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Peer-reviewed author version

GYSELAERS, Wilfried; Mesens, Tinne; TOMSIN, Kathleen; MOLENBERGHS, Geert & Peeters, Ludo (2010) Maternal renal interlobar vein impedance index is higher in early- than in late-onset preeclampsia. In: ULTRASOUND IN OBSTETRICS & GYNECOLOGY, 36(1). p. 69-75.

DOI: 10.1002/uog.7591

Handle: <http://hdl.handle.net/1942/10637>

# **Maternal Renal Interlobar Vein Impedance Index is higher in early than in late onset preeclampsia.**

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**Running title:** Renal Venous Dopplers in early and late onset Preeclampsia

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## **Abstract**

**Aims:** To compare Renal Interlobar Vein (RIV) Doppler parameters during uncomplicated pregnancy (UP), early onset (EPE) and late onset preeclampsia (LPE), and to evaluate postnatal persistence of gestational abnormalities.

**Methods:** All women had a renal duplex scan according to a standard protocol. Women with UP were evaluated at 28 to 32w and at 34 to 37 weeks, those with preeclampsia were evaluated once during pregnancy, and all women were rescanned between 4 w and 18 months after delivery. During the scan, 3 consecutive measurements of RIV maximum (MxV) and minimum (MnV) velocities per kidney were printed ; afterwards, the mean of these 3 values was recorded, and Delta velocity (DeltaV) and Impedance Index (RIVI) were calculated respectively as  $MxV - MnV$  and  $\Delta V / MxV$ . Preeclampsia at gestation < 34 weeks was defined EPE, and at gestation  $\geq 34$  weeks was defined LPE. For UP, EPE and LPE, gestational and non-gestational values were categorised. Group- specific means  $\pm$  SD were calculated and compared with T- and F-test.

**Results:** A total of 18 women with UP, 21 with EPE and 19 with LPE were evaluated. For both left and right kidney, RIVI was significantly higher in EPE than in LPE ( $0.48 \pm 0.11$  versus  $0.41 \pm 0.07$ ,  $p=0.02$ , resp.  $0.46 \pm 0.15$  versus  $0.36 \pm 0.11$ ,  $p=0.02$ ), and also higher than in UP ( $0.48 \pm 0.11$  versus  $0.36 \pm 0.04$ ,  $p = 0.0001$  resp.  $0.46 \pm 0.15$  versus  $0.33 \pm 0.04$ ,  $p = 0.001$ ). For LPE, the differences with UP were not or borderline significant. None of the gestational differences persisted after delivery.

**Conclusion:** RIV Impedance Index is significantly higher in EPE than in LPE and UP. This observation is consistent with other reports, showing evidence for high systemic vascular resistance in EPE, but not in LPE. RIV Doppler studies are not useful to evaluate persistence of hemodynamic abnormalities after preeclampsia.

## Introduction

Venous Impedance Index is considered the Doppler equivalent of arterial Resistance Index, and is defined as  $[\text{Maximum flow velocity (MxV)} - \text{Minimum flow velocity (MnV)}] / \text{MxV}$ .

Renal Interlobar Vein (RIV) Impedance Index (RIVI) has been reported as a Doppler parameter to assess renal venous hemodynamics during pregnancy and postpartum <sup>1;2</sup>.

Compared with normal pregnancy, an increase of RIVI was observed in preeclampsia (PE) <sup>3</sup>.

Increased systemic vascular resistance is considered a strong predisposing factor for early onset PE (EPE) <sup>4</sup>. Late onset PE (LPE) however may occur with normal or low vascular resistance <sup>5</sup>. Persistence of vessel wall and hemodynamic dysfunction has been reported for women, who formerly had PE. Both arterial and venous endothelial function was diminished<sup>6</sup> and conjunctival venular diameters were smaller <sup>7</sup> in postpartum of women who had PE compared to those with normal pregnancy outcome. Relative hypovolemia, reduced effective renal plasma flow and increased renal vascular resistance and filtration fraction have been observed in postpartum of women with PE <sup>8</sup>.

To our knowledge, comparison of maternal venous Doppler parameters between early and late onset PE, or persistence of abnormal PE related venous Doppler parameters have not yet been published. The study, presented in this paper, was set out to evaluate whether (1) Renal Interlobar Venous Doppler parameters were different between early and late onset PE, and (2) persistence of PE-related increase of RIVI was still present weeks or months after delivery.

## Materials and methods

Before study onset, approval of the local ethical committee was obtained.

Only women with singleton pregnancies were evaluated: (1) 18 women with uncomplicated pregnancies (UP) and normal outcome confirmed at birth, who were evaluated at 28 - 32 weeks, at 34 – 37 weeks and at 5-8 weeks postpartum, and (2) 40 women with PE, who were evaluated during admission at the Maternal Fetal Medicine Unit of the *Ziekenhuis Oost Limburg*, Genk Belgium, and again between 4 weeks and 18 months postpartum. PE was defined as: (1) pregnancy induced hypertension ( $\geq 140 / 90$  mm Hg) on at least two occasions  $\geq$  six hours apart, and (2) proteinuria  $\geq 300$  mg/24 h<sup>9</sup>. PE, diagnosed at gestation  $< 34$  weeks was defined early onset PE (EPE), whereas at gestation  $\geq 34$  weeks this was defined late onset PE (LPE).

After informed consent, all women had a conventional ultrasound scan together with a Doppler flow examination of both kidneys. All examinations were performed by the same ultrasonographer (WG), using a 3,5-7 MHz probe (Hitachi EUB 6500). All women were examined in supine position and both kidneys were scanned in the transverse plane. The antero-posterior pyelocalyceal diameter (PCD) was measured (mm) at the level just above the renal hilus. The interlobar arteries and veins were identified using colour Doppler flow mapping. The impact of breathing movements on the ultrasound image was demonstrated to every patient and the relevance of holding breath during Doppler measurements was explained and demonstrated. Once the patient was familiar with the instructions of the ultrasonographer, the examination was performed according to a standard protocol. (1) A simultaneous Doppler signal of both interlobar arteries and veins was required for unequivocal identification of the examined vessels. (2) The real time ultrasound image in combined B-D mode was frozen after visualisation of at least two to three similar Doppler flow patterns during interrupted breathing. (3) As the direction of the Doppler beam was

mostly in line with the examined vessels, adjustment of the beam was rarely needed. If so, the axis of adjustment was always within  $\pm 30^\circ$ . (4) Venous maximum velocity (MxV) and minimum velocity (MnV) were plotted and printed. Throughout the course of the ultrasound examination, the ultrasonographer was blinded for the depicted results at the screen. (5) For every woman, three consecutive measurements were printed for each kidney. (6) After the scan, Delta Velocity (DeltaV) and Renal Interlobar Venous Impedance Index (RIVI) were calculated respectively as  $MxV - MnV$  and  $\Delta V / MxV$ .

The mean of three measurements of MxV, MnV, DeltaV and RIVI was considered the kidney-specific value, which was registered in the database. The reproducibility of this methodology was evaluated by defining RIVI twice for each kidney in a set of 24 women: the intra-class or, in this study, the intra-kidney correlation coefficient was calculated using restricted maximum likelihood estimation<sup>10;11</sup>.

The presence or absence of a Venous pre-acceleration Nadir (VPAN), as described by Bateman<sup>3</sup>, was evaluated. Doppler wave prints of all 58 patients were labelled and pooled for blind evaluation (WG). When the waveforms showed a sharp deceleration of flow velocity prior to the acceleration of the following Doppler wave (Fig 1), VPAN was considered positive. When this deceleration was absent, VPAN was considered negative.

The data were categorized in groups: non-gestational and gestational values at 30 and 36 weeks of women with uncomplicated pregnancies, non-gestational and gestational values of women with EPE and of those with LPE. Mean and SD of MxV, MnV, DeltaV and RIVI were calculated for each group, and fractions of positive and negative VPAN were determined. T-test was used for comparison of means and F-test for comparison of Standard Deviations.

## Results

A total of 58 women were evaluated, 18 with uncomplicated pregnancies, 21 with EPE and 19 with LPE.

Intra-class or intra-kidney correlation between two consecutive RIVI measurements in a group of 24 women was 0.88.

Table 1 shows the comparison of RIV Doppler parameters between 30 weeks UP and EPE and between 36 weeks UP and LPE. As is shown, RIVI is significantly higher in EPE than in UP, whereas this is only borderline significant at 36 weeks. For both left and right kidneys, MnV is significantly lower and DeltaV is significantly higher in EPE than in UP. For MnV a similar trend is seen at 36 weeks, however this is only significant for the left kidney, but not for the right one. DeltaV values are not significantly different between UP and LPE. Results are presented graphically in Figure 2. The fraction of waveforms with VPAN is significantly larger in EPE than in LPE (Table 1). Due to an increasing number of VPAN from 30 to 36 weeks in uncomplicated pregnancies, the VPAN fractions are not different between LPE and UP.

Table 2 shows the comparison of patient characteristics and RIV Doppler parameters between EPE and LPE. As is shown, women's age, parity, medication use, pre-existing hypertension, serum uric acid and proteinuria are not different between both groups. For both kidneys, DeltaV and RIVI are significantly larger in EPE than in LPE. Apart from higher left kidney MxV values in EPE, no significant differences were found for other parameters between both groups.

In non-gestational conditions, the situation is different than during pregnancy. Table 3 shows the mean values and Standard Deviations of RIV Doppler parameters in both kidneys of women after UP, EPE and LPE. These values are not different at the 0.05 level of significance between the three groups. The only exception is in the right kidney of women with LPE,

where DeltaV is significantly higher than in women with EPE ( $p = 0.02$ ) and in those with UP ( $p=0.03$ ). As a result, RIVI is also significantly higher in women with LPE than in EPE ( $p = 0.02$ ). These non-gestational results show that the differences in RIV Doppler parameters during pregnancy, as presented in Table 1, do not persist post-delivery. Table 3 also shows that the Standard Deviations of several RIV parameters from women in the PE groups are larger than from women with uncomplicated pregnancies. For many of these parameters, differences are significant in F-test.



## Discussion

Human pregnancy is a physiologic condition, requiring major cardiovascular and hemodynamic adaptations of the female organism. Maternal gestational maladaptation is considered an important predisposing factor towards the development of pregnancy-specific diseases, such as preeclampsia <sup>4</sup> and/or fetal growth restriction <sup>12</sup>. Many of the maladapted hemodynamic parameters persist long-term after preeclampsia and may be of importance towards the development of cardiovascular disease in later life <sup>13</sup>. Cardiovascular and hemodynamic studies on preeclampsia have mainly focussed on the arterial, pre-cappillary site of the circulatory system. Evidence is growing on the important role to play for the venous, post-cappillary site of the circulation in gestational adaptation or maladaptation syndromes. The venous compartment contains as much as 80 % of the total blood volume, and the balance between venous tone and intravascular blood volume is crucial towards the regulation of cardiac output <sup>14</sup>. In preeclampsia, venous capacitance, expansion of the plasma volume and cardiac output are reduced, as compared with normal controls <sup>15</sup>. Methods to study human venous hemodynamics are complex and often difficult to perform in pregnancy <sup>14</sup>. Doppler measurement of Renal Interlobar Vein Impedance Index has been reported as a simple and non-invasive method to study gestational renal venous hemodynamics <sup>1;2</sup>. In uncomplicated pregnancy, RIVI decreases during the second trimester <sup>2</sup>. In preeclampsia however, an increase of RIVI has been reported <sup>3</sup>. The (patho)physiologic background mechanisms behind these observations are not yet well understood, as experimental and clinical studies on this subject are only just at the beginning. We performed the study, presented in this paper, to evaluate the feasibility and sense of measuring RIVI in women with preeclampsia, both in pregnant and non-pregnant conditions.

The methodology of RIVI measurement, as applied in this study, allows obtaining reproducible results for RIVI, which is illustrated by an intra-kidney correlation coefficient of 0.88.

Our results confirm the observation of Bateman, who reported higher RIVI values in PE than in normal pregnancies. Our data add to this observation by illustrating that this increase mainly accounts for EPE, and to a much lesser degree for LPE. In fact, LPE values are only slightly different from those of uncomplicated pregnancies. This difference between EPE and LPE can be attributed to significantly higher DeltaV values, defined as the difference between maximum and minimum velocities (Table 1). The RIV Doppler values, presented in Table 2, suggest a stronger PE-related RIV hemodynamic response in EPE than in LPE. As such, our data are consistent with reported data in literature. Easterling et al found a hyperdynamic circulation and high systemic vascular resistance in early onset PE, which is often associated with impaired fetal growth and low placental volumes <sup>16</sup>. Late onset PE however occurred with normal or low vascular resistance and normal birth weights and placental volumes <sup>5</sup>. Carbillon et al reviewed clinical and experimental data, illustrating that in EPE, vasopressor agents were already active at a much earlier stage in pregnancy than in LPE <sup>4</sup>. Doppler studies of the uterine artery have shown that abnormal notching of the Doppler waveform, suggestive for increased arterial wall resistance, appeared to be much better in predicting severe, early onset PE than late onset PE <sup>17</sup>. As Venous Impedance Index is considered the Doppler equivalent of Arterial Resistance Index, our results, as presented in Table 1, may be considered representative for reduced vessel wall compliance of the veins in early onset preeclampsia, similar to that observed in arteries. As such, our results may be considered the Doppler representation of reduced venous capacitance, reported for PE <sup>18</sup>. Whether these results can be attributed entirely to the presence or absence of VPAN, is subject of further research.

The differences of gestational RIVI Doppler values between UP and PE (Table 1) are not present anymore in the non-gestational state (Table 3). This indicates that RIV Doppler measurement is not useful to evaluate persistence of hemodynamic abnormalities after preeclampsia, such as relative hypovolemia, reduced effective renal plasma flow, increased renal vascular resistance and filtration fraction <sup>8</sup>. Standard Deviations of some non-gestational RIV Doppler parameters however are larger in the two groups of women with PE than in those with uncomplicated pregnancies (Table 3). This indicates a larger variability of Doppler measurements obtained in the post-PE groups. Although it might be hypothesised that this observation suggests different venous characteristics persisting after PE than after normal pregnancy, the relevance of this finding remains unclear.

We conclude that the current study on Doppler assessment of Renal Interlobar Veins shows remarkable differences between uncomplicated pregnancies and preeclampsia, and also between early and late onset preeclampsia. These differences do not persist after delivery, but the variability of non-gestational values in the post-PE groups is larger than in women with normal pregnancies. Our study illustrates that maternal gestational hemodynamic adaptation in normal pregnancy or PE-related maladaptation can also be documented by RIVI Doppler measurement, and therefore this parameter is worthwhile further investigation.

**Table 1** Comparison of Renal Interlobar Vein Doppler characteristics between normal, early onset (Early PE) and late onset (Late PE) preeclamptic pregnancies.

	Normal (n = 18)	Early PE (n = 21)	P	Normal (n = 18)	Late PE (n = 19)	P
<b>Gestat</b>	30,0+/-1,9	30,6+/-2,3	0,4	36,0+/-0,5	35,9+/-1,4	0,68
<b>Left kidney</b>						
<b>MxV</b>	9,20+/-1,73	8,47+/-1,69	0,19	8,41+/-1,38	7,25+/-1,59	0,02
<b>MnV</b>	5,90+/-1,24	4,39+/-1,09	0,0003	5,17+/-1,01	4,35+/-1,05	0,02
<b>DeltaV</b>	3,30+/-0,64	4,08+/-1,47	0,04	3,08+/-0,49	2,89+/-0,73	0,35
<b>RIVI</b>	0,36+/-0,04	0,48+/-0,11	0,0001	0,37+/-0,06	0,41+/-0,07	0,07
<b>VPAN n (%)</b>	6 (33,3)	15 (71,4)	0,04	11 (61,1)	9 (47,3)	0,61
<b>Right kidney</b>						
<b>MxV</b>	10,31+/-2,39	9,28+/-1,93	0,15	9,38+/-1,91	8,93+/-2,37	0,52
<b>MnV</b>	6,93+/-1,62	4,88+/-1,51	0,0002	6,58+/-1,42	5,80+/-1,48	0,1
<b>DeltaV</b>	3,38+/-0,87	4,40+/-1,92	0,04	2,80+/-0,82	3,13+/-1,71	0,46
<b>RIVI</b>	0,33+/-0,04	0,46+/-0,15	0,001	0,30+/-0,05	0,36+/-0,11	0,04
<b>VPAN n (%)</b>	2 (11,1)	13 (61,9)	0,004	4 (22,2)	8 (42,1)	0,35

MxV:	Maximum Velocity	Early PE:	Early onset Preeclampsia
MnV:	Minimum Velocity	Late PE:	Late onset Preeclampsia
DeltaV:	Delta Velocity (MxV-MvnV)	Gestat:	Gestation
RIVI:	Renal Interlobar Vein Impedance Index		
VPAN :	Venous Pre-acceleration Nadir		

**Table 2** Comparison of patient characteristics and Renal Interlobar Vein Doppler characteristics between early onset (Early PE) and late onset (Late PE) preeclampsia.

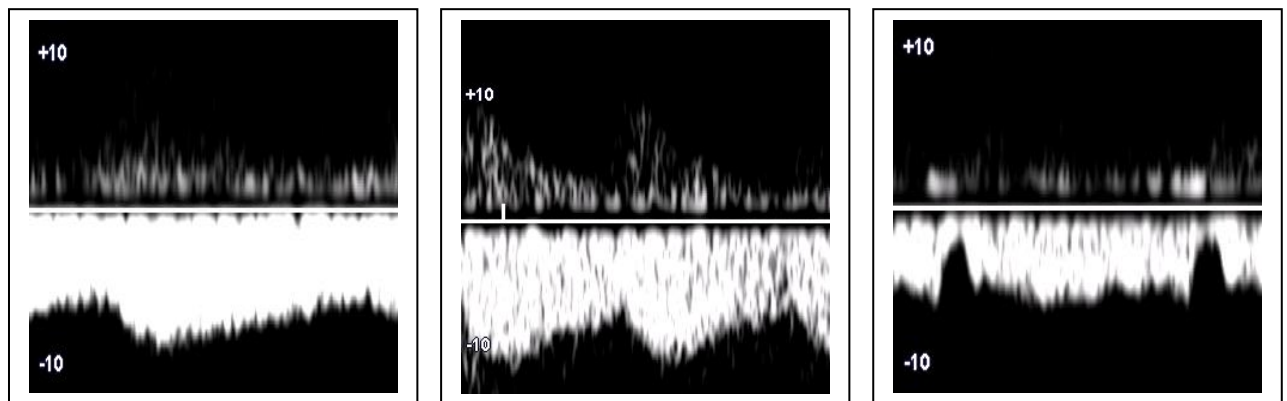
	<b>Early PE (n = 21)</b>	<b>Late PE (n = 19)</b>	<b>P</b>
<b>Age</b>	27,9+/-3,8	29,4+/-4,3	0,24
<b>Parity</b>	0,48+/-0,75	0,26+/-0,45	0,27
<u>Medication</u>			
<b>Anti-hypertensives n (%)</b>	9 (42,9)	8 (42,1)	0,79
<b>Anticoagulation n (%)</b>	3 (14,3)	1 (5,3)	0,68
<u>Pre-existing disease</u>			
<b>Chronic hypertension</b>	2 (9,5)	1 (5,3)	0,93
<b>Renal Disease</b>	0	1 (5,3)	NA
<b>Diabetes Mellitus Type 1</b>	0	2 (10,6)	NA
<b>Reumatic Disease</b>	0	1 (5,3)	NA
<u>Renal function</u>			
<b>Uric acid (µmol/L)</b>	410,1+/-85,9	366,0+/-85,8	0,11
<b>Proteinuria (mg/24 h)</b>	2282+/-2482	2013+/-2383	0,73
<b>Left Kidney</b>			
<b>MxV</b>	8,47+/-1,69	7,25+/-1,59	0,02
<b>MnV</b>	4,39+/-1,09	4,35+/-1,05	0,9
<b>DeltaV</b>	4,08+/-1,47	2,89+/-0,73	0,002
<b>RIVI</b>	0,48+/-0,11	0,41+/-0,07	0,02
<b>VPAN n (%)</b>	15 (71,4)	9 (47,3)	0,22
<b>Right Kidney</b>			
<b>MxV</b>	9,28+/-1,93	8,93+/-2,37	0,61
<b>MnV</b>	4,88+/-1,51	5,80+/-1,48	0,06
<b>DeltaV</b>	4,40+/-1,92	3,13+/-1,71	0,03
<b>RIVI</b>	0,46+/-0,15	0,36+/-0,11	0,02
<b>VPAN n (%)</b>	13 (61,9)	8 (42,1)	0,35

MxV: Maximum Velocity  
 MnV: Minimum Velocity  
 DeltaV: Delta Velocity (MxV-MvnV)  
 RIVI: Renal Interlobar Vein Impedance Index  
 VPAN : Venous Pre-acceleration Nadir  
 NA : Non-applicable

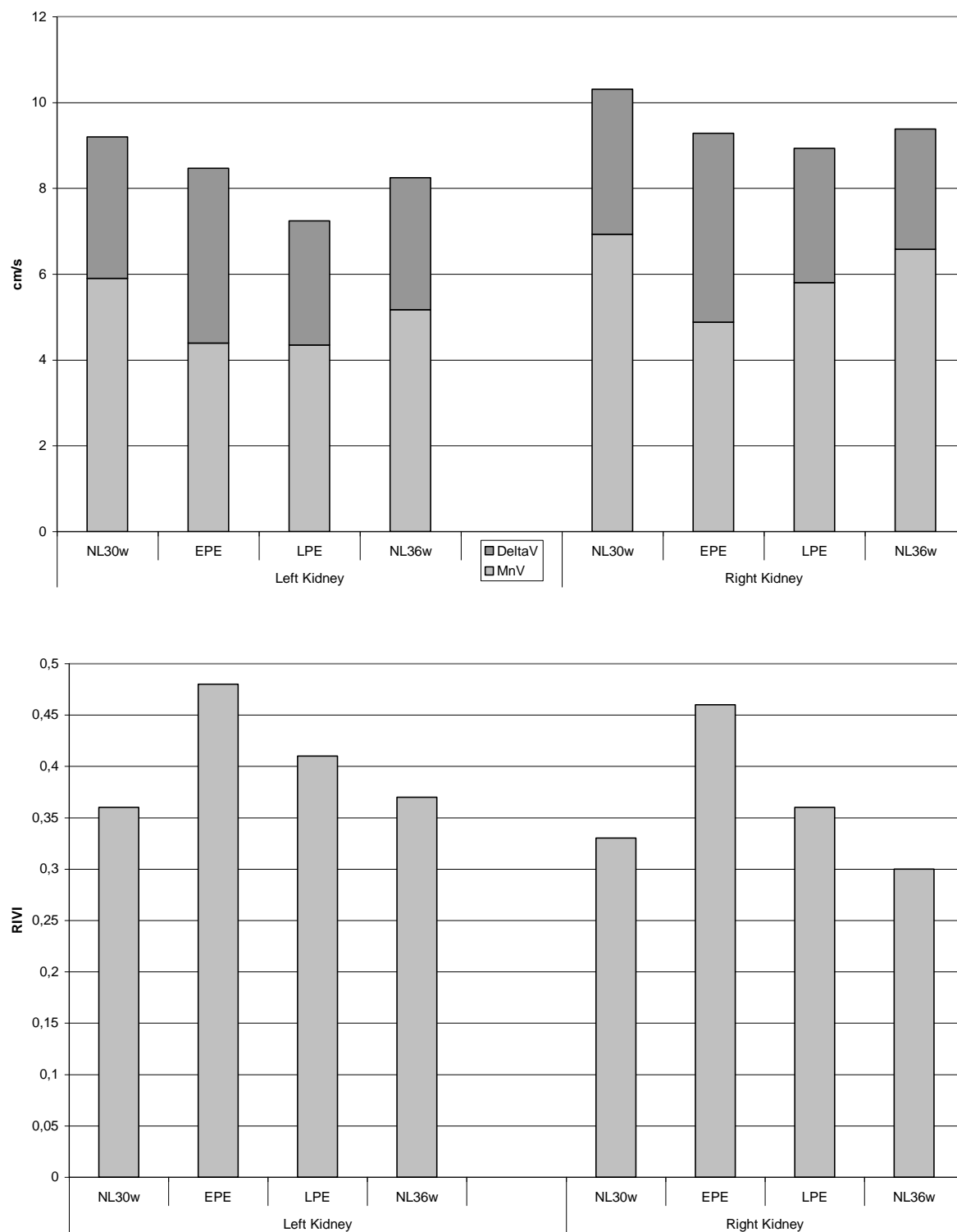
**Table 3** Comparison of Renal Interlobar Vein Doppler characteristics, measured between 4 weeks and 18 months after delivery, of women with normal pregnancies, early onset (Early PE) and late onset (Late PE) preeclampsia.

	<b>Early PE (n = 21)</b>		<b>Normal (n = 18)</b>		<b>Late PE (n=19)</b>
	Mean+/-SD	F-test	Mean+/-SD	F-test	Mean+/-SD
<b>Left kidney</b>					
<b>MxV</b>	8,29+/-1,56	0,014	7,59+/-0,91	0,005	8,45+/-1,74
<b>MnV</b>	5,00+/-1,18	0,07	4,24+/-0,83	0,004	4,70+/-1,61
<b>DeltaV</b>	3,29+/-0,95	0,31	3,35+/-0,85	0,46	3,75+/-0,93
<b>RIVI</b>	0,40+/-0,08	0,31	0,44+/-0,09	0,1	0,45+/-0,11
<b>Right kidney</b>					
<b>MxV</b>	9,91+/-1,91	0,12	9,26+/-1,44	0,014	10,29+/-2,48
<b>MnV</b>	5,78+/-1,96	0,004	5,00+/-1,02	0,002	5,11+/-2,08
<b>DeltaV</b>	4,13+/-1,07	0,27	4,26+/-0,92	0,02	5,18+/-1,53
<b>RIVI</b>	0,42+/-0,12	0,01	0,46+/-0,07	0,02	0,51+/-0,12
MxV: Maximum Velocity MnV: Minimum Velocity DeltaV: Delta Velocity (MxV-MvnV) RIVI: Renal Interlobar Vein Impedance Index VPAN : Venous Pre-acceleration Nadir					

**Figure 1** Examples of Doppler waveforms in normal and preeclamptic pregnancies. The left Figure shows a uniform pattern in a 28 weeks uncomplicated pregnancy, with absence of a venous pre-acceleration nadir (VPAN). The middle Figure represents a Doppler waveform from a 36 weeks uncomplicated pregnancy, showing a small but clearly visible VPAN. The right Figure shows a Doppler wave from an early onset preeclamptic pregnancy, with a deep VPAN.



**Figure 2** Renal Interlobar Vein Minimum (MnV), Delta (DeltaV) and maximum velocities (Upper graph) and Impedance Index (RIVI, lower graph) of left and right kidneys during normal pregnancy at 30 w (NI 30w) and 36 w (NI 36w) and during early onset (EPE) and late onset (LPE) preeclampsia.





## Reference List

- (1) Karabulut N, Baki YA, Karabulut A. Renal vein Doppler ultrasound of maternal kidneys in normal second and third trimester pregnancy. *Br J Radiol* 2003; 76(907):444-447.
- (2) Gyselaers W, Verswijvel G, Molenberghs G, Ombelet W. Interlobar Venous Flow Is Different between Left and Right Kidney in Uncomplicated Third Trimester Pregnancy. *Gynecol Obstet Invest* 2007; 65(1):6-11.
- (3) Bateman GA, Giles W, England SL. Renal venous Doppler sonography in preeclampsia. *J Ultrasound Med* 2004; 23(12):1607-1611.
- (4) Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. *Obstet Gynecol Surv* 2000; 55(9):574-581.
- (5) Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol* 1990; 76(6):1061-1069.
- (6) Agatista PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol* 2004; 286(4):H1389-H1393.
- (7) Houben AJ, de Leeuw PW, Peeters LL. Configuration of the microcirculation in pre-eclampsia: possible role of the venular system. *J Hypertens* 2007; 25(8):1665-1670.
- (8) van Beek E, Ekhardt TH, Schiffers PM, van Eyck J, Peeters LL, de Leeuw PW. Persistent abnormalities in plasma volume and renal hemodynamics in patients with a history of preeclampsia. *Am J Obstet Gynecol* 1998; 179(3 Pt 1):690-696.
- (9) Walfisch A, Hallak M. Hypertension. In: James D, Steer P, Weiner C, Gonik B, editors. *High risk pregnancy: management options*. Philadelphia, Pennsylvania: Elsevier Inc, 2006: 772-789.
- (10) Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. 2 ed. New York: Springer, 2001.
- (11) Laenen A, Vangeneugden T, Geys H, Molenberghs G. Generalized reliability estimation using repeated measurements. *Br J Math Stat Psychol* 2006; 59(Pt 1):113-131.
- (12) Carrera JM, Devesa R, Serra B. Etiology and pathogenesis of intrauterine growth retardation. In: Kurjac A, editor. *Textbook of Perinatal Medicine: a comprehensive guide to modern clinical perinatology*. London, New York: The Parthenon Publishing Group Ltd, 1998: 1171-1191.
- (13) Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *BJOG* 2003; 110(11):1029-1031.

- (14) Pang CC. Measurement of body venous tone. *J Pharmacol Toxicol Methods* 2000; 44(2):341-360.
- (15) Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv* 1994; 49(12 Suppl):S1-14.
- (16) Easterling TR, Benedetti TJ, Carlson KC, Brateng DA, Wilson J, Schmucker BS. The effect of maternal hemodynamics on fetal growth in hypertensive pregnancies. *Am J Obstet Gynecol* 1991; 165(4 Pt 1):902-906.
- (17) Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; 18(5):441-449.
- (18) Sakai K, Imaizumi T, Maeda H, Nagata H, Tsukimori K, Takeshita A et al. Venous distensibility during pregnancy. Comparisons between normal pregnancy and preeclampsia. *Hypertension* 1994; 24(4):461-466.