Paper III

The left portal vein as a watershed in the fetal circulation: development during the second half of pregnancy and a suggested method of evaluation

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Abstract

Objective: The left portal vein represents a watershed area in fetal circulation and the change of flow direction suggested marker of circulatory compromise. Our aim was to study the left portal vein of uncompromised human pregnancies and establish reference ranges.

Methods: 160 low-risk pregnant women were recruited to a longitudinal study that included 4-5 Doppler measurements at monthly intervals during the second half of pregnancy.

Results: Based on 554 Doppler recordings we found time-averaged maximum flow velocities increasing from mean 10.6 to 14.2 cm/s during 21-31 weeks of gestation, remaining stable until 37 weeks and decreasing towards term. Intermittent flow reversal occurred during fetal respiratory movements, and continuous flow reversal was seen in 2/160 fetuses close to delivery.

Conclusion: We suggest time-averaged maximum blood velocity for the quantification of the watershed phenomenon in the left portal branch and have provided reference ranges for single observations and serial measurements.

Introduction

There is a striking difference between the venous blood supply to the liver before and after birth. While the portal vein is the only contributor in postnatal life, prenatally the liver receives an additional large volume of venous blood from the umbilical circulation. During fetal life the left portal vein connects the umbilical with the portal circulation (Fig.1), indicating that the watershed between them is localized in the right liver lobe. Animal experiments have shown that during prenatal life umbilical venous blood circulates the left liver lobe and a blend of umbilical and portal blood the right lobe [1, 5]. In physiologic human pregnancies, the umbilical venous return first supplies the left liver lobe, then the ductus venosus (20-30%) [2, 20], and the remainder flows towards the right liver lobe blending with blood from the main portal stem. The observation of near zero flow or flow reversal in the left portal vein in cases of fetal hemodynamic compromise suggests a shift of the watershed area between the portal and umbilical circulation to the left portal vein [19, 21]. A reversal of blood flow in the left portal vein may help keeping up perfusion pressure and ductus venosus flow, but by doing so adds blood of lower oxygen content to the ductus venosus shunting. Although the reversed flow velocity in the left portal vein is suggested as a sign of fetal hemodynamic compromise, no systematic information exists on the velocity pattern during normal development, apart from a recent study showing forward flow in all 91 fetuses at 36 weeks of gestation [13].

The aim of the project was therefore to study the blood velocity pattern of the left portal vein and its development during the second half of pregnancy, and secondly, to test the hypothesis that reversal of flow in the left portal vein may be a normal phenomenon.

Methods

Subjects. Women attending the ultrasound department for the routine scan between 17 and 20 weeks of gestation were invited to the present study as part of a larger hemodynamic study of the umbilical and portal venous circulation, where we previously reported on the ductus venosus flow velocities and waveform indices [18]. The study protocol was approved by the Regional Committee for Research Ethics (REK-Vest 04/3837) and the women were recruited after informed written consent. During a pilot study, which included 40 participants, we focused on the liver vessel anatomy to identify landmarks for orientation and consensus on sites for measurement. Then, 160 healthy pregnant women consecutively entered the study during the period August 2004 – July 2005. Gestational age was assessed by ultrasound in the second trimester [16]. Reasons for exclusion were twins, fetuses with a malformation or chromosomal aberration, maternal chronic diseases (i.e. hypertension, diabetes, rheumatic or autoimmune diseases, dyslipidemia) or complicated obstetric history (i.e. preeclampsia, growth restriction, placental abruption, gestational diabetes, delivery < 37 weeks of gestation). The participation included four to five examinations at four weeks intervals starting at 20-22 weeks of gestation. Each session lasted 60 minutes. After birth, information on gender, weight, length, Apgar score, mode of delivery, transfer to the neonatal intensive care unit (NICU) and neonatal complications were collected from the medical records.

We also included a clinical case of intrauterine growth restriction in a triplet to illustrate the potential use of the method.

Measurement. A Sonos 7500 ultrasound machine (Philips, Seattle, USA) with a 3.5 MHz (2-6 MHz) curved linear transducer including color Doppler (2.5 MHz) and pulsed Doppler (3 MHz) facilities was used for the study. The high-pass filter was set at 50 Hz. The mechanical index (MI) and the thermal index for soft tissue (TIS) were usually at the level of 1.1 or below. In a few obese participants, higher energy output was occasionally needed increasing TIS and MI to 1.4.

The left portal vein was identified with color Doppler in a transverse insonation as the extension of the umbilical vein after the branching site of the ductus venosus (Figs.1 and 2). The flow velocities were measured over five heart cycles in the absence of fetal and respiratory movements with an insonation along the vessel axis. The angle of insonation was kept as low as possible and always ≤ 30 °. The sample volume was adapted to the vessel size and placed close to the branching site of the ductus venosus to avoid recording velocities from the main stem or the right branch of the portal vein (Fig. 3). The main focus of the study was the measurement of velocities during fetal quiescence. When respiratory movements occurred and time permitted, the time-averaged maximum velocity (TAMXV) in the left portal vein was measured (N=19) and compared with the velocities during fetal quiescence during the same examination.

Statistics. The power calculation was based on the same assumptions as those published earlier for the present study population [18]. Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL). Multilevel modeling was used in order to construct mean- and percentile curves for each variable by gestational age using the MlWin program (MlWin, Centre for Multilevel Modelling, University of Bristol, UK) following the previously described principles [18].

Differences in TAMXV during fetal quiescence and breathing were tested by a paired sample t-test and $p < 0.05$ was considered significant.

Results

The mean maternal age was 29 (range, 20-43) years at inclusion. The mean gestational age at delivery was 40+3 (range, 33+3 to 42+4) weeks. The neonates had a mean birth weight of 3350 (range, 2100-4700) g. A total of 589 examinations were done in the 160 participants (1-6 per participant, median 4) and blood velocity recordings in the left portal vein were obtained in 554 sessions (success rate 94 %). The flow was pulsatile in 382/554 (69 %). We observed a continuum from non-pulsatile flow pattern to marked pulsations (Fig. 4). Commonly, the pulsations consisted of minor and regular velocity variations characterized by one or two velocity peaks during the heart cycle (Fig. 4). The proportion of fetuses with pulsatile blood flow pattern was stable throughout the observation period. The pulsatility pattern in the left portal branch commonly represented a mirror image of the ductus venosus (Fig. 5). The average TAMXV in the left portal vein was 10.6 cm/s at 21 weeks, increasing to 14.2 cm/s at 31 weeks and remaining stable until 37 weeks. During the remaining period towards term TAMXV decreased slightly to 12.1 cm/s at 39 weeks (Fig. 6, Tab.1). Terms for calculating conditional ranges for repeated measurements are presented in Appendix I, and a spreadsheet can be downloaded from the website. Serial measurements of the TAMXV in the left portal branch are illustrated in a case of severe IUGR in a triplet pregnancy (Fig. 7).

We observed two cases of reversed flow in the left portal vein in the absence of fetal respiratory movements. They both occurred within a week before birth and represent 8% (2/24) of the measurements done between 38-40 weeks of gestation.

Case 1: Para 2 with uncomplicated pregnancies and deliveries (birthweights 3320 g and 3050g). The present pregnancy was uneventful. The fetus had been examined at 23+0, 27+1 and 31+0 weeks of gestation and forward flow in the left portal vein had been noted. At 39+1 weeks a continuous reversed flow in the left portal vein was noted (Figs. 8 and 9). The ductus venosus PIV and umbilical artery PI were normal. Six days later she delivered a girl with a birthweight of 2990 g, who had an uneventful neonatal period.

Case 2: Para 0 with a normal pregnancy course. The fetus had been examined at 23+1, 29+2 and 34+3 weeks of gestation and forward flow in the left portal vein was recorded each time. At 38+3 weeks blood flow reversal in the left portal vein was noted during fetal quiescence. Four minutes later, still in the absence of fetal respiratory movements, the forward flow had been restored. Two days later the woman gave birth to a boy with a birthweight of 3040 g and a normal neonatal course.

The presence of respiratory movements modified the blood flow pattern in the left portal vein. Typically, the flow velocity decreased during expiration (Fig. 10 a), in some cases there was hardly any forward flow (Fig. 10 b) or even reversed flow (Fig. 10 c) during expiration. During such respiratory activity the average forward velocity in the left portal vein would be markedly reduced or absent. Pulsed Doppler traces of the left portal branch in the presence of fetal respiratory movements were available in 19 fetuses at different gestational ages, and 16 of those had also velocity measurements

during fetal quiescence at the same examination (Fig. 11). After 36 weeks of gestation fetal breathing caused a significant fall of the TAMXV (p=0.007).

Discussion

In the fetus, the left portal vein represents the connection between the umbilical venous return and the portal blood from the intestine and spleen. In the present study we have shown that blood in the left portal vein of the fetus flows towards the main portal stem and right branch during the second half of normal pregnancies, with the rare exception of reversed direction shortly before birth and during respiratory movements. Additionally, we suggest the blood velocity as a marker of this watershed function and have established reference ranges for the second half of pregnancy. Compared with the previous cross-sectional study at 36 weeks [13] our results of TAMXV (Fig. 6, Tab. 1) are identical, which is reassuring for the general use of the method.

The fetal liver lobes differ not only in color, micro architecture, level of hematopoesis and iron content [8], but also in gene and enzyme expression [4, 25]. These findings may be linked to different sources of venous blood supply for the left and right lobes. The umbilical vein provides oxygen and nutrient rich blood predominantly to the left liver. On the other hand side, the portal vein directs poorly oxygenated blood from the splanchnic circulation to the right liver. Our study of the blood direction in the left portal vein, confirmed that the concept of selective liver lobe perfusion shown in animal experiments [5] is also valid in the human fetus. The results of our longitudinal study during the second half of pregnancy are also in line with two recent cross-sectional studies [13, 27].

When the umbilical circulation ceases after birth, the flow in the left portal branch changes direction as the splanchnic blood takes over the entire portal perfusion. The portal pressure is maintained at a comparable level to that before birth and produces high velocities in the postnatal ductus venosus [9]. In 2/160 fetuses in our study this reversal of blood flow in the left portal branch occurred already prenatally (2/24 observation at 38-40 weeks), without signs of placental compromise (Figs. 8 and 9). This is in contrast to the repeated observation of blood flow reversal in the left portal branch in cases of fetal hemodynamic compromise [3, 19, 21]. We assume, that an increasing flow in the main portal stem [17], combined with the reduced fraction of cardiac output directed to the umbilical circulation towards the end of uncomplicated pregnancies [22], may shift the distribution in the venous liver supply leading to an increased likelihood for zero or reversed flow the left portal vein. Thus, for all practical purposes, reversed left portal flow is non-existent until shortly before birth.

An experimental reduction of the umbilical venous return in fetal sheep does not cause a corresponding reduction of blood shunted through the ductus venosus since an increased proportion of umbilical blood is directed through the shunt [6]. Interestingly, there was no sign that portal blood contributed in the ductus venosus shunting in these fetuses [6, 15]. The implication would have been a reversal of the left portal vein flow direction. However, in human pregnancies with placental compromise associated with decreased umbilical flow and increased shunting through the ductus venosus [3, 23], the pattern of portal flow seems to be different. The observation of reversed blood flow in such cases indicates a shift of the watershed area and probably an increased portal contribution to keep up the pressure [19]. Measurement of the blood velocity in the left portal vein may therefore be of clinical importance whenever umbilical pressure

changes are expected, e.g. fetal growth restriction (i.e. Fig. 7), twin-twin transfusion syndrome or fetal hemorrhage.

The velocity reversal in the left portal vein may also signify important physiologic consequences. First, the right liver lobe turns from a mixture of portal and umbilical blood to be exclusively fed by less well oxygenated portal blood. Second, areas of the left liver lobe are now exposed to poorly oxygenated portal blood. Third, portal blood is shunted through the ductus venosus thereby decreasing the oxygen saturation in the shunt. This could then be one of the local mechanisms contributing to the increased degree of recirculation of blood within the fetal body recently demonstrated in placental compromise [22]. Another observation, fetuses exposed to asphyxia more often showed right liver damage [11], fits well with the present concept. Growth restricted fetuses shunt relatively more umbilical blood through the ductus venosus [23], ensuring appropriate oxygenation of the myocardium and the brain. However, the admixture of portal blood in the ductus venosus reduces the beneficial effect of this redistributional mechanism. To some extent, liver growth and development seems to be flow-driven [10, 26]. We speculate that the regional differences in flow may have corresponding consequences for gene expression in the fetal liver [4] and possibly long-term consequences for metabolic function.

The blood flow pattern in the left portal branch was modified by fetal respiratory movements (Fig. 10 a-c). A similar effect was previously described for the umbilical circulation [14, 24] and attributed to intra-thoracic pressure variation. Near term fetal respiratory movements are present during 30 % of the time [12]. At this stage of pregnancy, our study showed that fetal breathing caused a decrease in TAMXV of the

left portal branch (Fig. 11), thus reducing the proportion of well-oxygenated umbilical blood to the right liver lobe, the main site of erythropoiesis [7].

Around 70 % of the recordings showed a pulsatile blood flow pattern (Figs.3 and 4 b, c), which is similar to the study by van Splunder et al. [27]. It was previously shown that in the circulatory compromised fetus the pulsation pattern in the left portal branch is an inverse image of the ductus venosus [21]. Our data indicate that the pulse transmission from the ductus venosus to the left portal branch can also be recorded in most of the uncompromised fetuses (Fig. 5). Kilavuz et al. [19] classified the left portal branch blood flow as pathological when pulsations were present. The results of our study show that pulsatility in the left portal branch is a normal phenomenon in healthy fetuses.

In summary, we have established longitudinal reference ranges for the left portal branch flow velocities in the second half of gestation, and suggest using them for the quantification of the watershed function using a standardized technique. Terms for calculating conditional ranges are also provided making the method suitable for monitoring fetuses with serial measurements. The occurrence of pulsations in the left portal branch is a normal phenomenon, and so is reversal of flow, but rare, and only during the last days of pregnancy or during fetal breathing.

Acknowledgements

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Figure legend

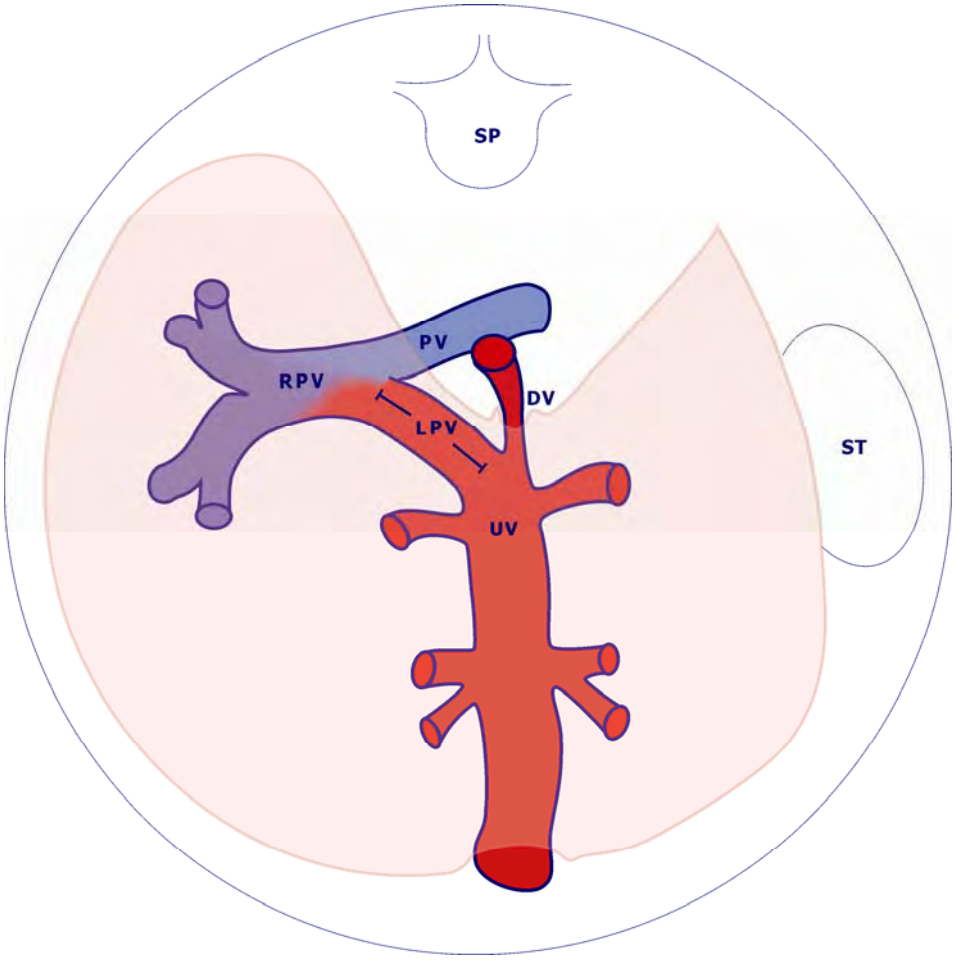

Figure 1: Venous blood supply of the fetal liver with level of oxygenation. Red color: high oxygen saturation, blue color: low oxygen saturation, purple color: mixture of blood with high and low saturation. UV: umbilical vein, DV: ductus venosus, LPV: left portal vein, RPV: right portal vein, PV: main stem of the portal vein, ST: stomach, SP: spine.

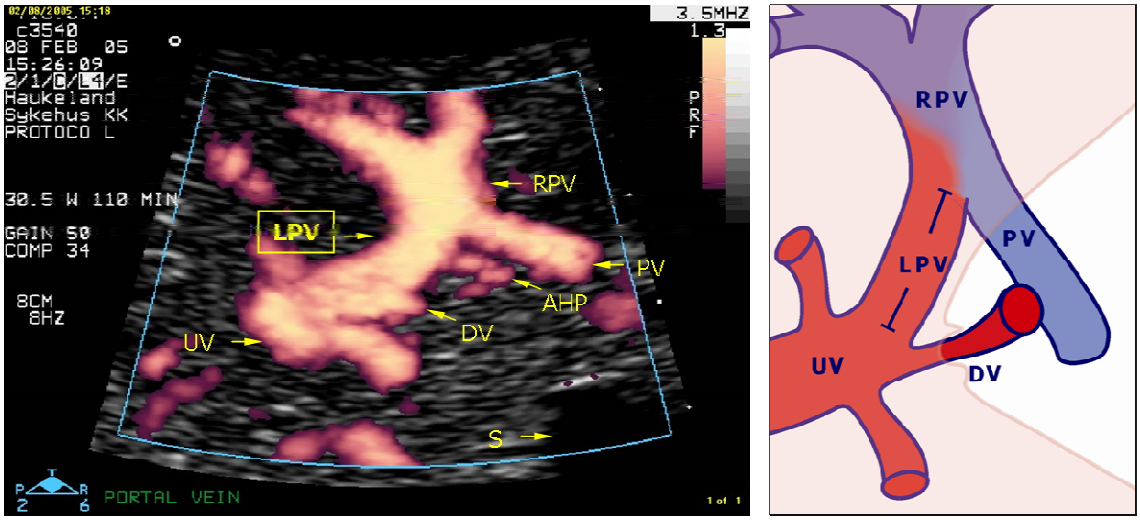

Figure 2: Visualisation of the left portal vein with Power Doppler at 30+5 gestational weeks (left) and schematic picture of the vessel nomenclature (right). Note the branching ductus venosus as the proximal and the portal main stem as the distal bounds of the left portal vein. UV: umbilical vein, DV: ductus venosus, LPV: left portal vein, RPV: right portal vein, PV: main stem of the portal vein, AHP: arteria hepatica propria, S: stomach. The level of oxygenation is illustrated by colors (red – well oxygenated, blue – poorly oxygenated, purple – mixture of well and poorly oxygenated blood)

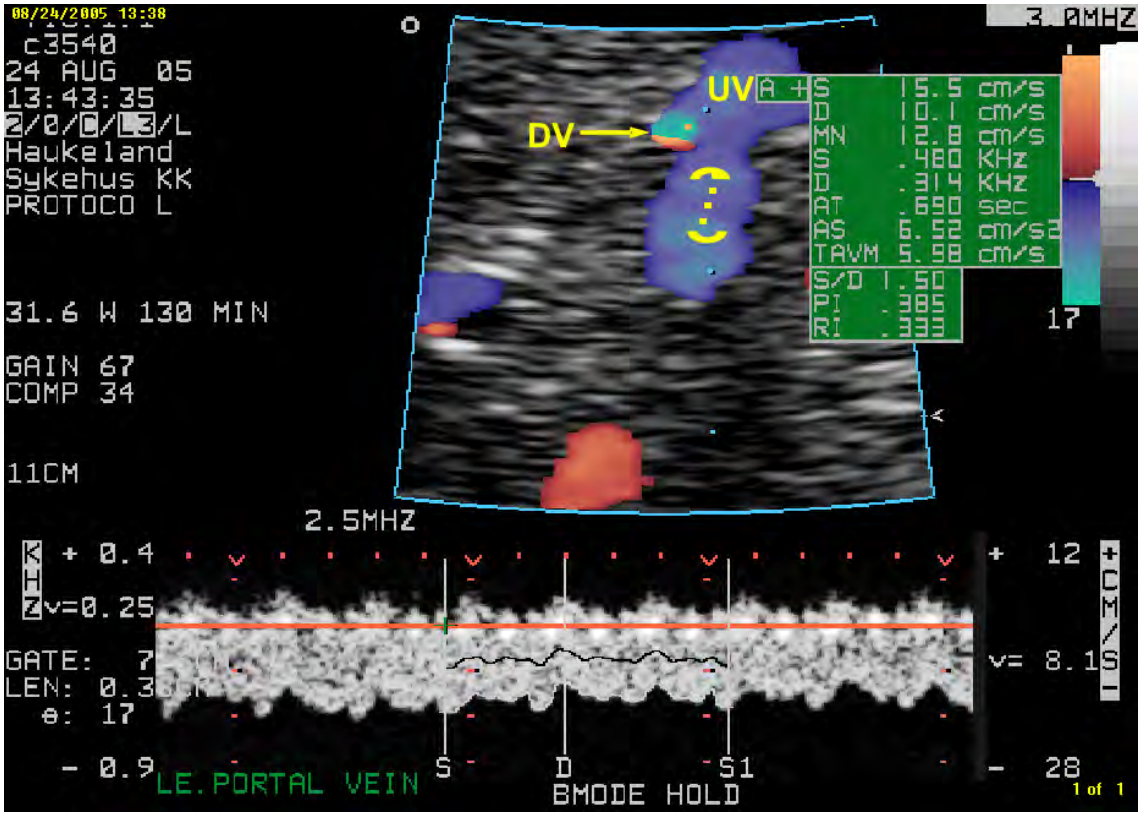

Figure 3: Pulsed Doppler recording of the left portal vein at 31+6 weeks of gestation. The sample volume is placed immediately distal to the branching site of the ductus venosus (DV) to avoid simultaneous recording of velocities of the main stem or the right branch of the portal vein. UV: umbilical vein

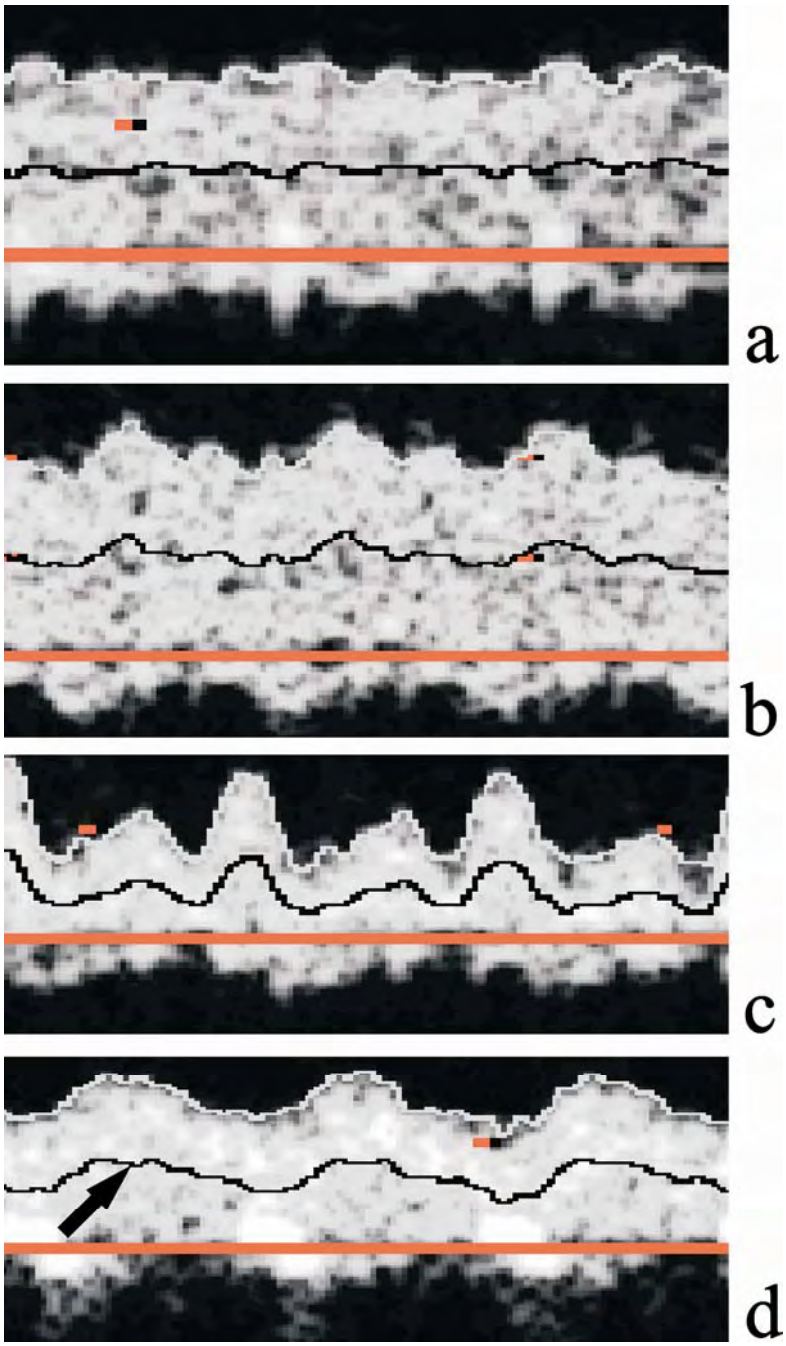

Figure 4: Blood flow pattern in the left portal vein, a: non-pulsatile, b-c: pulsatile with two velocity peaks, d: pulsatile with one velocity peak during one heart cycle. Intensity weighted mean velocity (black line, marked with arrow)

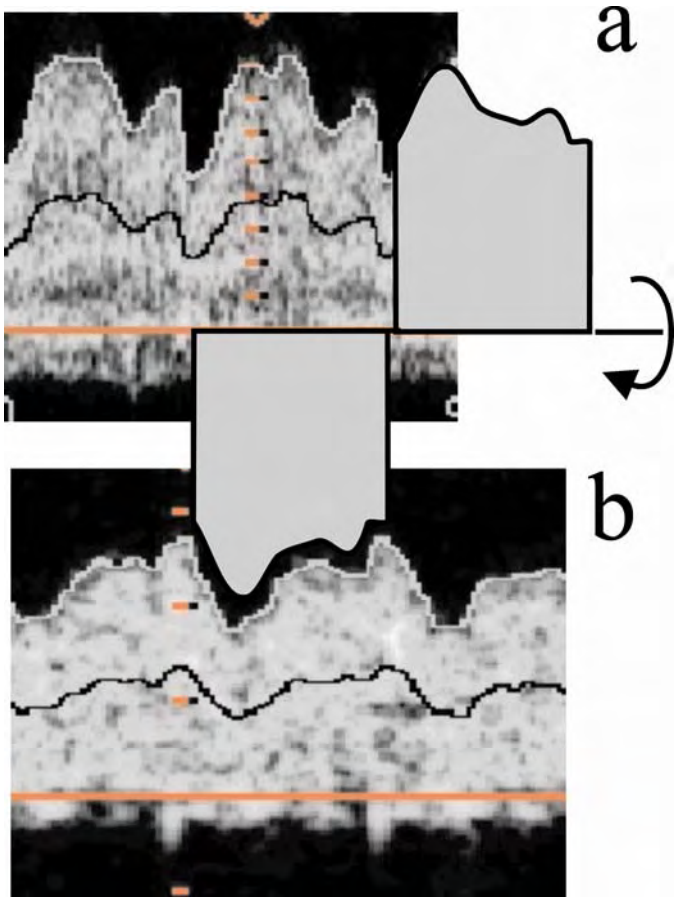

Fig. 5: Pulsed Doppler recording at 28+5 weeks of gestation. The pulsatility pattern in the left portal branch (b) is an inverse image of the ductus venosus (a).

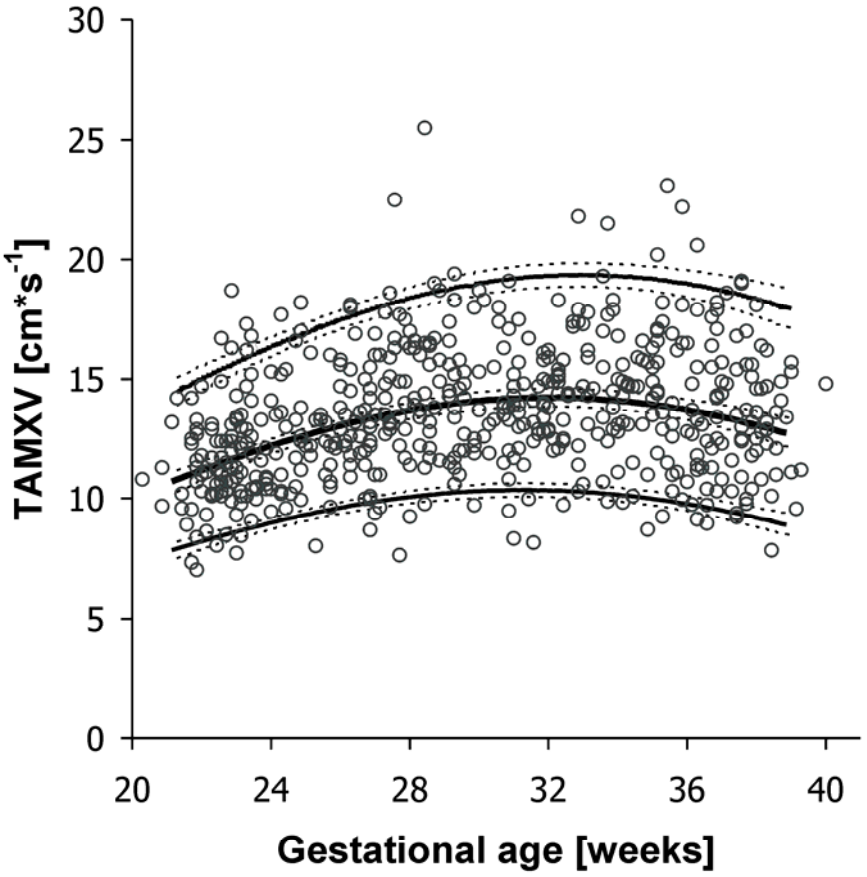

Fig. 6: Time averaged maximum velocity in the left portal vein. 553 longitudinal observations in 160 low- risk pregnancies. 5, 50 and 95 percentile (solid lines) with 95% confidence interval (broken lines). Not shown on the graph: measurement at 39+2 weeks: - 13.7 cm/s (case 1). Orthograde flow velocity is shown for the case with both orthograde and retrograde flow velocity during one examination (case 2).

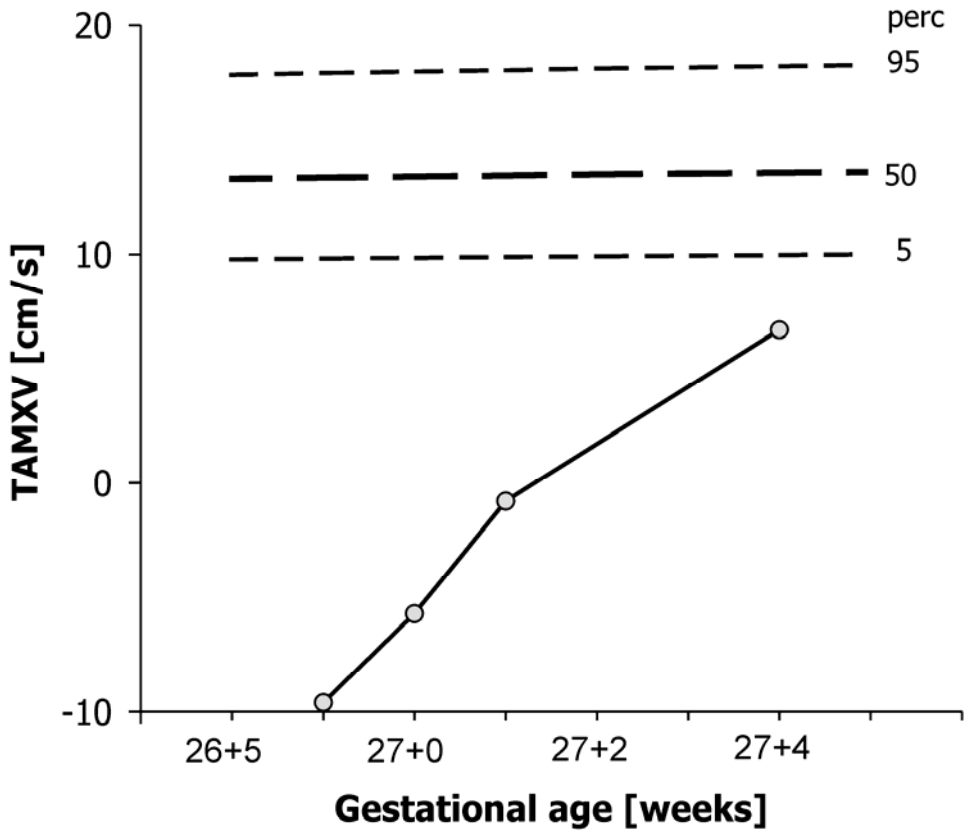

Fig.7: Serial measurements of the time averaged maximum velocity in the left portal branch showing an unstable portal circulation with marked changes in a case of severe IUGR in a triplet pregnancy. The fetus was part of a monochorionic pair, while the third twin was dichorionic. There were no signs of acute or chronic twin transfusion syndrome. The fetus had ARED flow in the umbilical artery and brain sparing, and finally pathologic pulsatility in the ductus venosus. At 27+4 weeks of gestation a girl with birthweight 460 g was delivered by cesarean section, Apgar score 3/6. The neonatal course was complicated by necrotising enterocolitis with repeated surgical treatment. The child died at age of 8 months in multi organ failure.

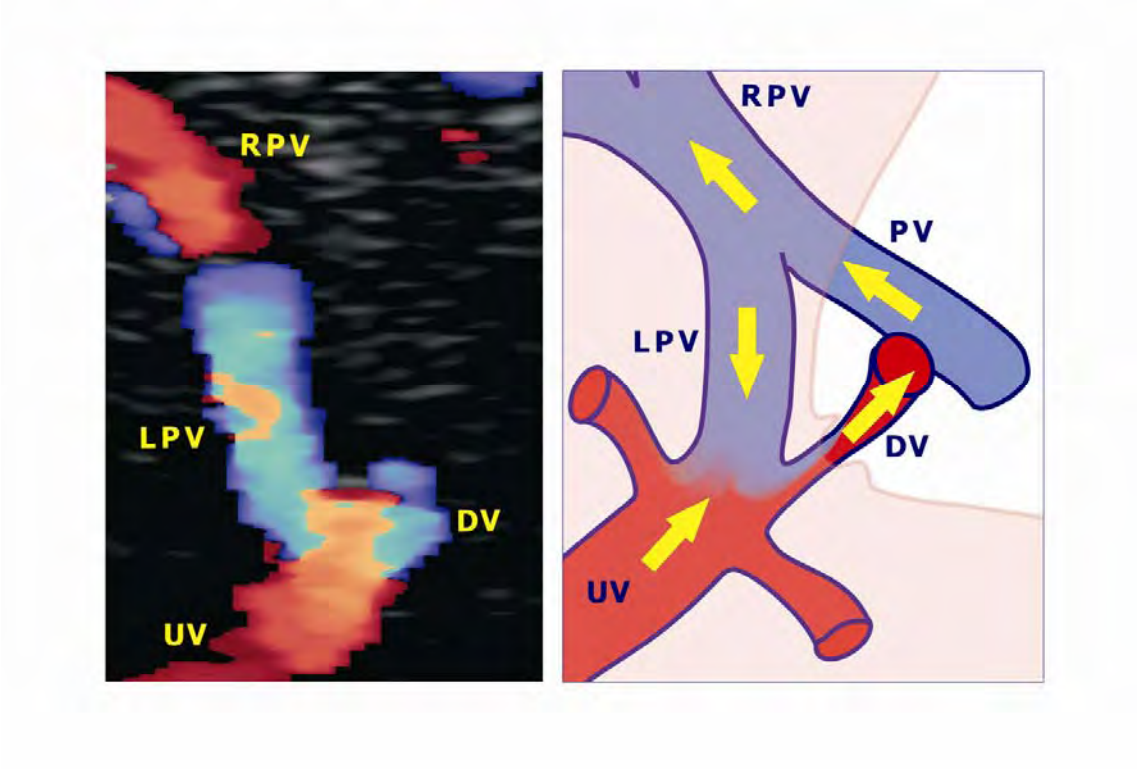

Figure 8: Reversed flow in the left portal vein (LPV) in a normal pregnancy at 39+1 weeks of gestation. Color Doppler image (left side) and schematic picture with flow direction (arrows) and level of oxygenation (illustrated by colors: red – well oxygenated, blue – poorly oxygenated, purple – mixture of well and poorly oxygenated blood). UV: umbilical vein, DV: ductus venosus, PV: main stem of the portal vein. RPV: right portal branch

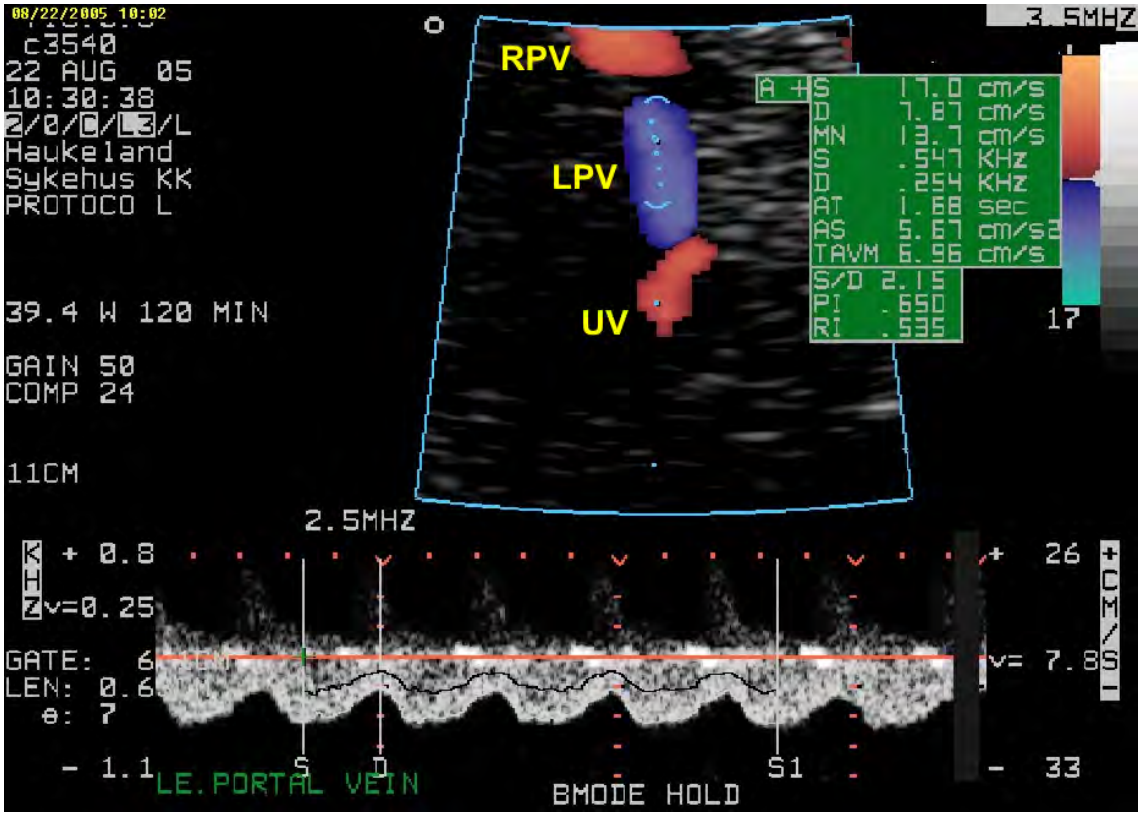

Figure 9: Pulsed Doppler recording of reversed flow in the left portal vein in a normal pregnancy at 39+1 weeks of gestation. UV: umbilical vein, LPV: left portal branch, RPV: right portal branch

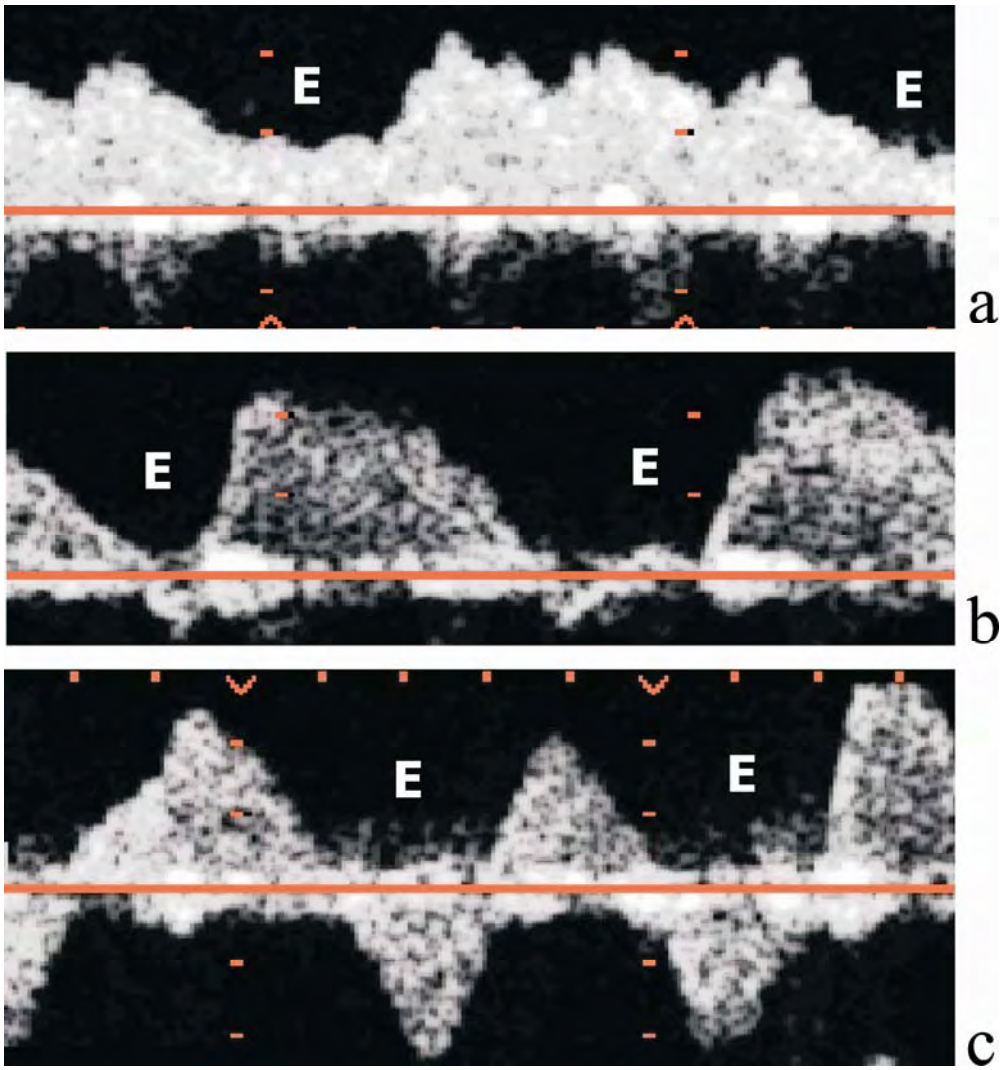

Figure 10: Blood flow pattern in the left portal vein during respiratory movements of the fetus. Expiration causes a reduction (a,b) or reversal (c) of the blood flow.

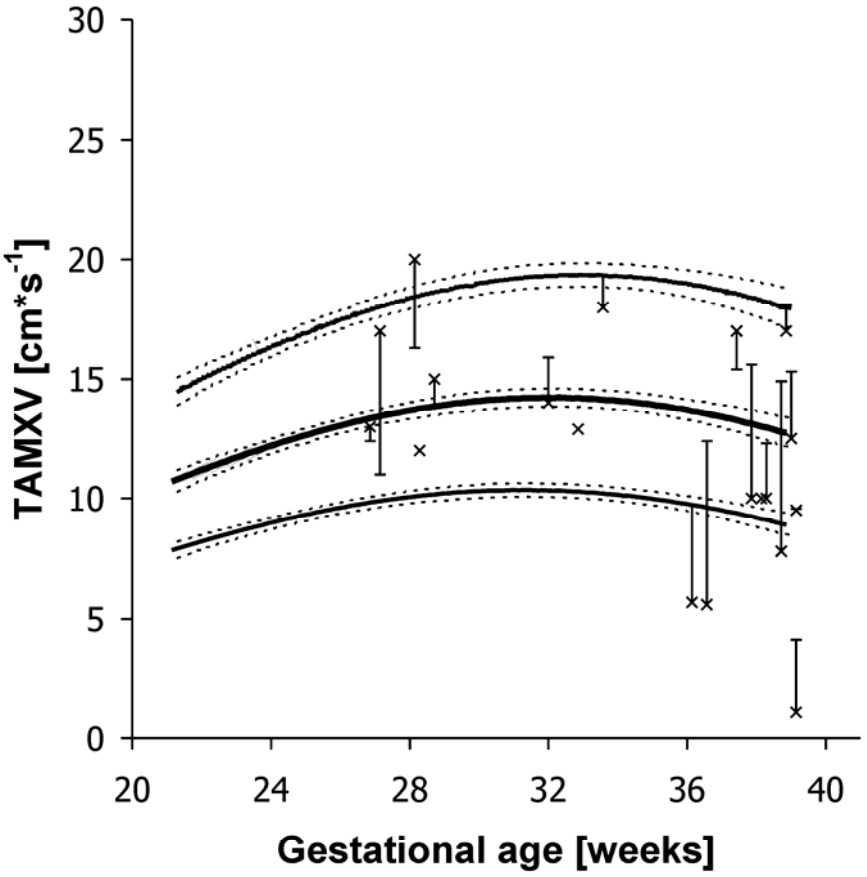

Figure 11: Time-averaged maximum velocity (TAMXV) during fetal quiescence (-) and breathing (×) in the left portal branch. Measurements in the same fetus during one examination are connected with vertical solid lines. Reference ranges presented with 5, 50 and 95 percentile (bold solid lines) and 95% confidence interval (broken lines). After 36 weeks of gestation fetal breathing causes a significant drop in TAMXV (p=0.007).

Gestation	Percentile								
[weeks]	**50**	2.5	5	10	25	75	90	95	97.5
21	**10.6**	7.3	7.8	8.3	9.4	12.0	13.4	14.3	15.2
22	**11.2**	7.7	8.2	8.8	9.9	12.7	14.1	15.1	15.9
23	**11.7**	8.1	8.6	9.2	10.3	13.2	14.8	15.7	16.6
24	**12.2**	8.5	9.0	9.6	10.8	13.8	15.4	16.4	17.3
25	**12.6**	8.8	9.3	10.0	11.2	14.3	15.9	17.0	17.9
26	**13.0**	9.1	9.6	10.3	11.5	14.7	16.4	17.5	18.5
27	**13.4**	9.3	9.9	10.6	11.8	15.1	16.9	18.0	19.0
28	**13.7**	9.5	10.1	10.8	12.1	15.5	17.3	18.4	19.5
29	**13.9**	9.6	10.2	10.9	12.3	15.7	17.6	18.7	19.8
30	**14.1**	9.7	10.3	11.1	12.4	15.9	17.8	19.0	20.1
31	**14.2**	9.7	10.3	11.1	12.5	16.1	18.0	19.2	20.3
32	**14.2**	9.7	10.3	11.1	12.5	16.1	18.1	19.3	20.5
33	**14.2**	9.6	10.3	11.0	12.4	16.1	18.1	19.3	20.5
34	**14.1**	9.5	10.2	10.9	12.3	16.0	18.0	19.3	20.5
35	**13.9**	9.4	10.0	10.8	12.2	15.9	17.9	19.2	20.3
36	**13.7**	9.1	9.8	10.5	11.9	15.7	17.7	19.0	20.1
37	**13.4**	8.9	9.5	10.3	11.7	15.4	17.4	18.7	19.9
38	**13.1**	8.6	9.2	9.9	11.3	15.0	17.0	18.3	19.5
39	**12.7**	8.2	8.8	9.6	11.0	14.6	16.6	17.9	19.1

Tab. 1: Time averaged maximum velocity ($cm*s^{-1}$) in the left portal vein. 554 longitudinal observations in 160 low- risk pregnancies.