec)	0.320 (0.267;0.375) $Q	0.287 (0.252;0.340) $Q	0.274 (0.231;0.310) Q°*	0.227 (0.218;0.288) $°*
R Aut APTT (sec)	0.340 (0.285;0.405) $Q	0.303 (0.253;0.340) $Q	0.272 (0.233;0.308) Q°*	0.235 (0.209;0.290) $°*

* Significantly different from Uncomplicated Pregnancy (UP)

° Significantly different from Gestational Hypertension (GH)

$ Significantly different from Late-onset Preeclampsia (LPE)

Q Significantly different from Early-onset Preeclampsia (EPE)

LK RIVI : Left kidney, renal interlobar vein impedance index

RK RIVI: Right kidney, renal interlobar vein impedance index

HVI: Hepatic vein impedance index

LK VPTT: Left kidney, venous pule transit time (sec)

RK VPTT : Right kidney, venous pule transit time (sec)

L VPTT: Liver venous pule transit time (sec)

L Aut RI: Left Uterine Arcuate Artery Resistivity index

L Aut PI : Left Uterine Arcuate Artery Pulsatility index

R Aut RI: Right Uterine Arcuate Artery Resistivity index

R Aut PI: Right Uterine Arcuate Artery Pulsatility index

L Aut APTT: Left Uterine Arcuate Artery Pulse transit time (sec)

R Aut APTT: Right Uterine Arcuate Artery Pulse transit time (sec)

Table 4: Summary of most important findings of Tables 2 & 3. Arrows indicate significant differences relative to uncomplicated pregnancy.

Blood pressures				
		GH	LPE	EPE
	SBP	↑	↑	↑
	DBP	↑	↑	↑
	MAP	↑	↑	↑
Arterial hemodynamics				
		GH	LPE	EPE
Aorta	VI	↓	↓	↓
	ACI	↓	↓	↓
Ut Arc Art	Rt APTT		↓	↓
	Lt APTT		↓	↓
	R RI			↑
	L RI			↑
Venous hemodynamics				
		GH	LPE	EPE
Rt kidney	Rt RIVI		↑	↑
	Rt VPTT			↓
Lt kidney	Lt RIVI		↑	↑
	Lt VPTT			↓
Liver	Hep VI		↑	↑
	Hep VPTT			↓

GH : Gestational hypertension

LPE : Late onset preeclampsia

EPE : Early onset preeclampsia

ACI : Aorta flow acceleration index

Rt : Right

APTT : Arterial pulse transit time

RIVI : Renal Interlobar vein impedance index

Hep VI : Hepatic vein impedance index

SBP : Systolic blood pressure

DBP : Diastolic blood pressure

MAP : Mean arterial pressure

VI : Aorta flow velocity index

Ut Arc Art : Uterine Arcuate Artery

Lt : Left

RI : Right resistivity index

VPTT : Venous pulse transit time

Hep VPTT : Hepatic vein pulse transit time

Figure captions

Figure 1

Flow chart of inclusions and exclusions in this study from the total number of women, admitted for hypertension in pregnancy to the Fetal Maternal Medicine Unit of Ziekenhuis Oost Limburg Genk Belgium during the study period. EH: essential hypertension, PE : preeclampsia, IUGR: Intra-uterine growth restriction, HELLP : Hemolysis Elevated Liver enzymes Low Platelets, Atypical PE: non-hypertensive proteinuria and/or elevated liver enzymes and/or low platelets.

Figure 2

Schematic presentation of the intra-abdominal locations where combined ECG-Doppler assessment were performed in study subjects: Hepatic Veins, Renal Interlobar Veins and Uterine Arcuate Arteries. Next to this, blood flow velocity characteristics in the thoracic aorta were assessed using Impedance Cardiography. (Figure adapted from http://www.cancer.gov/images/cdr/live/CDR649519-750.jpg).

Figure 1

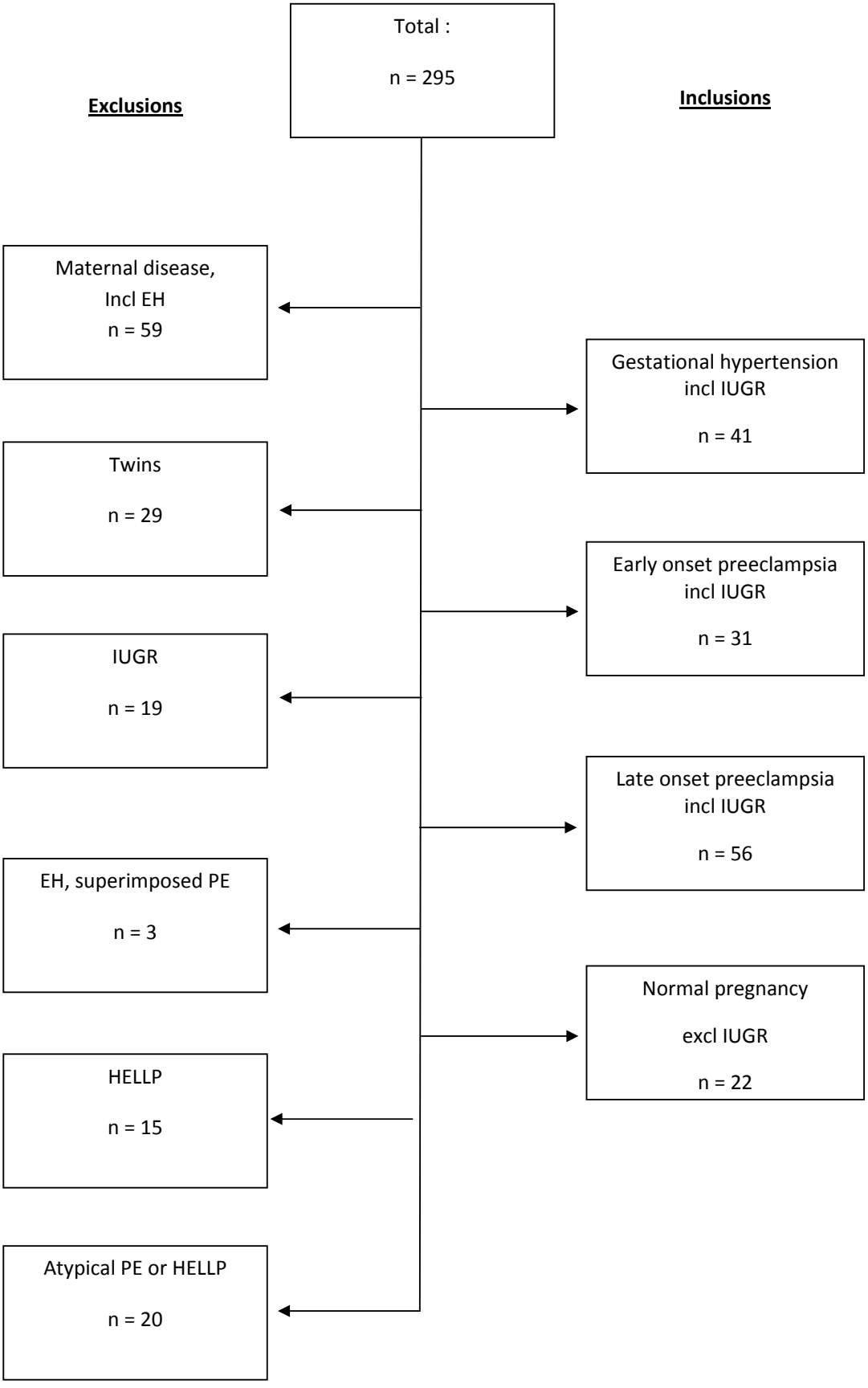
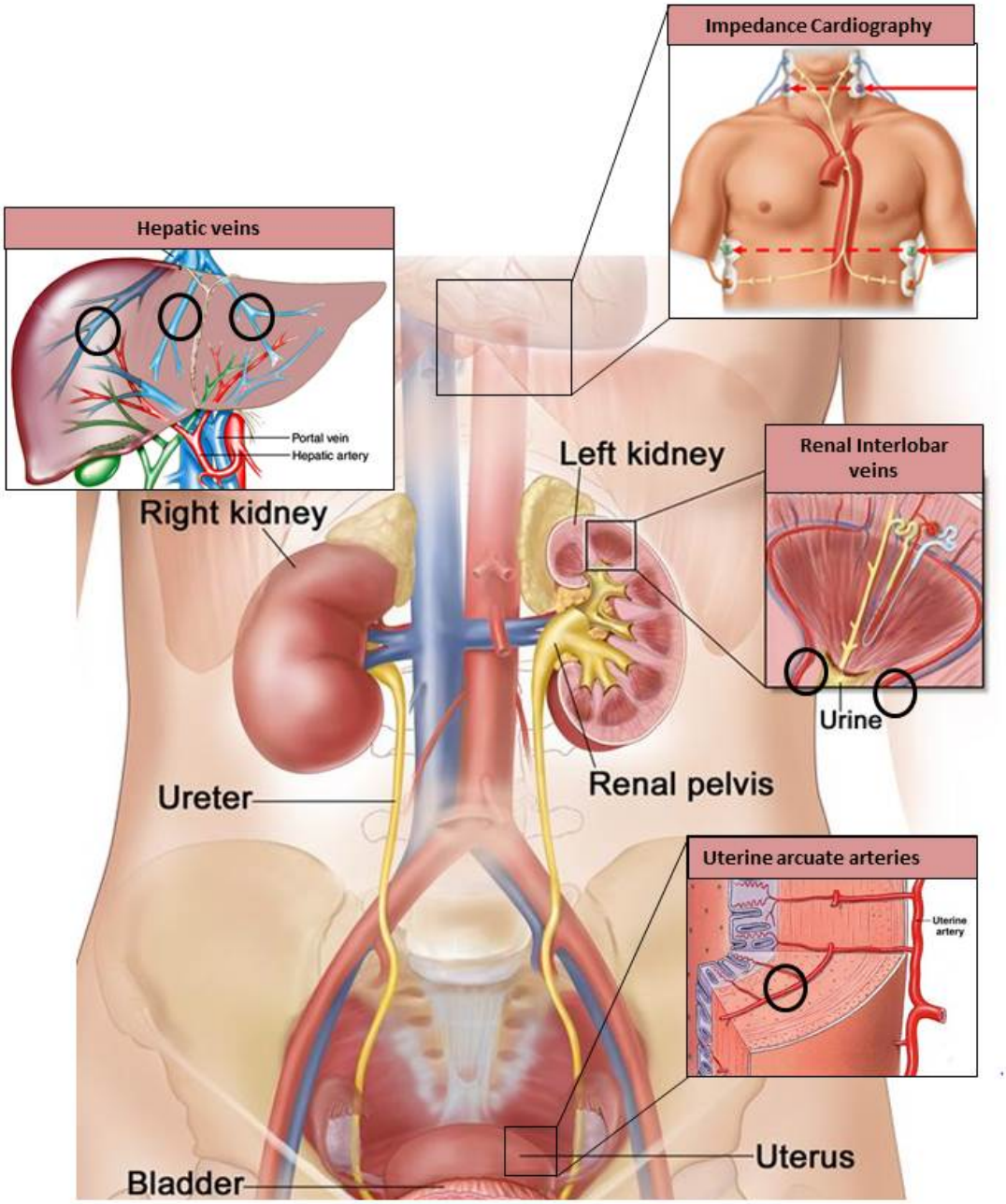


Figure 2



References

1. Heilmann L, Siekmann U. Hemodynamic and hemorheological profiles in women with proteinuric hypertension of pregnancy and in pregnant controls. Arch Gynecol Obstet. 1989;246(3):159-68.
2. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. BJOG. 2013;120(4):496-504.
3. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. Hypertension. 1991 Jun;17(6 Pt 2):1072-7.
4. Tomsin K, Vriens A, Mesens T, Gyselaers W. Non-invasive cardiovascular profiling using combined electrocardiogram-Doppler ultrasonography and impedance cardiography: An experimental approach. Clin Exp Pharmacol Physiol. 2013 Jul;40(7):438-42.
5. Gyselaers W. Hemodynamics of the maternal venous compartment: a new area to explore in obstetric ultrasound imaging. Ultrasound Obstet Gynecol. 2008;32(5):716-7.
6. Tomsin K, Mesens T, Molenberghs G, Gyselaers W. Impedance cardiography in uncomplicated pregnancy and pre-eclampsia: A reliability study. J Obstet Gynaecol. 2012;32(7):630-4.
7. Staelens A, Tomsin K, Grieten L, Oben J, Mesens T, Spaanderman M, Jacquemyn Y, Gyselaers W. Non-invasive assessment of gestational hemodynamics: benefits and limitations of impedance cardiography versus other techniques. Expert Rev Med Devices. 2013 Nov;10(6):765-79.
8. Khalil A, Jauniaux E, Harrington K. Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy. Obstet Gynecol. 2009 Mar;113(3):646-54.
9. Spasojevic M, Smith SA, Morris JM, Gallery ED. Peripheral arterial pulse wave analysis in women with pre-eclampsia and gestational hypertension. BJOG. 2005 Nov;112(11):1475-8.
10. Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L, Mangos G. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. Hypertens Pregnancy. 2007;26(1):77-87.
11. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M, Thilaganathan B. Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. Hypertens Pregnancy. 2012;31(4):454-71
12. Myatt L, Clifton RG, Roberts JM, Spong CY, Hauth JC, Varner MW, Wapner RJ, Thorp JM Jr, Mercer BM, Grobman WA, Ramin SM, Carpenter MW, Samuels P, Sciscione A, Harper M, Tolosa JE, Saade G, Sorokin Y, Anderson GD; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU). The utility of uterine artery Doppler velocimetry in prediction of preeclampsia in a low-risk population. Obstet Gynecol. 2012 Oct;120(4):815-22.
13. Gyselaers W, Mesens T, Tomsin K, Molenberghs G, Peeters L. Maternal renal interlobar vein impedance index is higher in early- than in late-onset pre-eclampsia. Ultrasound Obstet Gynecol. 2010;36(1):69-75.
14. Masuyama H, Segawa T, Sumida Y, Masumoto A, Inoue S, Akahori Y, Hiramatsu Y. Different profiles of circulating angiogenic factors and adipocytokines between early- and late-onset pre-eclampsia. BJOG. 2010 Feb;117(3):314-20.
15. Cornette J, Herzog E, Buijs EA, Duvekot JJ, Rizopoulos D, Hop WC, Tibboel D, Steegers EA. Microcirculation in women with severe pre-eclampsia and HELLP syndrome: a case-control study. BJOG. 2014 Feb;121(3):363-70.
16. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003;102(1):181-92.
17. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1):S1-S22.

18. Tomsin K, Mesens T, Molenberghs G, Gyselaers W. Diurnal and position-induced variability of impedance cardiography measurements in healthy subjects. Clin Physiol Funct Imaging. 2011;31(2):145-50.
19. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp Med. 1966;37(12):1208-12.
20. Gyselaers W, Molenberghs G, Van Mieghem W, Ombelet W. Doppler measurement of renal interlobar vein impedance index in uncomplicated and preeclamptic pregnancies. Hypertens Pregnancy. 2009;28(1):23-33.
21. Gyselaers W, Molenberghs G, Mesens T, Peeters L. Maternal hepatic vein Doppler velocimetry during uncomplicated pregnancy and pre-eclampsia. Ultrasound Med Biol. 2009;35(8):1278-83.
22. Mesens T, Tomsin K, Molenberghs G, Gyselaers W. Reproducibility and repeatability of maternal venous Doppler flow measurements in renal interlobar and hepatic veins. Ultrasound Obstet Gynecol. 2010;36(1):120-1.
23. Tomsin K, Mesens T, Molenberghs G, Gyselaers W. Venous pulse transit time in normal pregnancy and preeclampsia. Reprod Sci. 2012;19(4):431-6.
24. Pedersen JF, Madsen LG, Larsen VA, Hamberg O, Horn T, Federspiel B, Bytzer P. A Doppler waveform index to characterize hepatic vein velocity pattern and evaluate hepatic fibrosis. J Clin Ultrasound. 2008;36(4):208-11.
25. Tomsin K, Mesens T, Molenberghs G, Peeters L, Gyselaers W. Time Interval Between Maternal Electrocardiogram and Venous Doppler Waves in Normal Pregnancy and Preeclampsia: A Pilot Study. Ultraschall Med. 2012; 33(7):E119-25.
26. Parrish MR, Laye MR, Wood T, Keiser SD, Owens MY, May WL, Martin JN Jr. Impedance cardiography facilitates differentiation of severe and superimposed preeclampsia from other hypertensive disorders. Hypertens Pregnancy. 2012;31(3):327-40.
27. Bateman GA, Giles W, England SL. Renal venous Doppler sonography in preeclampsia. J Ultrasound Med. 2004;23(12):1607-11.
28. Sakai K, Imaizumi T, Maeda H, Nagata H, Tsukimori K, Takeshita A, Nakano H. Venous distensibility during pregnancy. Comparisons between normal pregnancy and preeclampsia. Hypertension. 1994 Oct;24(4):461-6.
29. Vaschillo EG, Vaschillo B, Buckman JF, Pandina RJ, Bates ME. Measurement of vascular tone and stroke volume baroreflex gain. Psychophysiology. 2012;49(2):193-7.
30. Naka KK, Tweddel AC, Doshi SN, Goodfellow J, Henderson AH. Flow-mediated changes in pulse wave velocity: a new clinical measure of endothelial function. Eur Heart J. 2006;27(3):302-9.
31. Smith RP, Argod J, Pepin JL, Levy PA. Pulse transit time: an appraisal of potential clinical applications. Thorax. 1999;54(5):452-7.
32. Kaihura C, Savvidou MD, Anderson JM, McEniery CM, Nicolaides KH. Maternal arterial stiffness in pregnancies affected by preeclampsia. Am J Physiol Heart Circ Physiol. 2009;297(2):H759-64.
33. Gyselaers W, Mullens W, Tomsin K, Mesens T, Peeters L. Role of dysfunctional maternal venous hemodynamics in the pathophysiology of pre-eclampsia: a review. Ultrasound Obstet Gynecol. 2011;38(2):123-9.
34. Schnermann J. Homer W. Smith Award lecture. The juxtaglomerular apparatus: from anatomical peculiarity to physiological relevance. J Am Soc Nephrol. 2003;14(6):1681-94.
35. Yoshioka T, Mitarai T, Kon V, Deen WM, Rennke HG, Ichikawa I. Role for angiotensin II in an overt functional proteinuria. Kidney Int. 1986;30(4):538-45.
36. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Eng J Med. 2002;346(12):913-23.

37. Lindheimer MD Conrad KP, Karumanchi SA. In 'Seldin and Giebisch's The Kidney': Elsevier; 2008. P. 2339-2398.
38. van der Graaf AM, Toering TJ, Faas MM, Lely AT. From preeclampsia to renal disease: a role of angiogenic factors and the renin-angiotensin aldosterone system? Nephrol Dial Transplant. 2012;27 Suppl 3:iii51-7.
39. Garovic VD, Wagner SJ, Petrovic LM, Gray CE, Hall P, Sugimoto H, Kalluri R, Grande JP. Glomerular expression of nephrin and synaptopodin, but not podocin, is decreased in kidney sections from women with preeclampsia. Nephrol Dial Transplant. 2007;22(4):1136-43.
40. Doty JM, Saggi BH, Sugerman HJ, Blocher CR, Pin R, Fakhry I, Gehr TW, Sica DA. Effect of increased renal venous pressure on renal function. J Trauma. 1999;47(6):1000-3.
41. Ha TS, Lee EJ. ACE inhibition can improve orthostatic proteinuria associated with nutcracker syndrome. Pediatr Nephrol. 2006;21(11):1765-8.