

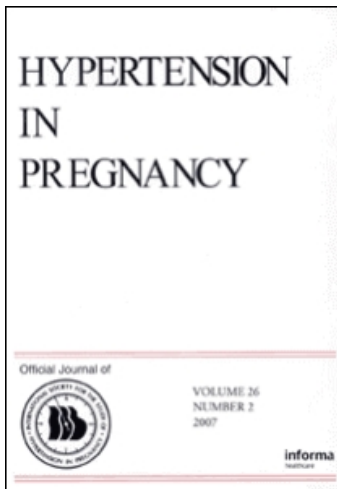
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Doppler Measurement of Renal Interlobar Vein Impedance Index in Uncomplicated and Preeclamptic Pregnancies

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Objective: To define normal values of Renal interlobar vein impedance index (RIVI) throughout gestation, as a reference to RIVI in preeclampsia (PE). **Methods:** Longitudinal evaluation of 20 uncomplicated pregnancies (UP) by standard renal duplex scan, every 4 weeks during pregnancy and postpartum. Comparison of RIVI between 40 PE and UP, and plotting of PE values against the normal reference range at corresponding gestation. **Results:** In PE, RIVI is significantly higher than in UP, the difference being larger at the left side and in cases of preeclampsia remote from term. **Conclusion:** Increase of RIVI in women with PE is gestation-dependant.

Keywords Renal interlobar veins, Venous impedance index, Preeclampsia, Doppler, Venous tone.

INTRODUCTION

Venous impedance index (VI), as measured by Duplex ultrasonography, is considered the venous equivalent of arterial resistance index: $VI = [\text{Maximum Velocity (MxV)} - \text{Minimum Velocity (MnV)}] / \text{MxV}$. Application of this parameter to renal interlobar veins (RIV) was reported to be useful in obstructive uropathy (1,2). In uncomplicated pregnancies (UP), a decrease of renal interlobar venous impedance index (RIVI) was observed, and this decrease was more pronounced in the right kidney (RK) than in the left one (LK) (3,4). It was hypothesized that this observation resulted from retro peritoneal compression

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by the gravid uterus (3,4). In pre-eclampsia (PE) however, higher values of RIVI were reported as compared to UP (5).

Because the etiological background mechanisms behind these reported observations have not yet been well studied, we set out this pilot study to: 1) evaluate the Doppler characteristics of RIV at different stages of normal pregnancy and postpartum, in order to illustrate and understand better the hemodynamic background of gestational RIVI changes; 2) establish a normal RIVI reference range during pregnancy; 3) compare RIVI values in PE with the normal reference range.

MATERIALS AND METHODS

Before study onset, approval of the local ethical committee was obtained. Only women without previous history or symptoms of renal disease were included, and only singleton pregnancies were considered.

We evaluated two groups of women—Group 1: 20 women with UP and normal outcome confirmed at birth, who were evaluated prospectively every four weeks between 12 and 36 weeks of gestation and in early (days) and late (weeks) postpartum (PP), and Group 2: 40 women with PE, admitted to the Maternal Fetal Medicine Unit of the Ziekenhuis Oost Limburg, Genk, Belgium. PE was defined as: 1) pregnancy-induced hypertension ($\geq 140 / 90$ mm Hg) on at least two occasions ≥ 6 hours apart, and 2) proteinuria ≥ 300 mg/24 h. PE pregnancies were categorized irrespective of gestational age as mild or severe, according to the criteria set by the International Society for the Study of Hypertension in Pregnancy (6).

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 using a 3,5–7 MHz probe (Hitachi EUB 6500). All women were examined in supine position to evaluate a possible retroperitoneal compressive effect from the gravid uterus. 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 visualization of at least two to three similar Doppler flow patterns during interrupted breathing (Figures 1 and 3). 3) Doppler wave duration (DWD) was measured by measuring the length of

the cycle from start to end (msec). 4) 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 $\pm 30^\circ$. 5) 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 results at screening. 6) For every woman, three consecutive measurements were printed for each kidney. 7) After the scan, delta velocity (DeltaV) and renal interlobar venous impedance index (RIVI) were calculated as $MxV - MnV$ and $\Delta V / MxV$, respectively.

The mean of three measurements of MxV, MnV, 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 (7,8).

The data of UP were aligned according to gestational age: 12w, 16w, 20w, 24w, 28w, 32w, 36w, days postpartum (PPD), and weeks postpartum (PPW). By way of preliminary analysis, mean and SD of DWD, PCD, MxV, MnV, DeltaV, and RIVI were calculated for each stage of gestation, and the evolution of these parameters during UP and PP was presented graphically. For our principal analysis, differences between left and right kidneys were evaluated using an appropriate *F*-test, resulting from a repeated-measures model of the so-called mixed- model type (7). Such models generalize the well known repeated-measures analysis of variance design, by allowing for flexible subject-specific regression functions and a wealth of variance and correlation structures. In our case, we avoided imposing specific time functions, thereby minimizing the risk of model mis-specification and subsequent biases (7).

For UP RIVI, 5th, 50th, and 95th percentiles were calculated and presented graphically to represent a study- and population-specific normal reference range. RIVI-values of individual mild and severe PE pregnancies were plotted against these reference values. A *t*-test was used for comparison between UP at 32 weeks and PE. The nominal level was $\alpha = 0.05/3$, to account for multiple comparisons.

RESULTS

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

The 20 women with UP had nine RIV Doppler measurements, respectively at gestation 12.1 ± 0.9 weeks, 15.8 ± 0.7 weeks, 20.0 ± 0.6 weeks, 24.0 ± 0.8 weeks, 28.4 ± 0.9 weeks, 32.1 ± 0.6 weeks and 36.0 ± 0.4 weeks, and in PP at 3.4 ± 1.3 days and 45.6 ± 4.5 days post-delivery (Figure 1). PE pregnancies were evaluated once at gestations varying between 22 and 40 weeks, depending

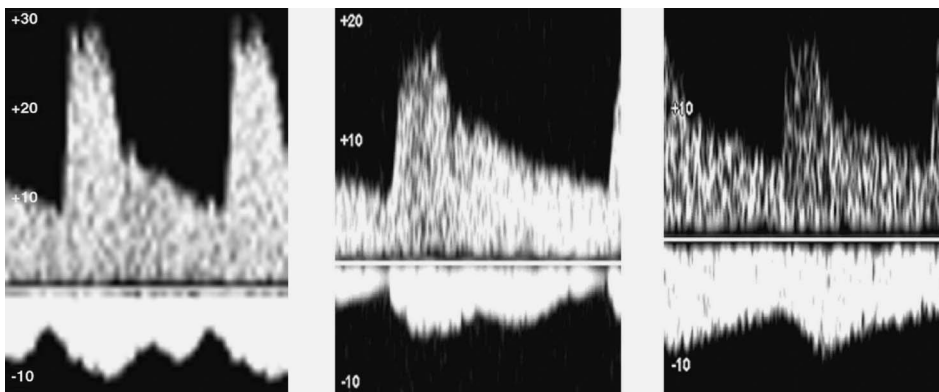


Figure 1: Example of three different types of renal interlobar venous waveforms, observed in uncomplicated pregnancies: pulsatile (*left*), intermediate (*middle*) and uniform (*right*). Similar to the gestational changes reported for hepatic veins (29), the pulsatile type was observed more frequently at early gestation and in postpartum, whereas the uniform type was mainly present in third trimester pregnancies. For the study presented in this paper, a quantitative assessment of gestational evolution was performed by measurement of Doppler wave duration (DWD), maximum (MxV) and minimum (MnV) flow velocities at different stages of gestation.

on the moment of hospital admission (Figure 3): mean gestation at admission was 32.9 ± 3.8 weeks. Seventeen of 40 (42.5%) PE pregnancies were classified as severe and 23 (57.5%) as mild.

Throughout uncomplicated pregnancy, DWD decreased gradually during gestation from 832 ± 150 milliseconds (mean heart rate [HR] 72 / min) at 12 weeks to 660 ± 84 ms (HR 91 / min) at 36 weeks, and increased fast in PP to a maximum of 920 ± 146 ms (HR 65/min) at 6 weeks PP.

The evolution of intrarenal PCD in UP was significantly different between both kidneys (F -value = 18.62, $p < 0.0001$). RK PCD was significantly larger at 36 than at 12 weeks (9.2 ± 5.3 versus 4.8 ± 1.0 mm, $p < 0.001$), whereas this was not true for LK (4.8 ± 1.0 versus 4.3 ± 1.0 , $p = 0.1$). This difference disappeared in postpartum.

Figure 2 shows the gestational evolution of RIV Doppler parameters in UP and PP: MxV, MnV, DeltaV and RIVI. In both kidneys, MxV increased to a peak value at 16 weeks, whereas it decreased gradually until PP (Figure 2a). MnV also increased to a maximum value at gestations 24 w (RK) or 28 w (LK), after which it decreased until PP (Figure 2b). RK MxV and MnV were consistently higher than in LK. This was also true for DeltaV between 12 and 24 weeks and in PP; between 28 and 36 weeks however, DeltaV was equal in both kidneys (Figure 2c). As a result, RIVI was lower in RK than in LK at gestation 28 to 36 weeks (Figure 2d). The evolution of all Doppler parameters was significantly different between both kidneys: the F -value was 4.48 for MxV ($p = 0.004$), 6.89 for MnV ($p = 0.0003$), 6.07 for DeltaV ($p = 0.0007$) and 8.45 for RIVI ($p < 0.0001$).

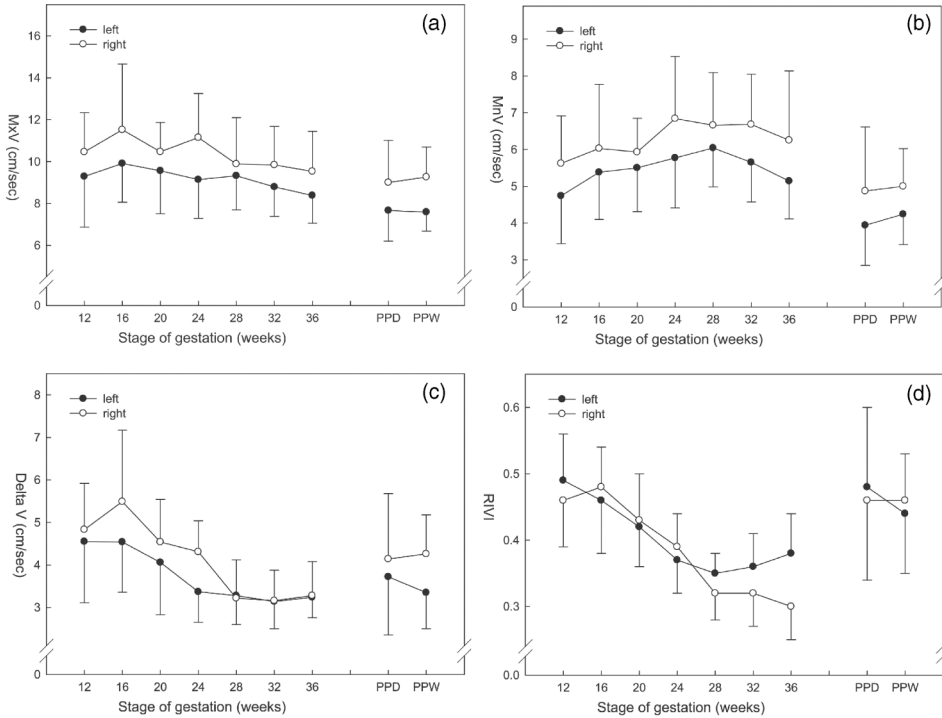


Figure 2: Evolution of renal interlobar vein (RIV) maximum velocity (MxV), minimum velocity (MnV), Delta velocity (DeltaV = MxV-MnV) and impedance index (RIV = DeltaV/MxV), as measured in left and right kidneys of 20 women with uncomplicated pregnancies, at different stages of gestation and postpartum (PPD = days postpartum, PPW = weeks postpartum). The patterns of MxV (2a) and MnV (2b) show similarity with known gestational evolutions of respectively cardiac stroke volume (11) and parameters of renal function, such as glomerular filtration, effective renal plasma flow and physiologic proteinuria (19). Right renal velocities are consistently higher than the left ones, except for DeltaV between 28 and 36 weeks (2c). As a result, third trimester RIV (2d) is lower in the right kidney than in the left.

Table 1 shows the comparison of RIV Doppler parameters between 32w UP and PE. Except for RK MxV, both MxV and MnV were significantly lower in the PE than in the UP group. This was not true for DeltaV. As a result, RIV was significantly higher in the PE than in the UP group. The interkidney difference of RIV, observed in UP, was not significant in PE ($p > 0.05/3$)

Figure 4 shows the 5th, 50th, and 95th percentiles of left kidney RIV in 20 UP. These values can be considered the study- and population-specific normal reference range. Against this reference range, values were plotted of RIV as measured in mild (○) and severe (■) PE pregnancies. As is shown, PE RIV was mostly higher than the normal 95th percentiles, and this was particularly true at gestation between ≤ 34 weeks. At > 34 weeks, PE RIV-values were mainly within the normal reference range. Similar data were found for the right kidney (data not presented).

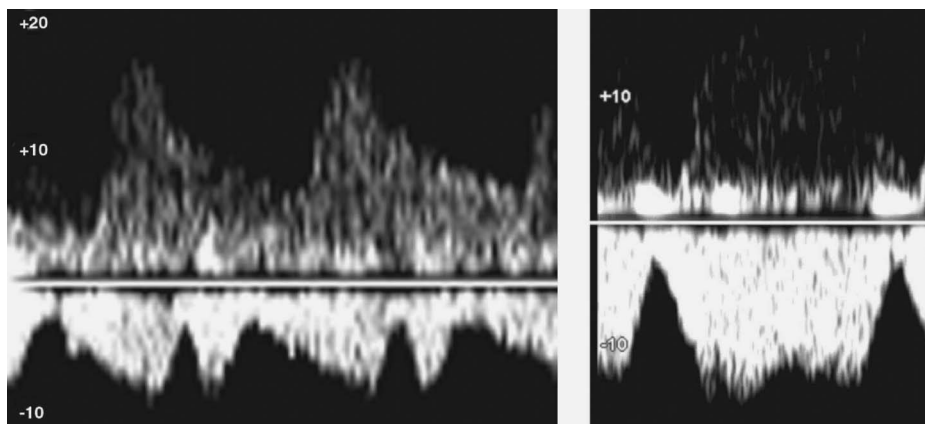


Figure 3: Two examples of renal interlobar venous Doppler flow patterns in preeclamptic (PE) pregnancies, showing sharp decelerations to low flow velocities. This was not observed in our group of uncomplicated third trimester pregnancies (Figure 1). As a result, the shape of renal interlobar venous Doppler waveforms in PE pregnancies was highly variable, which troubled qualitative classification. It is unclear whether this characteristic simply reflects a passive collapse of venous walls following the known PE related plasma volume restriction(25), or whether this represents the Doppler presentation of reduced venous distensibility in PE(26).

Table 1: Comparison of RIV Doppler parameters and intrarenal pyelon diameter (mm) between 40 preeclamptic (PE) and 20 uncomplicated pregnancies (UP) at mean gestation of 32.9 ± 3.8 and 32.1 ± 0.6 weeks respectively ($p > 0.05/3$). To account for multiple comparisons, the nominal level is $\alpha = 0.05/3$

	Left kidney			Right kidney		
	UP	PE	p	UP	PE	p
MxV	8.8 ± 1.4	7.6 ± 1.7	<0.01	9.8 ± 1.8	9.2 ± 2.3	0.26
MnV	5.7 ± 1.1	4.2 ± 1.1	<0.0001	6.7 ± 1.4	5.3 ± 1.6	<0.01
DeltaV	3.1 ± 0.6	3.4 ± 1.1	0.36	3.2 ± 0.7	3.9 ± 1.9	0.09
RIVI	0.36 ± 0.05	0.44 ± 0.09	<0.001	0.32 ± 0.07	0.42 ± 0.13	<0.01
Pyelon	5.0 ± 1.6	5.0 ± 1.5	0.97	8.4 ± 3.4	7.5 ± 8.9	0.68

RIVI Renal Interlobar Venous Impedance Index (DeltaV/MxV)
MxV Maximum velocity (cm/s)
MnV Minimum velocity (cm/s)
DeltaV MxV - MnV (cm/s)
UP Uncomplicated Pregnancies
PE Pre-eclampsia

DISCUSSION

Obtaining Doppler parameters through Duplex ultrasound scan often shows high intra- and inter-observer variability (9,10). Standardisation of scanning methodology therefore is mandatory. We already reported elsewhere a low

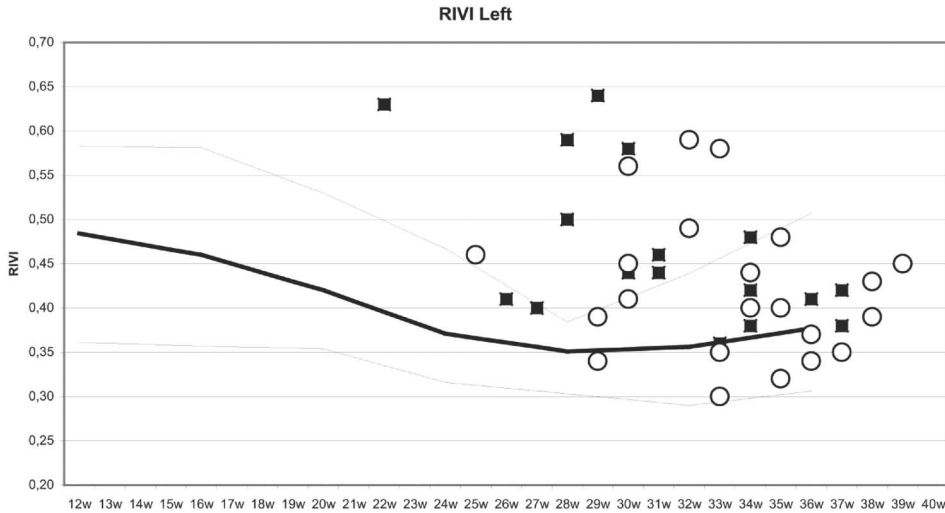


Figure 4: Left renal interlobar venous impedance index (RIVI) of 40 preeclamptic (PE) pregnancies (mild PE (○): $n = 23$, severe PE (■): $n = 17$) relative to gestational age, and plotted against the reference values of 20 uncomplicated pregnancies. Increased values of RIVI were mostly present at gestation ≤ 34 weeks, whereas at > 34 weeks they were mainly within the normal range. Similar data were found for the right kidney (data not presented).

intra-class correlation coefficient of 0.31 to 0.35 between individual RIVI measurements according to our scanning protocol (4). However, the use of mean values from three consecutive RIVI measurements produced more stable data, represented by an intra-kidney correlation coefficient of 0.88. This illustrates that our current methodology allows us to obtain stable and reproducible values for RIVI, eligible for application in this study.

Our observations on Doppler wave duration (DWD) and pyelocaliceal diameter (PCD) are consistent with well known features of gestational physiology. During pregnancy, heart rate is known to increase gradually until term (11): we observed a gradual shortening of DWD, which correlates well with this change. The gestational evolution of right PCD is different from left PCD, as it increases gradually throughout pregnancy until term and decreases again in postpartum. Pressure of the gravid uterus on the ureters, mostly on the right side, is a well known phenomenon during pregnancy (12,13): cushioning by the recto-sigmoid, causing a dextrorotation of the gravid uterus (13), and the anatomical crossover of the right ureter by the right ovarian vein (14,15) are considered responsible for this.

Physiologic mechanisms behind arterial and venous blood flow are totally different. Arterial flow results from a positive propulsive force, caused by the contracting ventricle, whereas in the venous compartment, a negative pressure gradient between systemic veins and the right atrium is the driving force behind forward venous flow. Venous return also depends on intravascular

filling and vessel wall compliance (16). Therefore, the functional meaning of Doppler flow characteristics in the venous system is totally different from those on the arterial side, and are currently not yet well understood. In this study, we have tried to unravel some of the hemodynamic background mechanisms behind the gestational evolution of intrarenal venous flow and behind a reported interkidney difference of RIVI (3–5). As presented in Figure 2a, the gestational evolution of MxV shows an increase in the first trimester to a maximum at 16 weeks, after which there is a gradual decrease until term. This evolution is consistent with the known rise in renal blood flow and concomitant fall in total peripheral vascular resistance, already noticeable in the first trimester of pregnancy (11,17). The MxV evolution shows a remarkable similarity with the well known evolution of cardiac stroke volume (SV) (11,18). It seems reasonable to assume a possible association between SV and RIV MxV, however this is an assumption, requiring further investigation.

Our observations also show that MnV increases in both kidneys to a maximum value in the late second trimester, after which there is a gradual decrease until term (Figure 2b). This evolution resembles the well known gestational evolution of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and physiologic proteinuria (19).

Our statistical analysis shows that the evolutions of MxV, MnV, DeltaV, and RIVI are different between both kidneys, which suggest that local interkidney differences are involved in the aetiology of their gestational changes. Similar to the results of our previous report(4), we consistently observed higher venous blood flow velocities in the right kidney than in the left one, and this applies to both MxV and MnV (Fig 2a and b). Doppler measurements of blood flow velocities are strongly performer- and methodology-dependant (10), which must be taken into account when interpreting our results. However, anatomical differences between left and right kidneys have been reported, and several morphological aspects are compatible with our results. On the right hand side, the proximal diameter of the renal vein is larger and additional renal veins are more frequent than on the left-hand side (20–22). This may enhance efflux from right intrarenal blood. For the left renal vein, drainage of left ovarian blood and (partial) compression between the aorta and superior mesenteric artery(23) may decelerate the efflux of left intrarenal venous blood. DeltaV, which is the difference between MxV and MnV, is also higher on the right than on the left hand side in early and midgestation and in postpartum, but not between 28 and 36 weeks (Figure 2c). By definition, $RIVI = \Delta V / MxV$, so the different gestational evolutions of these two parameters explains the third trimester interkidney difference of RIVI. An inverse relation between RIVI and PCD was reported both for non-pregnant (1) and pregnant individuals (3,4). Our observed evolution of right kidney PCD and RIVI (Figure 2d) during pregnancy and postpartum, is consistent with this. However, the hypothesis that retro peritoneal compression

by the gravid uterus may have a role to play in the etiology of interkidney differences in gestational venous Doppler measurements (3,4), cannot be confirmed by the present data and requires confirmation from further studies.

Our study illustrates clearly that knowledge of the evolution of RIVI Doppler parameters in normal pregnancies allows establishing a gestation-related normal reference range between the 5th and 95th percentile. Data from pathologic pregnancies, such as PE pregnancies, can be compared with these reference values (Figure 4). In our population of PE pregnancies, most RIVI values are above the normal 95th percentile between 24 and 34 weeks, whereas at later gestation they are mostly within the normal range. This result stimulates further expansion of our study population in order to evaluate whether the increase of RIVI in PE indeed is gestation dependant.

The data enlisted in Table 1 allow explaining the higher RIVI values in PE in terms of differences in MxV, MnV and DeltaV. DeltaV values did not differ between the PE and UP groups. MxV values are lower in the PE than in the UP group, however, in our study population this is only significant for the left kidney. Assuming a possible association between RIV MxV and cardiac SV, as discussed above, this observation is consistent with the known decrease of SV in PE (17). MnV values are significantly lower in PE than in UP for both kidneys, which is consistent with the known impaired glomerular filtration in PE (24). At present, it is unclear whether our observation of low RIV MnV in PE simply reflects a passive collapse of venous walls following the known PE related plasma volume restriction (25), or whether this represents the Doppler presentation of reduced venous distensibility in PE (26). The data from our study prompt us to consider the increase of RIVI in PE to result at least partly from maternal gestational maladaptation; however, active contribution from increased venous tone cannot be excluded. The results presented in Table 1 are consistent with the recently published paper by Houben et al. (27) reporting active involvement of the venous system in the process of preeclampsia.

RIVI measurement, as performed in this pilot study, may become a new method to study venous physiology and hemodynamics during pregnancy. Many of the current methods used to study venous tone are invasive or complex, and difficult to apply during pregnancy (28). Our reported methodology seems rather simple and is noninvasive. It is also easily accessible to pregnant women undergoing obstetric ultrasound scanning. The results presented in this paper show that RIVI measurement may offer some relevant information on venous function in both normal and pathologic pregnancies. Therefore, we believe that our observation opens a window towards a new and exciting area to explore in obstetric science: the area of renal venous hemodynamics studied by Doppler ultrasound. The preliminary results presented here stimulate further evaluation of the value, possibilities and limitations of RIVI measurement in gestational hemodynamics studies and/or as a clinical investigation method.

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