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Venous pulse transit time in normal pregnancy and pre-eclampsia

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Abstract

Uncomplicated pregnancies (n=16) were evaluated longitudinally and compared to early- (n=12) and late-onset (n=14) pre-eclampsia patients assessed once at diagnosis. Pulse transit time (PTT) was measured as the time-interval between corresponding characteristics of ECG and Doppler waves, corrected for heart rate, at the level of renal interlobar veins, hepatic veins, and arcuate branches of uterine arteries. Impedance cardiography was used to measure PTT at the level of the thoracic aorta. In normal pregnancy, PTT increased gradually ($p \leq 0.01$). PTT was significantly shorter in early-onset pre-eclampsia ($p < 0.05$). This was also true in late-onset pre-eclampsia, with exception for hepatic veins ($p = 0.07$). Our results indicate that PTT is a pregnancy-safe and easy-obtainable measure for vascular reactivity at both arterial and venous sites of the circulation. Our observations correlate well with known cardiovascular (mal)adaptation mechanisms. This study invites to explore the value of PTT as a new parameter in the work-up and prediction of pre-eclampsia.

Keywords:

Pulse Transit Time, Doppler, ECG, Pregnancy, Pre-Eclampsia

Introduction

Conduction of cardiac signals throughout heart and blood vessels, the so-called pulse transit time, can be measured by echocardiography (1) and photoplethysmography (2;3).The anatomical distance from the heart (2;4) and the organ-specific morphology and/or histology play a role in this signal transmission. On top of this, (patho)physiological and pharmacological conditions influence this conduction, such as ageing (2;5), medication (3) and disease (6). Here, arterial wall stiffness influences the transit time of the arterial pulse (2), and therefore vascular tone is considered to play a role in conduction of cardiac signals. Uptil now, pulse transit time has been evaluated extensively in arteries but no data are reported from the venous side of the circulation.

Pregnancy is a physiological condition, associated with a reduction of total peripheral resistance and increased vascular compliance (7). Pre-eclampsia is a gestational disease with increased vascular resistance, characterised with hypertension and proteinuria (8;9). The cardiovascular background mechanisms behind pre-eclampsia involve both the arterial and venous compartment (10;11). We recently reported a cross-sectional pilot study using Doppler Ultrasound in combination with the maternal electrocardiogram (ECG) and observed an increase in the venous ECG-Doppler time-interval or venous pulse transit time (PTT) in uncomplicated pregnancies. This parameter was significantly lower in pre-eclampsia (4).

A longitudinal study was set up for establishment of the normal reference range for venous PTT throughout pregnancy, as a reference for measurements in pre-eclampsia. Next to this, we also evaluated PTT at the uterine arcuate arteries using combined ECG-Doppler ultrasound, and at the thoracic aorta using impedance cardiography.

Materials and methods

A longitudinal study was performed in a population of randomly selected pregnant women, presenting at the department of obstetric ultrasound or admitted to the Fetomaternal Medicine unit of Ziekenhuis Oost-Limburg, Genk, Belgium. Approval of the local ethical committee was obtained before study onset (MEC ZOL reference: 08/049). Singleton pregnancies of women without history or symptoms of renal or liver diseases were included, thus avoiding disease-induced flow changes (12). Sixteen uncomplicated pregnancies (UP) were included at six to eight weeks of gestation and were evaluated monthly until six to eight weeks postpartum. A second group of 26 women with pre-eclamptic pregnancies (PE) was also included and divided into early- and late-onset PE according to gestational age at diagnosis (< and ≥ 34 weeks of gestation, respectively). PE was defined as gestational hypertension (≥ 140 /90 mmHg), measured on at least two occasions ≥ six hours apart, associated with de novo proteinuria ≥ 300 mg per 24 hours (8).

After oral informed consent, all women underwent a conventional ultrasound scan together with a Doppler flow examination of both kidneys, liver and uterus, simultaneously with a maternal ECG. All examinations were performed by two ultrasonographers (WG, TM) using a 3.5-7 MHz probe (Hitachi EUB 6500~~; Toshiba AplioMX~~).

The methodology of venous PTT measurement at the level of maternal renal interlobar and hepatic veins has been reported elsewhere (4). Next to this, we also obtained arterial signals at the level of the arcuate branches of the left and right uterine arteries in the myometrium (13). For every woman, three consecutive Doppler flow images of each kidney, of the liver and arcuate branches of both uterine arteries were stored digitally on the hard disk of the scanner for later analysis by the principal researcher (KT).

For the veins, the time-interval between the ECG P-wave and the corresponding venous Doppler A-wave (PA in msec) was measured as reported (4). The time-interval (msec) between the ECG Q-wave and the start of the systolic Doppler signal or end-diastolic point D (QD in msec, Figure 1) was measured at the level of the uterine arcuate arteries (Figure 1). As the heart rate increases with advancing gestation (7), all measured PA and QD intervals were expressed relative to the ECG wave duration measured between to consecutive R-signals in msec. Venous and arterial pulse transit times were labelled PA/RR and QD/RR respectively.

For normal pregnancies, mean values of three PA/RR and QD/RR intervals measured at each location were calculated and stored in our database. All data were categorised according to gestational age at measurement: 8, 12, 16, 20, 24, 28, 32, 36 weeks of gestation, term and 6 weeks postpartum. For each gestational age median, 5^{th} and 95^{th} percentiles were calculated and plotted as the normal reference range. Measurements in pre-eclampsia were obtained in a similar way, and results were plotted against the normal values (Figure 2).

Next to this, we also performed Impedance Cardiography (ICG) measurements on every woman included in the study, using the Non-Invasive Continuous Cardiac Output Monitor (NICCOMO™, Software version 2.0, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany). This system allows obtaining non-invasively multiple cardiovascular parameters under physiological and stressed conditions (14-16). The methodology of this assessment and reproducibility of the measured results has been reported elsewhere (17). The Pre-Ejection Period (PEP), measured by this device, is the time-interval in msec between the Q-wave of the maternal ECG and the start of systolic rise of blood flow velocity in the thoracic aorta. The heart period duration (HPD) is the time-interval in msec, measured between two consecutive ECG signals. As such, PEP/HPD can be considered the ICG equivalent of the ECG-Doppler time-interval QD/RR. Mean values of 30 consecutive measurements per minute, under standardised conditions comparable to

the ultrasound examinations, were stored in the database and handled as explained above.

Statistical comparison between grouped data was performed using t-test at nominal level $\alpha=0,05$. Simple linear regression models using ANOVA (SPSS) were used for statistical analysis of longitudinal data.

Results

Sixteen women with normal pregnancy, 12 women with early-onset and 14 with late-onset pre-eclampsia were included. Demographic characteristics of this study population are enlisted in Table 1. As is shown, gestational age and birth weight percentiles were lower in PE groups than in UP and this was most pronounced in early-onset PE.

All women with UP were evaluated at gestational age of 8.12±0.60, 12.04±0.48, 15.77±0.38, 19.98±0.61, 24.04±0.57, 27.86±1.00, 31.89±1.05, 35.98±0.55, 38.34±0.73 weeks of gestation and at 6.66±0.71 weeks postpartum (n=16). Women with pre-eclampsia were evaluated at the moment of hospital admission, i.e. early-onset PE at 30.87±2.60 (n=12) and late-onset PE at 36.91±1.91 (n=14) weeks of gestation.

Table 2 enlists numerical values of time-intervals PA/RR, QD/RR and PEP/HPD in uncomplicated pregnancies at different stages of gestation. These values were used to establish normal reference range values, as presented in Figure 2. As is shown, all pulse transit times increase during the course of normal pregnancy. Linear regression resulted into the following equations with proportion of variance (R^2): $y=0.0041x+0.3551$ ($R^2=0.83$) for left renal PA/RR, $y=0.0033x+0.3466$ ($R^2=0.77$) for right renal PA/RR, $y=0.0075x+0.1579$ ($R^2=0.91$) for hepatic PA/RR, $y=0.0019x+0.3165$ ($R^2=0.78$) for left uterine QD/RR, $y=0.0034x+0.2903$ ($R^2=0.83$) for right uterine QD/RR, and $y=0.0021x+0.0809$ ($R^2=0.84$) for aortic PEP/HPD. All linear trends were significant at nominal level $p \leq 0.002$.

Table 3 shows the statistical comparison between UP and early or late PE. As is shown, all pulse transit time-intervals were shorter in PE groups than in UP at corresponding gestation, and this was more pronounced for early- than for late-onset PE. Results are presented graphically in Figure 2.

Discussion

Pulse transit time (also labelled as pulse wave velocity) is defined as the time needed for a cardiac signal to travel through the vascular tree to distant locations or between two arterial sites (18). Under normal physiological conditions, it is influenced by autonomic nervous activity and therefore reflects vascular reactivity (19). Reported (patho)physiological conditions with impact on pulse transit time are genetic factors, age, gender, blood pressure, smoking and diseases such as atherosclerosis, hypertension, diabetes, renal failure and hypercholesterolaemia (20-22). Abnormal pulse wave velocity can be present before clinical manifestation of cardiovascular disease, and for this its value as a biomarker for prediction of cardiovascular disease is currently under investigation (23;24). It is influenced by pharmacological treatment and can be used to assess pharmacodynamic effects and efficacy in clinical studies (21;24-26). Methods to measure pulse transit time are applanation tonometry (27-30), photoplethysmography (18;19;31), venous occlusion plethysmography (32;33) or whole body impedance cardiography (34). For the study presented in this paper, we used Doppler ultrasound combined with maternal ECG to measure pulse transit time, after confirmation that this was a highly reproducible method (4;11).

Studies on arterial pulse wave velocity, i.e. the quotient of the distance between two arterial sites and the pulse transit time, during normal pregnancy show conflicting results: a slight increase after the second trimester has been reported (35), as well as marginally different values between gestational age groups (30;36), or a significant decrease throughout normal gestation (33;37;38). These contradictory results can be explained by the fact that other gestational hemodynamic adaptations in the arterial tree might mask or compensate the velocity changes and therefore decrease the usefulness of these parameters in the assessment of arterial stiffness in normal pregnancy (30;35;36). As a consequence, considerable interindividual variation of hemodynamic parameters was

observed after 32 weeks of gestation (39;40). We found a significant increase of QD/RR at the level of uterine arcuate arteries and of PEP/HPD at the thoracic aorta, with the widest range of variation at 36 weeks of gestation (Figure 2). We also found that in women with both pre-eclampsia, pulse transit time was significantly shorter than in uncomplicated pregnancies (Table 3), which is consistent with the observations of others (29;34;35). This correlates with the known increase of vascular tone and total peripheral resistance in pre-eclampsia (7), which induces faster transmission of cardiac signals through the circulation (29;34;35).

In normotensive pregnancies, a strong association of arterial stiffness with birth weight centiles and catch-up growth after birth has been reported (28). As shown in Table 1, birth weight percentiles were lower in pre-eclampsia than in normal pregnancies in our study.

In addition to these observations at the arterial site of the circulation, we found similar results in renal interlobar and hepatic veins. It is well known that the configuration of the venous Doppler waves represent characteristics of right atrial function of the heart (41;42). The ECG P-wave and Doppler A-wave are related to the same physiological event: right atrial contraction. Therefore, the time-interval between P and A can be used to study the retrograde transmission of cardiac signals in the venous circulation (4). As shown in Table 2 and Figure 2, there is an increase of the PA/RR interval during the course of pregnancy, both at the level of hepatic veins and renal interlobar veins. As for uterine and aortic pulse transit times, all venous pulse transit times were significantly shorter for early-onset pre-eclampsia, but for late-onset pre-eclampsia this was not true at the level of hepatic veins (Table 3). It is likely that this finding relates to the shorter distance from the heart to the liver than to the kidneys. Our results indicate that in pre-eclampsia, autonomic control of vascular hypertonia and pulse transit is not restricted to the arterial vascular tree but also affects the venous side of the circulation.

The finding of reduced pulse transit time in pre-eclampsia opens perspectives towards research into the role of vascular constitution in the etiology of pre-eclampsia. It has been reported that in women who had a history of pre-eclampsia, impaired vasodilatation was present several years after delivery (32), and this was associated with higher stiffness of joints and skin as compared to normal controls (28). It has also been suggested that reduced expansion capacity of the venous compartment in early pregnancy could predispose to the development of pre-eclampsia (43). The combination of these observations suggest that there might be a constitutionally determined connective tissue and/or venous vascular wall disorder, predisposing to the development of pre-eclampsia. Arterial and venous pulse transit time measurements might be an easy and highly accessible method to investigate this hypothesis.

We conclude that changes of pulse transit time throughout pregnancy are consistent with known physiological vascular adaptation mechanisms in normal pregnancy and with vascular hypertonia in pre-eclampsia. These changes occur at both arterial and venous sites of the circulation and can easily be measured using a combination of maternal ECG and vascular Doppler. Studies using this technology can improve our knowledge on gestational reactivity of maternal arteries and veins and may contribute towards a better understanding of cardiovascular background mechanisms behind pre-eclampsia.

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Tables

Table 1. Demographic characteristics and pregnancy outcome.

Demographic characteristics and pregnancy outcome of uncomplicated pregnancies (UP), early-onset (< 34 weeks) and late-onset (≥ 34 weeks) pre-eclampsia (PE). Data are represented as mean±standard deviation or numerical values (percentage). Significant differences at nominal level α=0,05 between UP and PE, and between early and late PE are labeled ¤ and * respectively.

	UP **n=16**	**Early PE** **n=12**	**Late PE** **n=14**
Demographic characteristics at inclusion			
Maternal age (years)	29.39±3.74	29.27±4.87	30.47±3.94
Body mass index (kg/m²)	23.19±2.90	26.70±4.93	25.69±4.92
Nulliparous (%)	9 (56.25)	8 (66.67)	11 (78.57)
Pregnancy outcome characteristics			
Birth weight (gr)	3387±485	1370±438¤*	2615±627¤*
Birth weight (percentile)	54±26	22±17¤	26±30¤
Gestational age at delivery (weeks)	38.96±1.31	31.31±2.45¤*	37.17±1.77¤*

Table 2. Venous and arterial pulse transit time values per gestational age category.

Venous and arterial pulse transit time values per gestational age category. Data are represented as mean±standard deviation. ArcUt Art=arcuate branches of the uterine arteries. PA/RR=pulse transit time between ECG P-wave and corresponding venous Doppler A-wave, corrected for heart rate (RR). QD/RR=pulse transit time between ECG Q-wave and corresponding arterial D-point, corrected for heart rate (RR). PEP=pre-ejection period. HPD=heart period duration.

Gestational age (weeks)	**Venous Doppler**			**Arterial Doppler**		**ICG**
	PA/RR			***QD/RR***		***PEP/HPD***
	Left kidney	*Right kidney*	*Liver*	*Left ArcUt Art*	*Right ArcUt Art*	*Thoracic Aorta*
8.12 ± 0.60	0.38±0.07	0.37±0.08	0.23±0.10	0.33±0.04	0.31±0.05	0.11±0.13
12.04 ± 0.48	0.40±0.09	0.38±0.11	0.23±0.08	0.34±0.05	0.34±0.05	0.11±0.09
15.77 ± 0.38	0.43±0.09	0.39±0.10	0.27±0.10	0.35±0.04	0.34±0.04	0.11±0.10
19.98 ± 0.61	0.43±0.06	0.41±0.08	0.34±0.12	0.35±0.05	0.35±0.05	0.11±0.11
24.04 ± 0.57	0.44±0.09	0.44±0.08	0.31±0.09	0.35±0.04	0.37±0.04	0.12±0.11
27.86 ± 1.00	0.49±0.07	0.45±0.07	0.35±0.14	0.38±0.05	0.41±0.06	0.13±0.11
31.89 ± 1.05	0.52±0.07	0.49±0.08	0.44±0.13	0.38±0.05	0.41±0.06	0.15±0.17
35.98 ± 0.55	0.50±0.09	0.46±0.08	0.44±0.08	0.40±0.08	0.43±0.09	0.17±0.18
38.34 ± 0.73	0.48±0.06	0.44±0.08	0.42±0.13	0.37±0.07	0.39±0.03	0.16±0.21
6.66 ± 0.71 PP	0.36±0.09	0.35±0.10	0.24±0.13	0.30±0.04	0.31±0.04	0.12±0.10

Table 3. Comparison between uncomplicated pregnancies (UP), early- and late-onset pre-eclampsia (PE).

Comparison between uncomplicated pregnancies (UP), early- and late-onset pre-eclampsia (PE). Data are represented as mean±standard deviation. ArcUt Art=Arcuate branches of the uterine arteries. PA/RR=pulse transit time between ECG P-wave and corresponding venous Doppler A-wave, corrected for heart rate (RR). QD/RR=pulse transit time between ECG Q-wave and corresponding arterial D-point, corrected for heart rate (RR). PEP=pre-ejection period. HPD=heart period duration.

Parameters	**UP 31.89±1.05 weeks**	**vs (p-value)**	**Early PE 30.87±2.60 weeks**	**vs (p-value)**	**Late PE 36.91±1.91 weeks**	**vs (p-value)**	**UP 35.98±0.55 weeks**
Left kidney PA/RR	0.52±0.07	0.0005	0.37±0.11	0.4266	0.40±0.07	0.0016	0.50±0.09
Right kidney PA/RR	0.49±0.08	0.0046	0.37±0.11	0.6364	0.39±0.09	0.0369	0.46±0.08
Liver PA/RR	0.44±0.13	0.0465	0.32±0.14	0.6074	0.35±0.14	0.0735	0.44±0.08
Left ArcUt Art QD/RR	0.38±0.05	0.0000	0.27±0.06	0.4408	0.29±0.08	0.0008	0.40±0.08
Right ArcUt Art QD/RR	0.41±0.06	0.0000	0.27±0.06	0.2328	0.31±0.07	0.0003	0.43±0.09
Thoracic Aorta PEP/HPD	0.15±0.17	0.0355	0.12±0.18	0.6132	0.12±0.16	0.0001	0.17±0.18

Legends to figures

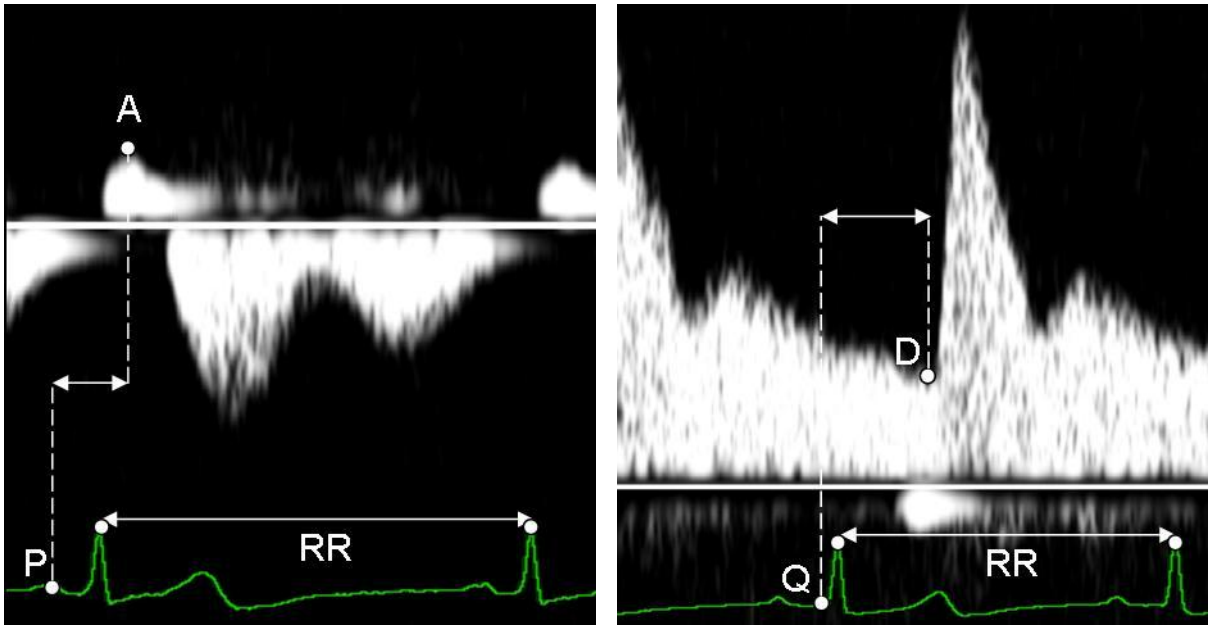
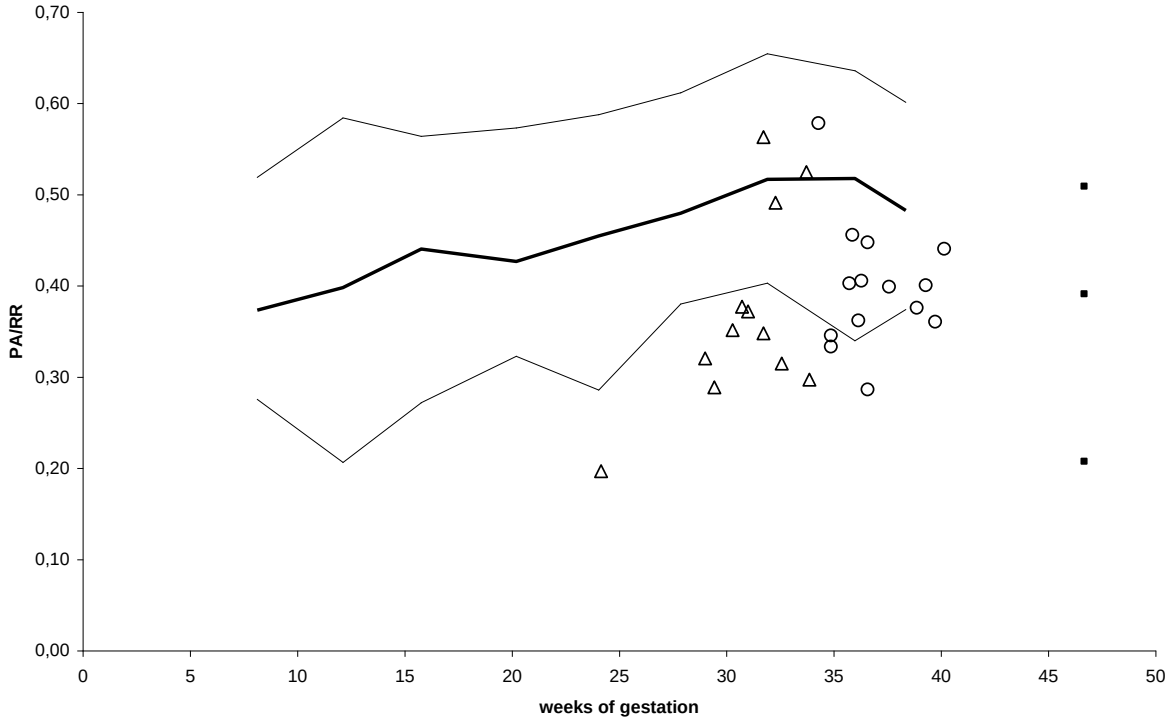
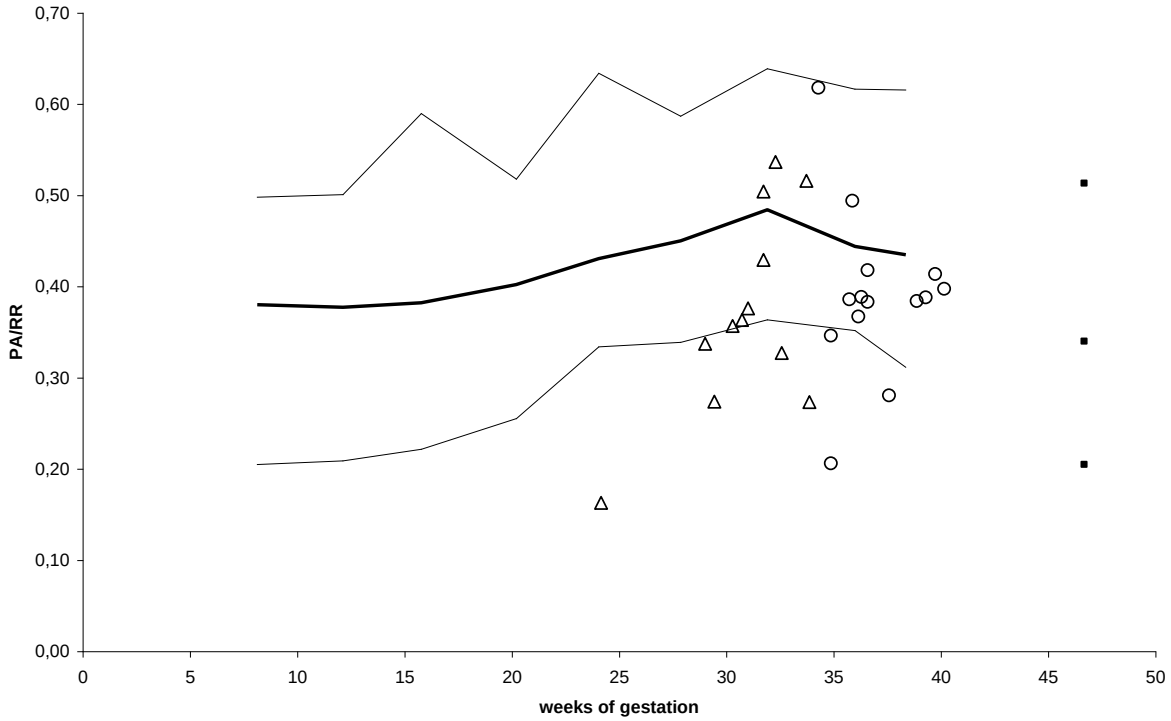


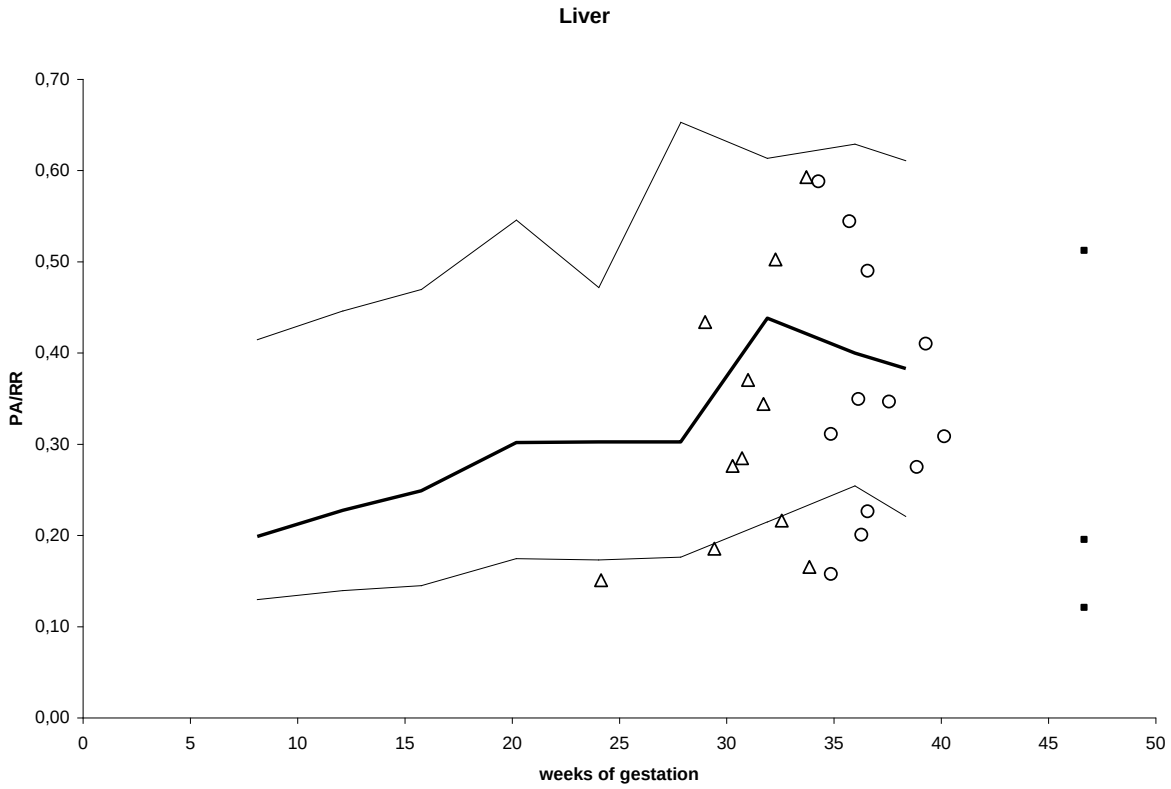
Figure 1. (a) The time-interval PA at the venous level. P and A both represent atrial contraction. (b) The time-interval QD at the level of the uterine arteries. Q and D both represent the start of systole. RR expresses the duration of the cardiac cycle.

Left kidney



Right kidney




Liver
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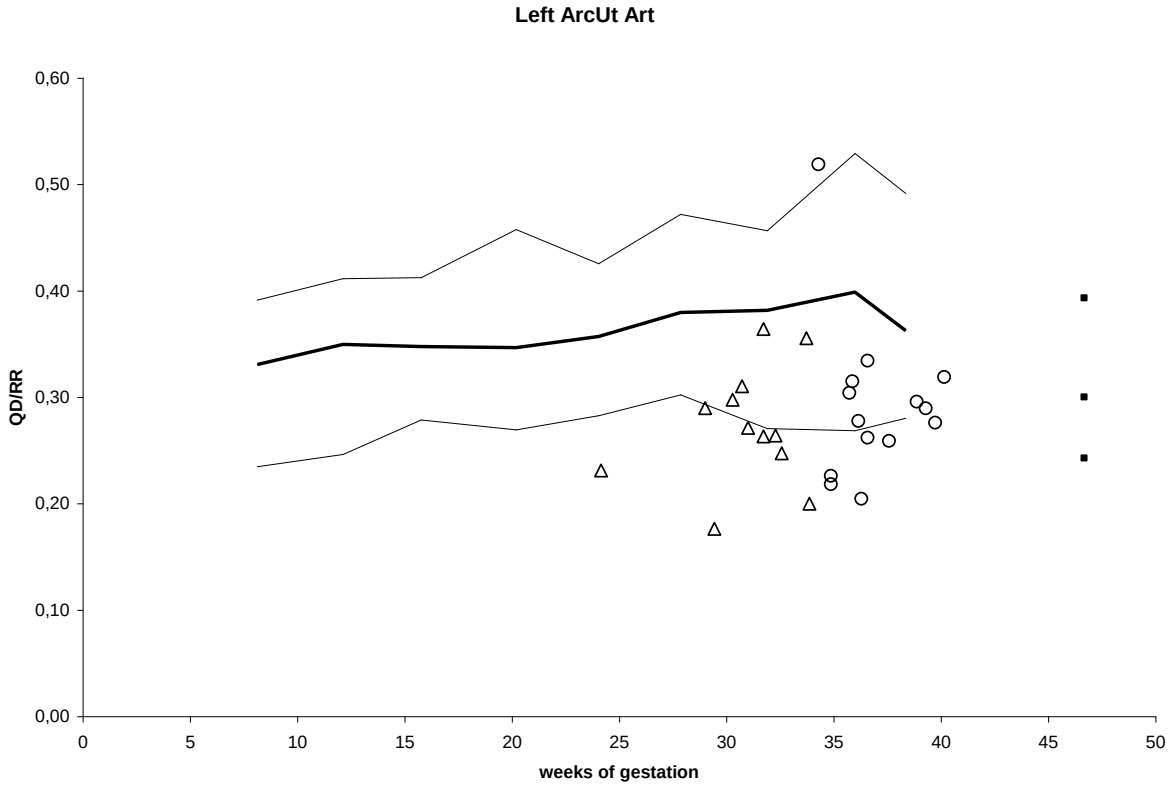
weeks of gestation


Left ArcUt Art
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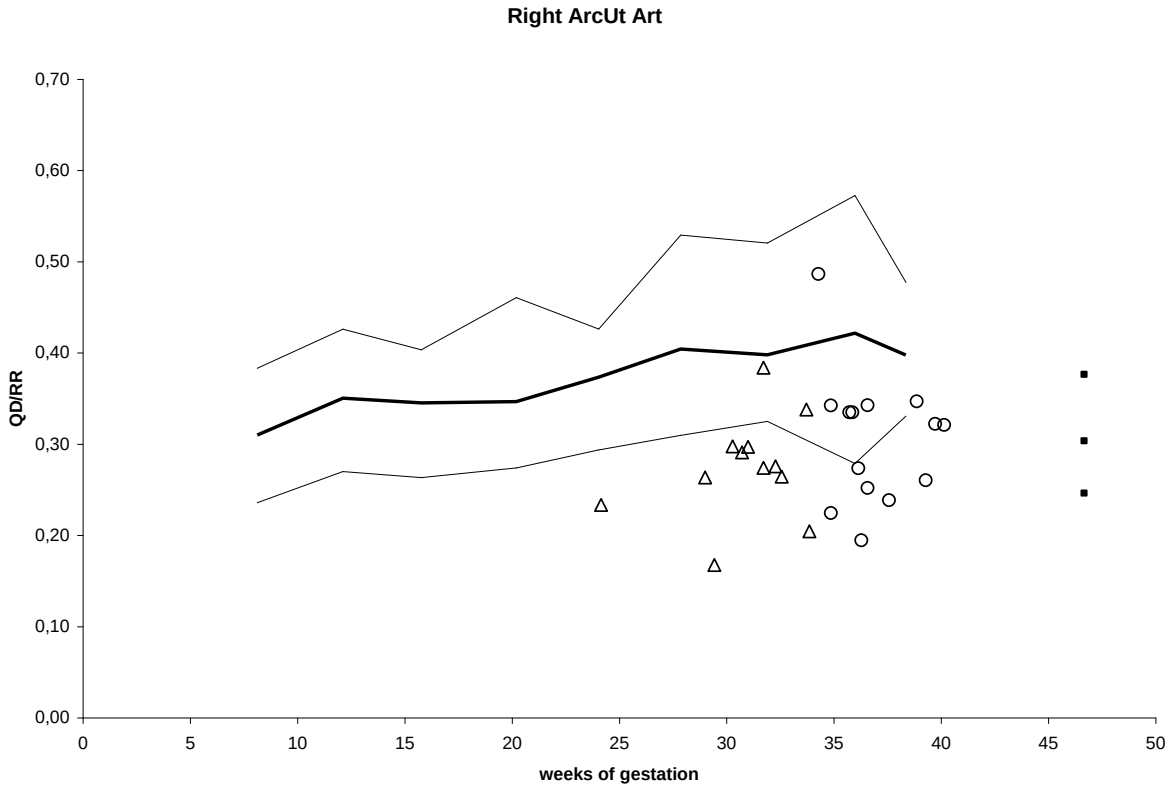
weeks of gestation


Right ArcUt Art
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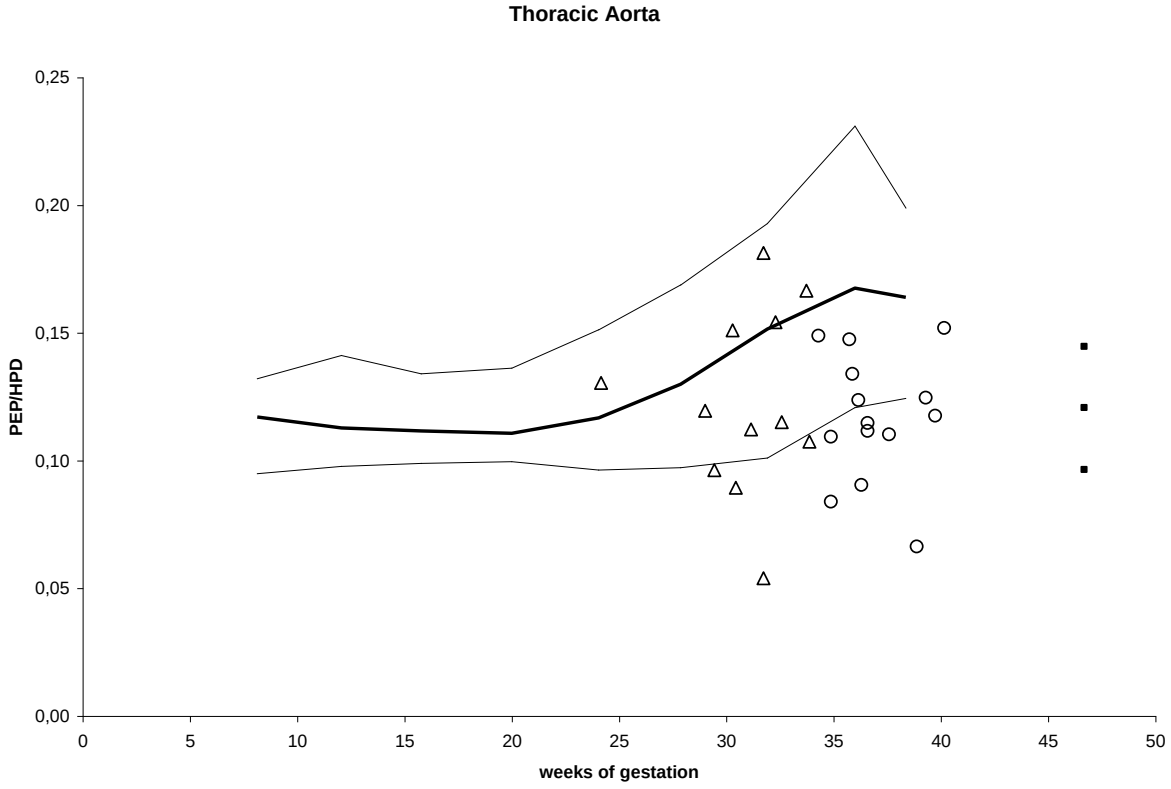
weeks of gestation


Thoracic Aorta
PEP/HPD
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weeks of gestation

Figure 2. For each gestational age median, 5^{th} and 95^{th} percentiles were calculated and plotted as the normal reference range. Measurements in early- and late-onset pre-eclampsia were plotted against the normal values (triangles and circles, respectively). (a) PA/RR in left renal interlobar veins. (b) PA/RR in right renal interlobar veins. (c) PA/RR in hepatic veins. (d) QD/RR in left arcuate branches of uterine arteries. (e) QD/RR in right arcuate branches of uterine arteries. (f) PEP/HPD in thoracic aorta.

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