Doppler velocimetry with emphasis on changing arterial downstream impedance in the human fetus

Cover: Colour Angio image of a first trimester fetus and Doppler flow velocity waveform recording obtained form the free-floating loop of the umbilical artery.

Doppler velocimetry with emphasis on changing arterial downstream impedance in the human fetus

Doppler bloedstroomsnelheidsmetingen met nadruk op veranderende arteriële vaatweerstand in de humane foetus

PROEFSCHRIFT

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Chapter 1

Introduction and definition of objectives

1.1 Introductory remarks

The introduction of transvaginal Doppler ultrasonography and colour coded Doppler techniques has opened the possibility of studying the embryonic and early fetal circulation as early as 5-6 weeks of gestation. Sonographic detection of the gestational sac at approximately 4.5 weeks of gestation is associated with characteristic changes in Doppler findings of the implantation vascular network (Jaffe and Warsof, 1991; Jauniaux et al., 1991; Mercé et al., 1995). The first colour and pulsed Doppler signals from the yolk sac were obtained as from 5-6 weeks of gestation with a gradual decline as from 9 weeks of gestation due to a reduction in functional activity of the yolk sac (Kurjak et al., 1994). Spiral and arterial blood flow increase dramatically during the first trimester of pregnancy. An exponential and significant increase in peak systolic velocity in the uterine artery has been demonstrated between 13 and 14 weeks of gestation (Jauniaux et al., 1991 and 1992; Jurkovic et al., 1991). At the same time continuous intervillous blood flow has been identified as from 12 weeks onward (Jaffe and Warsof, 1991; Jauniaux et al., 1991 and 1992). The latter seems to be related with the loosening and dislocation of trophoblast plugs, which block free circulation of maternal blood into the intervillous space by occluding the spiral arteries (Hustin et al., 1987 and 1988).

Flow velocity waveforms recordings, particulary in the fetal descending aorta and umbilical artery at 10-14 weeks of gestation, have demonstrated a marked drop in arterial downstream impedance, suggesting increased uteroplacental perfusion to meet oxygen and nutrient demands in the developing fetus (Wladimiroff et al., 1992). Extensive microangiogenesis at placental level is considered to be directly responsible for the observed reduction in pulsatile index values in the umbilical artery and fetal descending aorta (Brosens et al., 1967; de Wolf et al., 1973; Jauniaux et al., 1992). Later in pregnancy, i.e. during the late second and third trimester, impaired placental perfusion may be associated with a marked increase in arterial downstream impedance as expressed by elevated pulsatility index in the above arteries (Trudinger et al., 1985; Groenenberg et al., 1989).

From data in early normal pregnancies and late pregnancies associated with intrauterine growth-retardation, two models of changing arterial downstream impedance emerge: (i) a drop in arterial down stream impedance in normal early pregnancy and (ii) a rise in arterial downstream impedance as a result of impaired uteroplacental perfusion in late pregnancy. Based on these two human fetal models, the question arises as to the possible effects of these arterial downstream impedance changes on venous inflow (umbilical vein, ductus venosus, inferior vena cava) and at cardiac level on atrioventricular blood flow. At this stage, it should be stressed that fetal hemodynamic data both in early and late pregnancy are based solely on flow velocity waveform

recordings. No data are available on volume flow or pressure. This limits interpretation of hemodynamic changes as obtained from flow velocity waveform recordings at cardiac and venous inflow level associated with arterial down stream impedance changes.

Umbilical venous pulsations have been associated with severe intra-uterine growth retardation (Indik et al., 1991; Arduini et al., 1993; Hecher et al., 1995). However, these pulsations occasionally occur in otherwise normal circumstances. There is, therefore, a need to establish the reproducibility of the pulsatile waveform and to further elucidate their significance under both physiological and pathophysiological circumstances.

1.2 Definition of objectives

Following a literature review on the early and late fetal circulation in Chapter 2 the following objectives were addressed according to the two models described earlier:

Normal early pregnancy (8-20 wks):

1. What is the nature of venous flow velocity waveforms (umbilical vein, ductus venosus and inferior vena cava) and how are these venous flow velocity waveforms related to (i) gestational age and (ii) arterial waveforms? Data are presented in Chapter 3.

2. Is it possible to estimate pressure gradients across the fetal ductus venosus? If so, how do these pressure gradient estimations relate to gestational age. Non-invasive ultrasound techniques do not allow direct information on pressure changes. Instead, it is possible to obtain crude estimates of pressure gradients at venous flow level applying a simplified Bernoulli equation (Kiserud et al., 1994). Results of this part of the study are also presented in Chapter 3.

3. What is the nature of fetal atrioventricular waveforms and how do these flow velocity waveforms parameters relate to (i) arterial impedance indices (descending aorta and umbilical artery Pulsatility Index) and (ii) venous flow velocities and impedance indices (umbilical vein, ductus venosus, inferior vena cava)?

4. How do systolic (isovolumic contraction time, ejection time) and diastolic (filling time, isovolumic relaxation time) components of the cardiac cycle relate to gestational age?

Results from studies dealing with objectives 3 and 4 are discussed in Chapter 4.

Complicated late pregnancy:

1. What is the reproducibility and inter-observer variability of intra- and extra-abdominal umbilical venous flow velocity waveforms and left portal venous flow velocity waveforms? Do pulsations occur relative to these recording levels in normal late pregnancies?

2. Do flow velocity waveforms at arterial, atrioventricular and venous level depict changes in the small-for-gestational age fetus? If so, what is the nature of these changes. Do these flow velocity waveform parameters predict fetal distress and neonatal outcome.

Results from this part of the study are presented in Chapter 5. Finally, Chapter 6 provides conclusive statements derived from the early and late pregnancy Doppler studies presented in this thesis.

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Chapter 2

The normal early and abnormal late fetal circulation; a literature review

2.1 Normal early pregnancy

Since the introduction of Doppler ultrasonography in obstetrics, the fetal circulation has been studied in both normal and abnormal pregnancies. Particulary with the advent of transvaginal Doppler ultrasonography, it became feasible to examine the maternal and fetal circulation as early as the first trimester of pregnancy. During the late and early second trimester, marked developmental changes occur both at fetal and placental level which should have an impact on fetal cardiovascular performance. Fetal heart rate changes from 170-180 bpm to 140-150 bpm with appearance of beat-to-beat variation most likely resulting from parasympathetic nerve development (Wladimiroff and Seelen, 1972). At the same time there is a remarkable differentiation in fetal movement patterns (de Vries et al., 1982). Furthermore, around 14 weeks a continuous intervillous flow pattern has been observed (Jaffe and Warsof, 1991; Jauniaux et al., 1991; Jauniaux et al., 1992). This is associated with an abrupt increase of the mean uterine blood flow velocity, which possibly corresponds to the complete dislocation of the trophoblast plugs, allowing uninhibited blood supply to the intervillous space.

Colour coded Doppler will be helpful in locating blood flow in early pregnancy. Whereas under 13 weeks of gestation the superiority of the transvaginal approach is unchallenged, beyond 14 weeks fetal flow velocity waveforms will nearly always be obtained by means of transabdominal Doppler ultrasound.

Since the widespread application of ultrasonography in medicine, there is no verified documented epidemiologic evidence of adverse effects in patients caused by exposure to ultrasound (Ziskin and Petitti, 1988). However, if the intensity is sufficiently high, laboratory studies have shown that ultrasound is definitely capable of producing serious biological damage, resulting from thermal and nonthermal mechanisms (Barnett et al., 1994). No adverse effects due to hyperthermia have been reported from temperature elevations less than 1.5° C above normal body temperature, even for prolonged exposures. Serious embryonic and fetal damage can result from temperatures above 41°C when maintained for more than 15 minutes. The initiation of an adverse effect is directly proportional to the magnitude of the temperature elevation and to the logarithm of the exposure duration. The WFUMB (1992) has adopted a statement, reflecting international consensus on thermal effects in pulsed Doppler clinical applications, which is as follows:

"It has been demonstrated in experiments with unperfused tissue that some Doppler diagnostic equipment has the potential to produce biological significant temperature rises, specifically at bone/soft tissue interfaces. The effects of elevated temperatures may be minimized by keeping the time for which the beam passes through any point in tissue as short as possible. Where output power can be controlled, the lowest available power level consistent with obtaining the desired diagnostic information should be used. Although the data on humans are sparse, it is clear from animal

studies that exposures resulting in temperatures less than 38.5°C can be used without reservation on thermal grounds. This includes obstetric applications."

Moreover, it has been demonstrated that physical and psychomotor development of children exposed to transvaginal ultrasonography did not differ from that of non-exposed infants (Gershoni-Baruch et al., 1991). Cavitation-related events are believed to be responsible for most biological effects on *in vitro* cell suspensions. However, there is no evidence of any effect on tissues *in vivo* (Barnett et al., 1994).

Whereas with the transvaginal approach the fetus is closer to the transducer when compared to the transabdominal approach, less energy is needed to visualize the growing fetus. The Spatial Peak Temporal Average Intensity (SPTA) is most often used to describe the intensity from ultrasound equipment. In early pregnancy Doppler studies, spatial peak temporal average (SPTA) levels below 100 mW/cm^2 should be aimed for and are clearly situated in the lower regions for acoustic output of Japanese and American diagnostic ultrasound equipment (Ide 1989). Moreover, it has been demonstrated by Hussain et al. (1992) that the energy exposure on the surface of the fetus (1.2-1.9 mW/cm^2) is far below the Food and Drug Administration (FDA) guidelines of 94 mW/cm^2.

Late first and early second trimester pregnancies are characterized by marked changes at placental, fetal cardiac and extra-cardiac level. An overview on the early human fetal circulation is presented.

2.1.1 Utero-placental flow velocity waveforms

Early pregnancy is characterized by marked changes at placental level. Transvaginal colour coded Doppler has enabled detection of blood flow in the spiral and radial arteries along with gestational sac visualisation as early as 4.5 weeks of gestation (Mercé et al., 1996). In the latter study, clear signals were obtained from vessels running from the periphery of the gestational sac to the adjacent myometrium. Whereas recording of colour signals was always accompanied by the detection of a gestational sac, it has been suggested that pulsed and colour coded Doppler ultrasonography may serve as a tool to recognize the site of placental implantation before the chorion can be visualised in real-time.

The yolk sac is a highly important organ in early pregnancy. It plays not only a critical role in early haemopoiesis, but it is also the site where primordial germ cells first appear in the developing embryo. Between 5 and 6 weeks of gestation, the first colour coded and pulsed Doppler signals have been demonstrated in the yolk sac, whereas the vitelline duct was only visible as from 7 weeks of gestation (Kurjak et al., 1994a). A low velocity profile with absent end-diastolic

velocities was found. With advancing gestational age, the success rate in visualising both structures with colour coded and pulsed Doppler increased significantly with highest visualisation rates at 7-8 weeks of gestation. The decline in success rate as from 8 weeks of gestation may be explained by the fact that at the same time the process of elongation of the vitelline duct is taking place together with removal of the yolk sac from the body wall.

As pregnancy progresses, spiral and radial blood flow undergo a marked increase. Under the influence of trophoblast invasion (Pijnenborg et al., 1980 and 1981), spiral arteries are being transformed into low-resistance uteroplacental vessels, which are capable of accommodating the increased blood flow to the developing fetus. Besides the gestational age dependent decrease in downstream impedance, the impedance to blood flow also decreases from the main uterine to the spiral arteries (Deutinger et al., 1988; Jurkovic et al., 1990; Mercé et al., 1991; Kurjak et al., 1992, 1993 and 1994b). The reduction in vascular impedance is most likely the result of dilation of the spiral arteries. The latter may be induced by trophoblast invasion, hormones and a decrease in maternal blood flow viscosity (Kurjak et al., 1994c).

Several studies have reported on intervillous venous blood flow as from 12 weeks of gestation (Jaffe and Warsof, 1991; Jauniaux et al., 1991 and 1992). Intervillous flow has been accounted for to result from loosening and dislocation of trophoblast plugs. Hustin and co-authors (Hustin and Schaaps, 1987; Hustin et al., 1988) demonstrated that these plugs block the free circulation of blood flow into the intervillous space by occluding the spiral arteries. Recently, a study of Mercé and co-authors (1996) has demonstrated intervillous flow as from 6 weeks onwards, which would be in agreement with embryologic studies. In the latter studies, intervillous flow was established between 14 to 40 days of embryonic life (Wilkin, 1958; Kaufmann, 1981). Moreover, Moll (1995) noted that the absence of colour signals in studies in which intervillous flow was established as from 12 weeks of gestation, can not be attributed to absence of intervillous flow. In a commentary, the author pointed out that there are five reasons that suggest lack of evidence for the absence of intervillous flow. Firstly, plugging of the artery tips may be due to an artefact as the result of histologic preparation. Arteries, which are prepared by quick-freezing to preserve normal architecture, are much more distended than would appear in routinely prepared sections (Van Citters et al., 1962). Secondly, whereas absence of red cells in the intervillous space is normal throughout pregnancy, the absence of red cells in histologic specimens does not prove absence of blood flow in early pregnancy. Thirdly, the perfusion of the uterus with a barium sulphate suspension, did not reveal appearance of contrast medium in the intervillous space, whereas decidual vessels were filled with the contrast medium (Hustin and Schaaps; 1987). Also here, there should be caution to draw a parallel between histologic specimen and normal conditions. In the fourth place, using a hysteroscope no discolouring has been observed in the intervillous space

(Hustin and Schaaps, 1987). However, the intervillous clefts are so small, that red cells pass in a single file. Therefore, it is impossible to recognize red cells by their colour. Finally, low flow velocities of approximately 1 mm/s have been recorded in the intervillous space (Freese et al., 1966), which are excluded by the commonly used noise filter of 100 Hz.

Oxygen measurements in endometrial and trophoblastic tissues have revealed a significant rise in pO2 in early pregnancy, which would probably result from a marked increase in maternal blood flow in the intervillous space (Rodesch et al., 1992). These findings suggest embryonic development in a rather oxygen-poor environment when compared with later stages of fetal life.

2.1.2 Extra-cardiac arterial flow velocity waveforms

During the last decade, increasing attention has been paid to waveforms in the umbilical artery (Den Ouden et al., 1990; Guzman et al., 1990; Kurjak et al., 1990; Arduini and Rizzo, 1991; Wladimiroff et al., 1991a and 1992a), descending aorta (Kurjak et al, 1990; Wladimiroff et al, 1991a and 1992a) and intracerebral arteries (Wladimiroff et al., 1992a). Before 10 weeks of gestation, fetal flow velocity waveforms at extra-cardiac level are characterized by absent end-diastolic flow velocities, suggesting a high vascular resistance at fetal and umbilical placental level compared with late pregnancy. Whereas at fetal placental and fetal trunk level end-diastolic velocities are still absent between 10 and 12 weeks of gestation, gradual appearance of end-diastolic velocity has been observed in over 50 % of middle cerebral artery flow velocity waveforms, suggesting a relatively low cerebral vascular resistance and as a result preferential blood flow to the brain under otherwise physiological circumstances (Wladimiroff et al., 1992a). As from 12 weeks of gestation end-diastolic velocities also gradually appear in the umbilical artery and descending aorta indicating a reduction in fetal placental vascular resistance. This may be determined by trophoblast invasion into the spiral arteries (Pijnenburg et al., 1980), but particulary by microangiogenesis at placental level (Jauniaux et al., 1991).

2.1.3 Intracardiac flow velocity waveforms

Atrioventricular waveforms can be obtained from the four-chamber view characterized by an early diastolic (E-wave) component, coinciding with passive atrial filling, and a late diastolic (A-wave) component, which represents atrial contraction.

In the late first and early second trimester of pregnancy, E-wave velocities are rather low as compared to velocities later in pregnancy, resulting in an E/A ratio of approximately 0.5 as opposed to E/A ratio's ranging between 0.8 and 0.9 later in pregnancy (Wladimiroff et al., 1991b;

Van der Mooren et al., 1991). This gestational age-dependent rise in E/A ratio suggests a shift of blood flow from late diastole towards early diastole, which may be due to increased ventricular compliance and/or raised ventricular relaxation rate (Wladimiroff et al., 1991b).

Transtricuspid flow velocities are significantly higher than flow velocities at transmitral level (Wladimiroff et al., 1992b). Since volume flow is equal to time-averaged velocity multiplied by vessel area the higher transtricuspid velocities may reflect increased right ventricular stroke volume and output. This is in agreement with observations of right ventricular predominance in normal late pregnancy (Reed et al., 1990).

At outflow tract level, aortic and pulmonary artery flow velocities show a gestational age related rise in peak velocities during early gestation with highest velocities in the ascending aorta. At 11-12 weeks of gestation, peak velocities are reported with mean values of 32.1 $\pm$ 5.4 (1SD) cm/s in the ascending aorta and 29.6 $\pm$ 5.1 cm/s (1SD) in the pulmonary artery (Wladimiroff et al., 1991b). On the basis of similar findings in late pregnancy, it has been suggested that the higher peak systolic velocities in the ascending aorta may be the result of a difference in semilunar valve area between ascending aorta and pulmonary artery (Allan et al., 1987).

2.1.4 Extra-cardiac venous flow velocity waveforms

Pulsatile umbilical venous flow has been reported as early as 8 weeks of gestation (Rizzo et al. 1992a). Flat venous blood flow patterns are observed in the 2nd and 3rd trimester of pregnancy.

The ductus venosus functions exclusively in the fetal circulation as a shunt between the umbilical vein and inferior vena cava, allowing direct flow of well-oxygenated blood through the ductus venosus towards the foramen ovale and left heart to accommodate the needs of the developing fetal brain and trunk. The ductus venosus can often not be visualised in early gestation (Huisman et al., 1993). However, by placing the sample volume immediately distal to the umbilical sinus, waveforms can be accepted as originating from the ductus venosus on the basis of their similarity to ductus venosus flow velocity waveforms observed in late pregnancy (Kiserud et al., 1991; Huisman et al., 1992). Similar to the inferior vena cava, ductus venosus flow velocity waveforms are characterized by a systolic and early diastolic forward component without a late diastolic reverse flow component. Before 11-12 weeks of gestation differentiation between a clear systolic and early diastolic component is not always feasible. Ductus venosus time-averaged velocity is approximately three times the velocity in the umbilical vein and inferior vena cava, which may result in a tendency not to mix, and, thus, may support the idea of preferential streaming of oxygen rich blood through the ductus venosus towards the foramen ovale (Huisman et al., 1993).

The waveform profile of the inferior vena cava resembles the profile as can be seen in late gestation with a systolic and early diastolic forward component and a late diastolic retrograde component (Reed et al., 1990; Huisman et al., 1991). The percentage reverse flow at 11-12 weeks is as high as 25-30%, which is approximately six-fold of that observed in late third trimester pregnancies (Reed et al., 1990; Huisman et al., 1991). This may be due to a low cardiac compliance or decreased ventricular relaxation rate. Rizzo et al. (1992a) reported an association of increased reverse flow with umbilical venous pulsations, suggesting a relationship between these waveform characteristics and cardiac filling patterns.

2.1.5. Conclusions

Combined transvaginal and transabdominal ultrasound allows detailed study of fetal placental, cardiac and extra-cardiac arterial and venous flow velocity waveforms. Late first and early second trimester pregnancies are characterized by marked changes at all those levels, with emphasis on a change from a high placental vascular resistance in the late first trimester to a low fetal placental vascular resistance in the early second trimester of pregnancy. Microangiogenesis at placental level and trophoblast invasion into the spiral arteries, followed by a complete dislocation of the trophoblast plugs, may be responsible for these hemodynamic changes.

It should be kept in mind that as long as no volume flow and pressure measurements are available, we can only speculate on the observed changes in flow velocities. More studies will be needed to understand the exact underlying mechanisms. Moreover, the clinical relevance of Doppler ultrasonography at this early stage of gestation still needs to be determined.

2.2 Abnormal late pregnancy

An important aspect of prenatal care in late pregnancy is the timely detection of the small-for-gestational age fetus. Serial fetal biometry, in particular measurements of the upper abdominal circumference will be helpful in establishing fetal growth. A normal utero-placental circulation is necessary to ensure optimal oxygen supply and nutrients to the developing fetus.

2.2.1 Extra-cardiac arterial flow velocity waveforms

In small-for-gestational age fetuses as a result of uteroplacental insufficiency, end-diastolic velocities in the descending aorta, renal arteries and umbilical artery may be reduced or even

absent, reflecting a change from a low arterial downstream impedance to a high arterial downstream impedance at fetal trunk and placental level. Pulsatility index values in these vessels will be raised as a result of this (Trudinger et al., 1985; Tonge et al. 1986).

When pO_2 falls below and pCO_2 rises above a certain threshold, aortic and carotid chemoreceptors could be switched on, regulating a vasodilatory response at cerebral arterial level in order to ensure adequate oxygenation to the brain. Thus, in small-for-gestational age fetuses a hemodynamic compensatory mechanism will lead to an increase in blood supply to the brain and a reduction in the perfusion of the gastrointestinal tract, kidneys and lower extremities. Indeed, raised end-diastolic flow velocities have been established in intracerebral arteries of small-for-gestational age fetuses (Wladimiroff et al., 1987; Van den Wijngaard et al., 1989; Noordam et al., 1994). However, an increase in pulsatility index in the cerebral arteries has been described a few hours before fetal death (Mari and Wasserstrum, 1991; Chandran et al., 1991; Rizzo et al., 1994a; Chitrit et al., 1995). At this stage, a further deterioration in Doppler indices at arterial, cardiac and venous level was established, with even tricuspid insufficiency.

Time-averaged velocities in the descending aorta plateau at approximately 32 weeks and fall slightly after 40 weeks of gestation unlike time-averaged velocities in the common carotid artery which show an increase, suggesting a progressively increasing fraction of the cardiac output to be directed to the fetal brain (Bilardo et al., 1988).

2.2.2 Intracardiac flow velocity waveforms

Right ventricular predominance has been established in normally developing fetuses (Reed et al., 1986; Rizzo et al., 1988; Hecher et al., 1994). Also, a progressive rise in E/A ratio has been reported. In the SGA fetus, however, the transmitral flow velocities may exceed the transtricuspid flow velocities (Reed et al., 1987; Rizzo et al., 1988; Rizzo and Arduini, 1991). This may result from the fact that the left heart is exposed to reduced resistance of the coronary arteries and of neck and head arteries (Wladimiroff et al., 1986; Arduini et al., 1987; Gembruch and Baschat, 1996), whereas the right heart, ejecting through the ductus arteriosus into the descending aorta, is presented with an increased vascular resistance (Jouppila and Kirkinen, 1984a; Rizzo et al., 1987).

Hemodynamic adjustment in the small-for-gestational age fetus is associated with reduced peak systolic flow velocities in all three cardiac outflow tract vessels (Rizzo et al., 1988 and 1990; Groenenberg et al., 1989; Al-Ghazali et al., 1988 and 1989; Rizzo and Arduini, 1991). This reduction may be determined by reduced volume flow, increased valve size, reduced cardiac contraction force or increased arterial downstream impedance (Groenenberg et al., 1993). It has

been demonstrated that in the early stages of decline in growth, cardiac output is similar to that in normal fetuses, suggesting a relatively higher output with respect to fetal weight (Reed et al. 1987; Rizzo and Arduini, 1991). As pregnancy progresses, however, the cardiac output eventually declines in the small-for-gestational age fetus, whereas in normal fetuses the cardiac output increases (Reed et al., 1987; Rizzo and Arduini, 1991). It has been suggested that the fall in cardiac output and in peak velocities in the cardiac outflow tract vessels, may result from progressive fetal compromise with subsequent changes in fetal oxygenation and acid-base status (Rizzo and Arduini, 1991) .

It has been demonstrated that right ventricular dysfunction may be present in severe intra-uterine distress, without evident disturbances of left ventricular function (Räsänen et al., 1989). Right ventricular dysfunction, however, has little clinical implications, suggesting that the human fetal heart may have a considerable functional reserve in the presence of chronic intra-uterine distress (Räsänen et al., 1989). Increased isovolumic relaxation time may play a role in cardiac diastolic dysfunction, and may reflect a possible rise in transmitral pressure gradient as a result of enhanced left ventricular venous return (Tsyvian et al., 1995).

Recently, fetal coronary blood flow has been established in severe uteroplacental insufficiency (Gembruch and Baschat, 1996). Coronary blood flow was observed after normalization of cerebral flow and characteristic flow changes at venous level, thus indicating failure of compensatory mechanisms and a progressive decline in cardiac function. This may suggest maximal coronary dilatation in response to myocardial hypoxia and could be termed a 'heart-sparing effect'. The 'heart-sparing' effect is considered to be preterminal.

The compensatory mechanism(s) of cerebral arterial vasodilation may be lost when there is severe hypoxemia, metabolic disturbances or development of brain oedema, resulting in a rise in middle cerebral pulsatility index (Bilardo, 1994). An increase in middle cerebral artery pulsatility index in severe hypoxemia may also be the consequence of alterations in flow due to reduced cardiac contractility and to a fall in absolute cardiac output (DeVore, 1988).

2.2.3 Extra-cardiac venous flow velocity waveforms

During the process of hemodynamic adaptation as seen in small-for-gestational age fetuses, changes may also be observed in venous return to the heart. A further rise in arterial downstream impedance and ultimately cardiac compromise have been indicted as underlying causes of abnormal venous flow velocity waveform pattern.

Umbilical venous pulsations have been observed in the small-for-gestational age fetus (Indik et al., 1991; Arduini et al., 1993). In small-for-gestational age fetuses the presence of umbilical

venous pulsations have been associated with a neonatal mortality of 63%, compared to only 19 % in fetuses without umbilical venous pulsations (Arduini et al., 1993). Moreover, umbilical venous pulsations were associated with a shorter time-interval between the first occurrence of absent end-diastolic velocity in the umbilical artery and the development of abnormal fetal heart rate tracings and subsequent delivery (Arduini et al., 1993).

Whereas fetal hypoxia is associated with reduced umbilical venous flood flow (Jouppila and Kirkinen, 1984b), normal ductus venosus peak systolic flow velocities have been described (Kiserud et al., 1994). This may suggest redistribution of blood flow to maintain optimal oxygen supply to the developing fetus. On the other hand, end-diastolic velocities may be reduced or even reversed. This is most likely explained by the increase in downstream impedance at fetal trunk and placental level resulting in an increased ventricular afterload and subsequent ventricular end-diastolic pressure. In a study by Hecher et al. (1995), it has been demonstrated that pulsatility index values in both the arterial system and the ductus venosus may serve as a tool to estimate fetal hypoxia. With increasing severity of fetal hypoxemia and acidemia, the pulsatility index for veins in the ductus venosus increases as the result of diminished or even reversed velocities during atrial contraction.

The percentage reverse flow and the ratio between peak systolic and peak diastolic velocity in the inferior vena cava show an increase in the small-for-gestational age fetus (Reed et al., 1990; Rizzo et al., 1992b). Along with the umbilical venous pulsations and reduced end-diastolic velocities in the ductus venosus, the observed changes in the inferior vena cava may also be explained by a reduced venous return resulting from a raised afterload. Progressive changes at inferior vena cava and ductus venosus level appear to be related to the onset of late heart rate decelerations (Rizzo et al., 1992b; 1994b). Moreover, after an initial period of brain-sparing followed by a normalization of cerebral flow, a progressive worsening of venous flow patterns has been observed (Gembruch and Baschat, 1996). Venous flow velocity waveform recording may therefore be useful in the monitoring of the small-for-gestational age fetus in the presence of normal cerebral flow.

2.2.4 Conclusions

In small-for-gestational age fetuses as a result of uteroplacental insufficiency hemodynamic adjustment takes place, which is triggered by carotid and aortic chemoreceptors depending on the degree of fetal hypoxemia. Centralization of the fetal circulation with subsequent brainsparing seem to represent the most essential development in this hemodynamic adjustment.

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Chapter 3

Venous flow velocity waveforms in early pregnancy

3.1 Introductory remarks

The use of the transvaginal approach allows visualisation of fetal venous vessels as early as 8 weeks of gestation. Development of the venous system is completed at approximately 8-9 weeks of gestation (Barry, 1963). Little is known about venous hemodynamics in the early developing human fetus. Animal experimental data are scarse, which makes extrapolation to the human fetus virtually impossible. Venous flow studies in fetal lambs late in pregnancy have demonstrated the importance of ductus venosus blood flow in the oxygenation of the developing fetus (Edelstone et al., 1978; Edelstone and Rudolph, 1979; Rudolph et al., 1985).

The presence of a ductus venosus sphincter at the level of the umbilical sinus has long been questioned (Chacko and Reynolds, 1953; Meyer and Lind, 1965; Pearson and Sauter, 1968, 1969 and 1971; Ehinger, 1968; Saltzer, 1970). Data from a morphologic study carried-out on embryos in cooperation with the Department of Embryology and Anatomy, University of Leiden (Prof A.C. Gittenberger-de Groot) suggest the presence of a ductus sphincter. This was based on the observation of a "lip" or "rim" at the inlet of the ductus venosus in an embryo of 9 weeks of gestation, which is consistent with observations by Chacko and Meyer (1953). However, instead of a muscular sphincter only a scarcely developed smooth musculature could be visualised in the duct wall. Of interest is the small bundle of vagal nerve fibres that is formed by contributions from both the anterior and posterior vagal trunk, which runs caudally between the layers of the hepato-gastric ligament to the junction of the ductus venosus with the umbilical sinus. The functional implication of these nerve fibres, however, is yet to be determined. Similar observations have been made by Pearson and Sauter (1969). More advanced staining techniques will be needed to determine the functionality of the lip, which may act like a sphincter.

The nature of venous waveforms and their relationship to gestational age will be discussed in Chapter 3.2. As has been stated in Chapter 1, Doppler ultrasound does not allow direct information on fetal volume flow and pressure changes. Indirect estimates of ductus venosus pressure gradients can be obtained, however, through the application of a modified Bernoulli equation as first described by Kiserud et al. (1994). Insight into venous pressure gradients in the early developing fetus would aid in the understanding of the role of the ductus venosus with regard to fetal oxygen supply. Estimates of ductus venosus pressure gradients are presented in Chapter 3.3.

3.2 Fetal venous and arterial flow velocity waveforms between 8 and 20 weeks of gestation

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3.2.1 Summary

Our purpose was to study the nature and gestational age dependency of fetal venous Doppler flow velocity waveforms and their relationship with fetal arterial waveforms in early pregnancy.

Venous and arterial Doppler recordings were performed in 262 normal singleton pregnancies according to a cross-sectional study design at 8-20 weeks of gestation. A statistically significant age dependent increase is established for the umbilical vein, ductus venosus and inferior vena cava time-averaged velocity. Umbilical venous pulsatile flow patterns are observed up to 15 weeks of gestation. The Pulsatility Index for Veins in all three venous vessels displays a gestational age dependent reduction. No relation can be established between Pulsatility Index for Veins and the Pulsatility Index in the descending aorta and umbilical artery. This may be explained by the fact that the Pulsatility Index for Veins reflects cardiac ventricular preload, whereas the Pulsatility Index in the arterial vessels reflects downstream impedance at fetal placental level.

3.2.2 Introduction

Recent studies using combined transvaginal and transabdominal Doppler ultrasonography demonstrated that fetal venous, cardiac and arterial flow velocity waveforms can be recorded as early as 11-12 weeks of gestation (Wladimiroff et al., 1991; Wladimiroff et al., 1992; Huisman et al., 1993a).

Trophoblast invasion of the spiral arteries occurs during the late first and early second trimester of pregnancy resulting in low-resistance uteroplacental vessels (Brosens et al., 1967; de Wolf et al., 1973). At this time there is also appearance of intervillous flow and development of marked angiogenesis at placental level (Jauniaux et al., 1992). This may explain the significant drop in umbilical artery Pulsatility Index established in normal pregnancies at 11-14 weeks of gestation (Wladimiroff et al., 1992).

No information is available on gestational age related changes in venous flow velocity waveforms and their relationship with arterial waveform patterns, notably from the descending aorta and the umbilical artery early in pregnancy.

The objective of the current study, therefore, was:

(1) To determine the nature and gestational age dependency of flow velocity waveform patterns from the umbilical vein, ductus venosus and inferior vena cava and

(2) To determine the relationship between venous waveform patterns and waveform patterns from the descending aorta and umbilical artery between 8 and 20 weeks of gestation.

3.2.3 Material and methods

Subjects

Between August 1992 and March 1994, a total of 348 women with normal singleton pregnancies recruited from a normal out-patient population, consented to participate in the study. Maternal age ranged between 16 and 41 years (median 31 yrs). Gestational age varied between 8 and 20 weeks (median 14 wks). The study protocol was approved by the Hospital Ethics Committee. Pregnancy duration was estimated from the last menstrual period and confirmed by ultrasound measurement of the fetal crown-rump-length (8-12 wks) or biparietal diameter (12-20 wks). Each woman was included in the study once.

Only pregnancies which progressed uneventfully and resulting in the delivery of a normal infant with a birth weight between the 10th and 90th percentile corrected for maternal parity and fetal sex (Kloosterman, 1970), were included in the data analysis.

Doppler recordings

Ultrasound Doppler studies were performed with a Hitachi EUB 450 (Hitachi Medical Corporation, Tokyo, Japan). We used a combined transvaginal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time) and 6.5 MHz (Doppler) at 8-13 weeks of gestation or a combined transabdominal real-time and Doppler system with a carrier frequency of 3.5 MHz (real-time) and 3.0 MHz (Doppler) at 14-20 weeks of gestation. Doppler recordings were performed by one examiner (IPvS).

Flow velocity waveforms from the umbilical vein and umbilical artery were obtained from the free-floating loop of the umbilical cord. The sample volume was placed over a straight section of the umbilical cord allowing determination of the vessel interrogation angle, which was always

kept below 20 degrees. Flow velocity waveforms from the ductus venosus were obtained from a slightly oblique transection through the fetal abdomen. An imaginary line can be drawn from the fetal spine to the anterior chest wall, dividing the fetal abdomen in two equal parts. At an angle of approximately 10 degrees to the left or right of this imaginary line, depending on fetal position, the ductus venosus will be presented just proximal from the umbilical sinus. The sample volume was placed immediately distal from its origin above the umbilical sinus. In early gestation, the ductus venosus was not always visible. However, waveforms were accepted as originating from the ductus venosus on the basis of the method described above and the similarity with waveforms observed later in pregnancy (Huisman et al., 1992). Flow velocity waveforms from the inferior vena cava were recorded in a sagittal view, which included the fetal right atrium, right ventricle and ascending aorta (Reed et al., 1990). The sample volume was placed over the inferior vena cava immediately distal to its widening and entrance in the right atrium. Flow velocity waveforms from the lower thoracic part of the descending aorta were obtained from a sagittal cross-section through the fetal trunk, displaying a major section of the fetal spine (Eik-Nes et al., 1980).

All Doppler studies were performed with the woman in the semirecumbent position and during fetal apnea, since the latter may modulate flow velocity waveform (Maršál et al., 1984). The total examination time was limited to 15 minutes in each instance. All flow velocity waveforms were recorded on hard copies. Waveform analysis was performed by one examiner (IPvS) using a microcomputer (Olivetti M24; Olivetti B.V., Leiden, the Netherlands) linked to a graphical tablet.

Umbilical venous pulsations were defined as at least three consecutive negative deflections of the venous waveform each comprising at least 10% of the time-averaged velocity and synchronous to fetal heart rate. In all recordings displaying umbilical venous pulsations, maximal velocity (cm/s), minimal or late diastolic velocity coinciding with atrial contraction (a; cm/s), and time-averaged velocity (cm/s) were determined for three consecutive cardiac cycles from the maximum frequency envelop. In case of umbilical venous waveforms without pulsations, the time-averaged velocity was analyzed at three different measuring points on the maximum frequency envelop in the continuous flow velocity waveform. Waveform analysis in the ductus venosus and the inferior vena cava consisted of calculation of (i) peak velocity (cm/s) during both systole (S) and diastole (D) and (ii) time-averaged velocity (TAV; cm/s). Moreover, the late diastolic flow velocity component coinciding with atrial contraction, was determined in the ductus venosus as minimal forward velocity (a; cm/s) and in the inferior vena cava as peak reverse velocity (a; cm/s). Also, in the inferior vena cava time-velocity integral as expressed by the percentage of total forward flow was calculated. The degree of pulsatility in all three venous vessels was determined according to the following equation (Hecher et al., 1995): PIV=(S-a)/TAV, in which PIV=Pulsatility Index for Veins, S = peak systolic velocity, a = late diastolic velocity and TAV

= time-averaged velocity. The degree of pulsatility in the descending aorta and umbilical artery was expressed by the Pulsatility Index (PI) as calculated according to Gosling et al. (1975). Three consecutive flow velocity waveforms with the highest velocity and similar appearance were used to calculate the different parameters in each vessel.

Data analysis

To establish the relationship between gestational age and (i) venous flow velocity indices and (ii) the Pulsatility Index in the descending aorta and umbilical artery the Spearman rank correlation test was used. Multiple linear regression analysis was employed to determine the relationship between Pulsatility Index for Veins in all three vessels and gestational age. For the construction of gestational age specific percentiles the AVAS algorithm (Tibshirani, 1980) was used. Correlation coefficients were computed using the Spearman correlation test to assess the relationship between the Pulsatility Index for Veins from each vein and the Pulsatility Index from the descending aorta and the umbilical artery. The two-sample Wilcoxon test, corrected for gestational age by stratification, was used to establish the relationship between the absence or presence of umbilical venous pulsations and venous flow velocity waveform parameters. P values < 0.01 were considered statistically significant.

3.2.4 Results

Of the 348 women included in the study, 20 women were excluded because no Doppler signals could be obtained as a result of maternal obesity, fetal position or fetal movements, 34 women subsequently dropped out due to pregnancy pathology and a further 32 women were excluded because of a fetal birth weight below 10th percentile or above 90th percentile for weight of gestation. Flow velocity waveform recordings from 262 women were available for further analysis. In 240 women waveform recordings were obtained in more than one venous vessel and in 97 women waveform recording was successful in all three venous vessels. Arterial flow velocity waveforms were obtained in every instance.

Venous flow velocities relative to gestational age

Umbilical vein

A pulsatile flow pattern is observed up to 15 weeks of gestation (Figure 1). At 8 weeks the Pulsatility Index for Veins (PIV) (P50) is 0.33, at 11 weeks: 0.27 and at 14 weeks: 0.22. The PIV

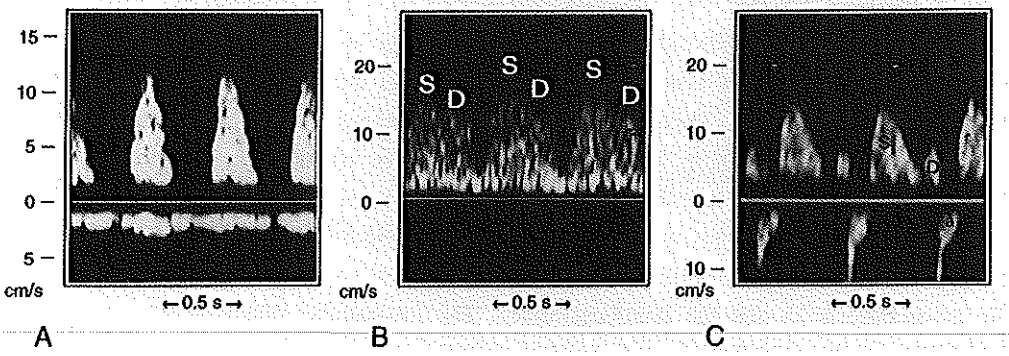

Figure 1 *Doppler flow velocity waveform tracings from the pulsatile umbilical vein and artery (A), ductus venosus (B) and inferior vena cava (C) at 11 weeks of gestation. S = systole; D = diastole; a = minimal velocity coinciding with atrial contraction*

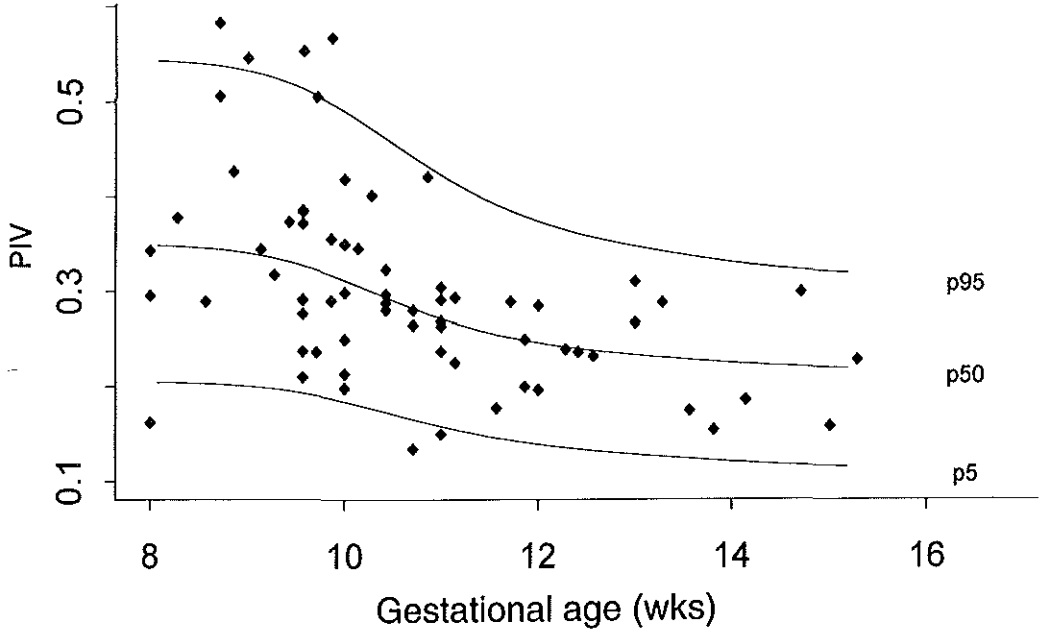

Figure 2 *Individual data and reference ranges (p5, p50, p95) are presented for the pulsatility index for veins (PIV) in the umbilical vein relative to gestational age (wks)*

shows a statistically significant linear reduction ($p<0.001$; Figure 2) and time-averaged velocity (TAV, cm/s) a statistically significant non linear increase ($p<0.001$; Figure 3) with advancing gestational age.

Ductus venosus

Distinction between a systolic and diastolic forward component can be made as from 9 weeks of gestation (Figure 1). A statistically significant non linear increase with advancing gestational age is established for the peak systolic velocity (S, cm/s; $p<0.001$), peak diastolic velocity (D, cm/s; $p<0.001$) and time-averaged velocity (TAV, cm/s; $p<0.001$; Figure 4). The PIV in the ductus venosus shows a statistically significant linear decrease ($y=1.31-0.028x$; $p<0.001$; Figure 5) with advancing gestational age.

Inferior vena cava

A systolic and diastolic forward component as well as a late diastolic reverse flow component is present as from 8 weeks of gestation (Figure 1). A statistically significant non linear increase with advancing gestational age is established for the peak systolic velocity (S, cm/s; $p<0.001$), peak diastolic velocity (D, cm/s; $p<0.001$) and time-averaged velocity (TAV, cm/s; $p<0.001$; Figure 6). Percentage reverse flow remains constant up to 14 weeks of gestation with a significant reduction during the remainder of the study period ($p<0.001$; Figure 7). A statistically significant linear decrease with advancing gestational age is present for the PIV in the inferior vena cava ($y=4.93-0.097x$; $p<0.001$; Figure 8).

Interrelationship between venous flow velocity waveforms

The presence or absence of umbilical venous pulsations corrected for gestational age does not result in a statistically significant change in venous flow velocity parameters.

Pulsatility Index for Veins relative to arterial Pulsatility Index values

End-diastolic velocities are absent in both the descending aorta and umbilical artery up to 10 weeks, but are present in at least 32.6% between 11 and 16 weeks and in 100% after 16 weeks of gestation. A statistically significant negative correlation with gestational age is established for the umbilical artery PI ($r_s=-0.80$, $p<0.001$; Figure 9) and fetal descending aorta PI ($r_s=-0.75$, $p<0.001$; Figure 10). When adjusted for gestational age, no statistically significant correlation between the PIV in the three venous vessels and the PI in the descending aorta and umbilical artery is observed.

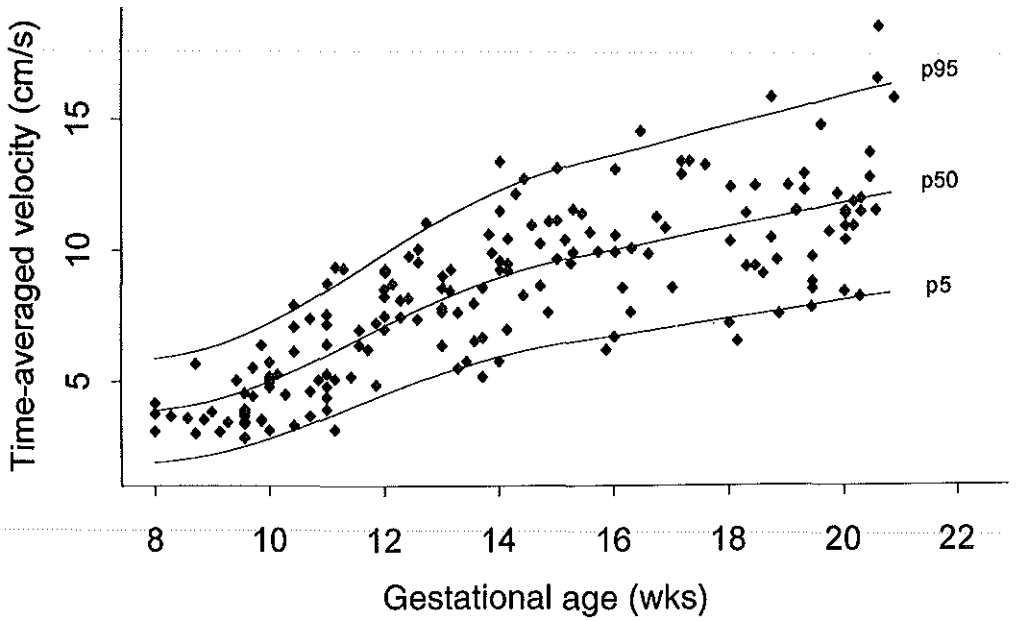

Figure 3 *Individual and reference ranges (p5, p50, p95) are presented for umbilical venous time-averaged velocity (cm/s) relative to gestational age (wks)*

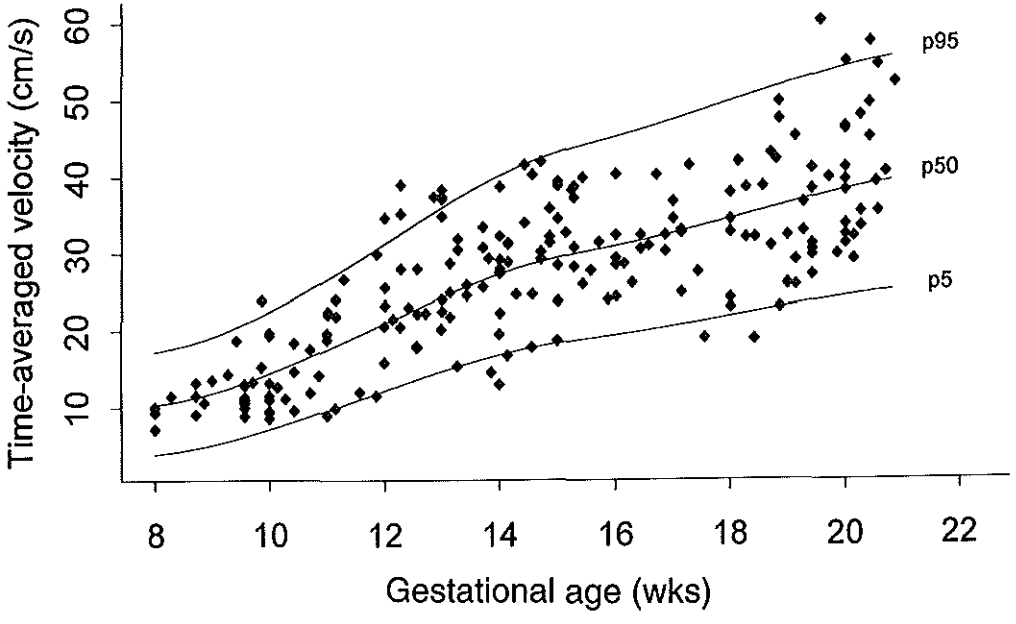

Figure 4 *Individual and reference ranges (p5, p50, p95) are presented for ductus venosus time-averaged velocity (cm/s) relative to gestational age (wks).*

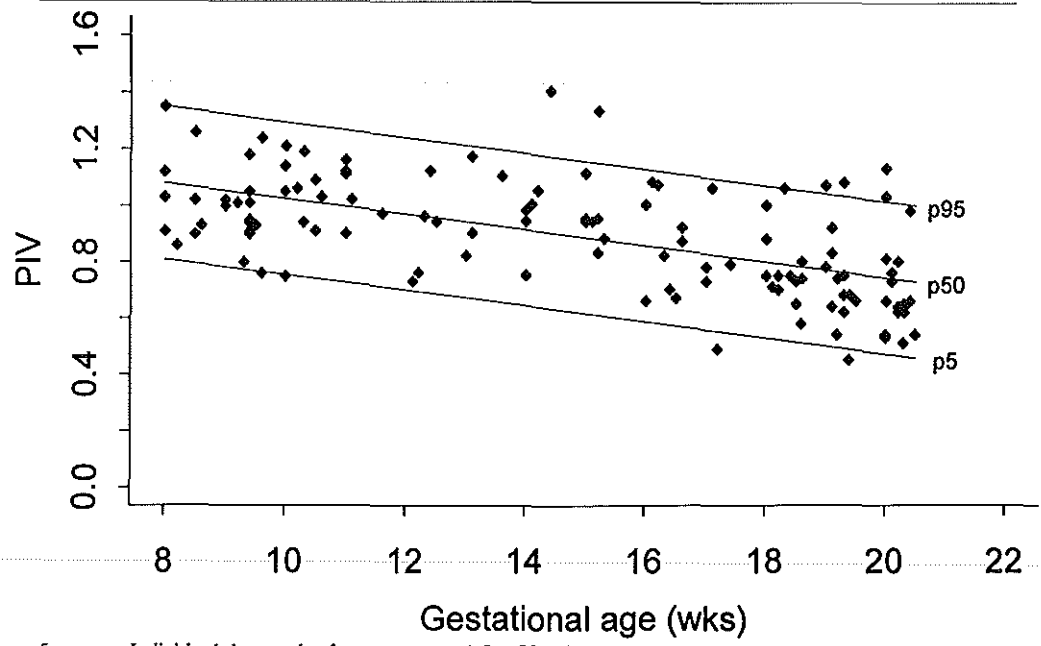

Figure 5 *Individual data and reference ranges (p5, p50, p95) are presented for the pulsatility index for veins (PIV) in the ductus venosus relative to gestational age (wks)*

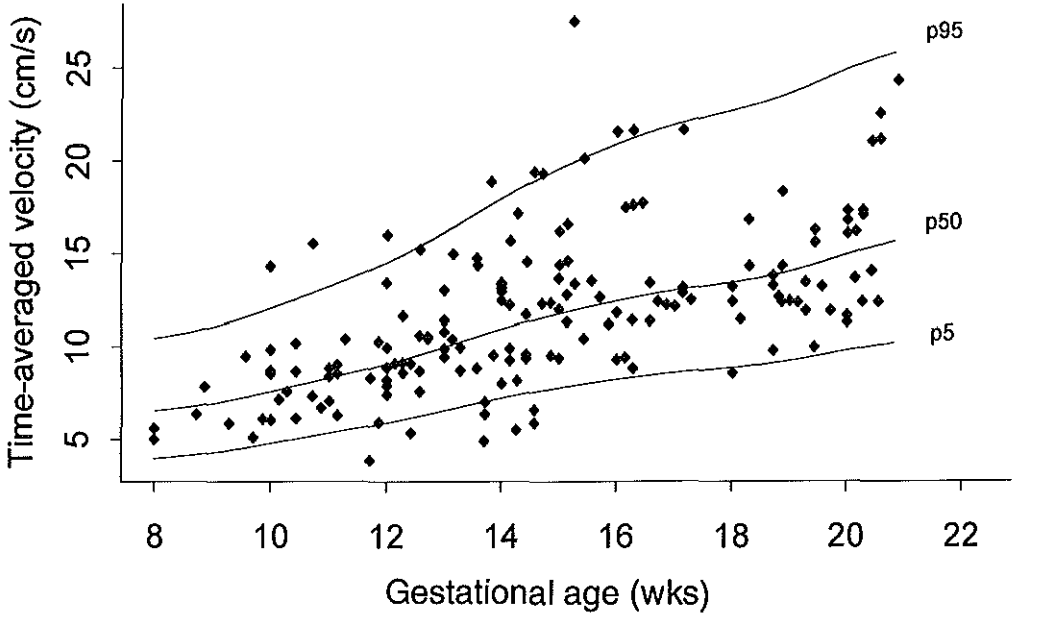

Figure 6 *Individual data and reference ranges (p5, p50, p95) are presented for the inferior vena cava time-averaged velocity (cm/s) relative to gestational age (wks)*

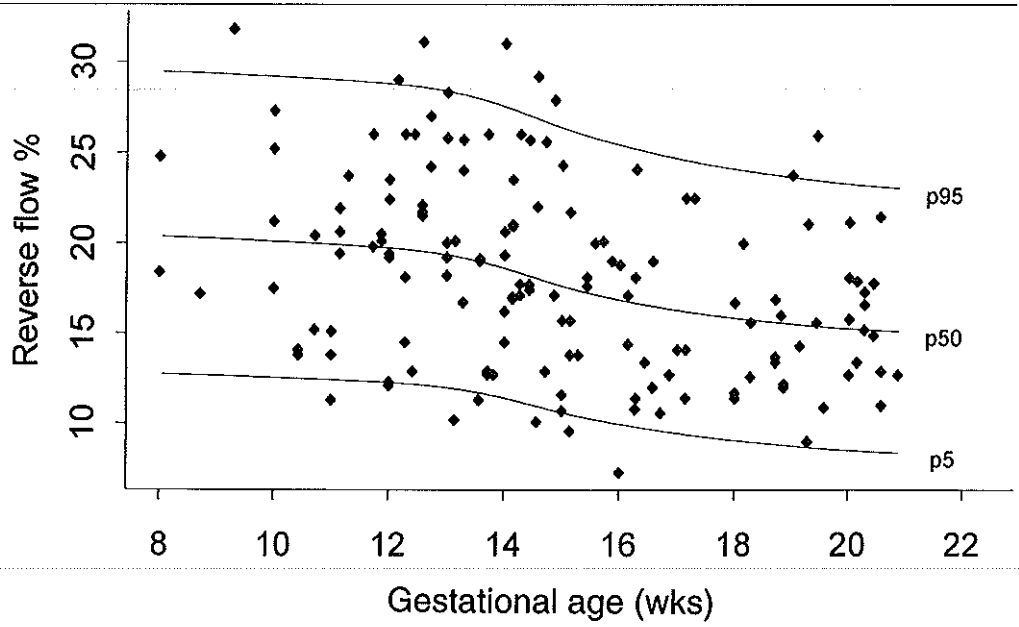

Figure 7 *Individual data and reference ranges (p5, p50, p95) are presented for percentage reverse flow during atrial contraction in the inferior vena cava (%) relative to gestational age (wks)*

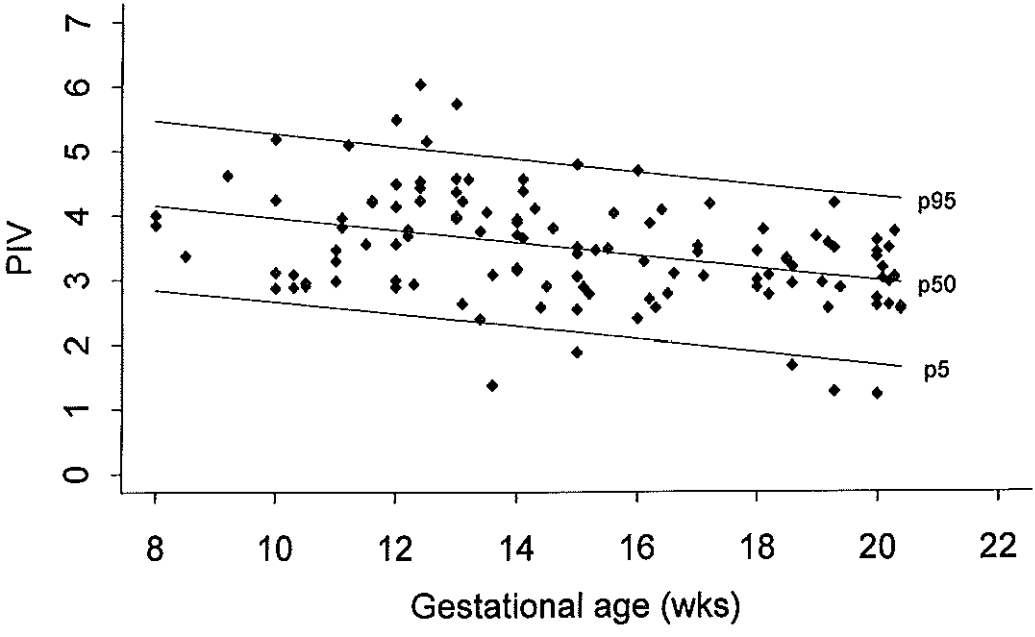

Figure 8 *Individual data and reference ranges (p5, p50, p95) are presented for the pulsatility index for veins (PIV) in the inferior vena cava relative to gestational age (wks)*

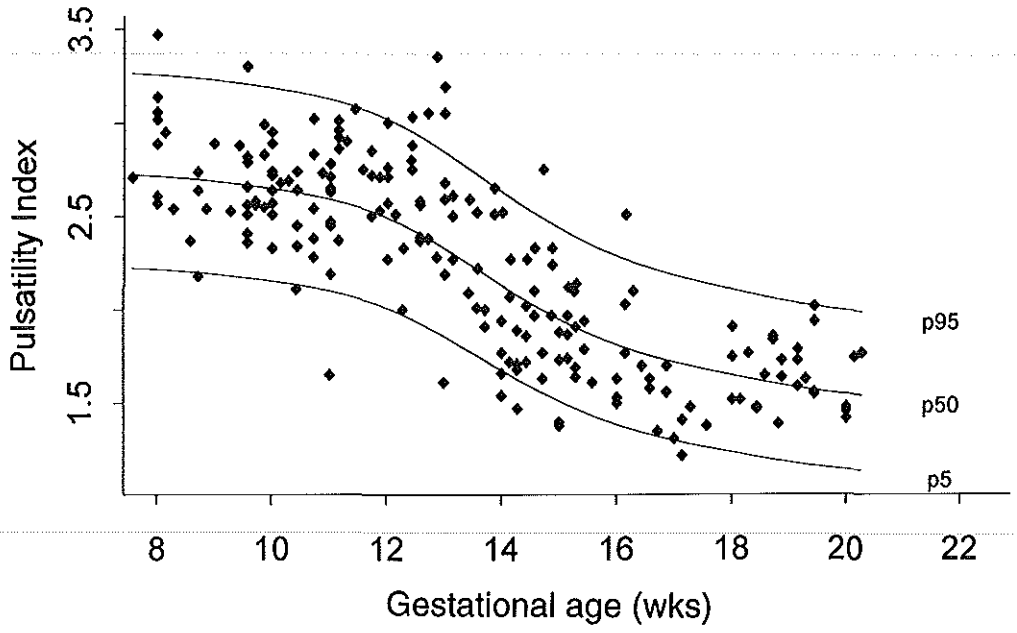

Figure 9 *Individual data and reference ranges (p5, p50, p95) are presented for the pulsatility index (PI) in the descending aorta relative to gestational age (wks)*

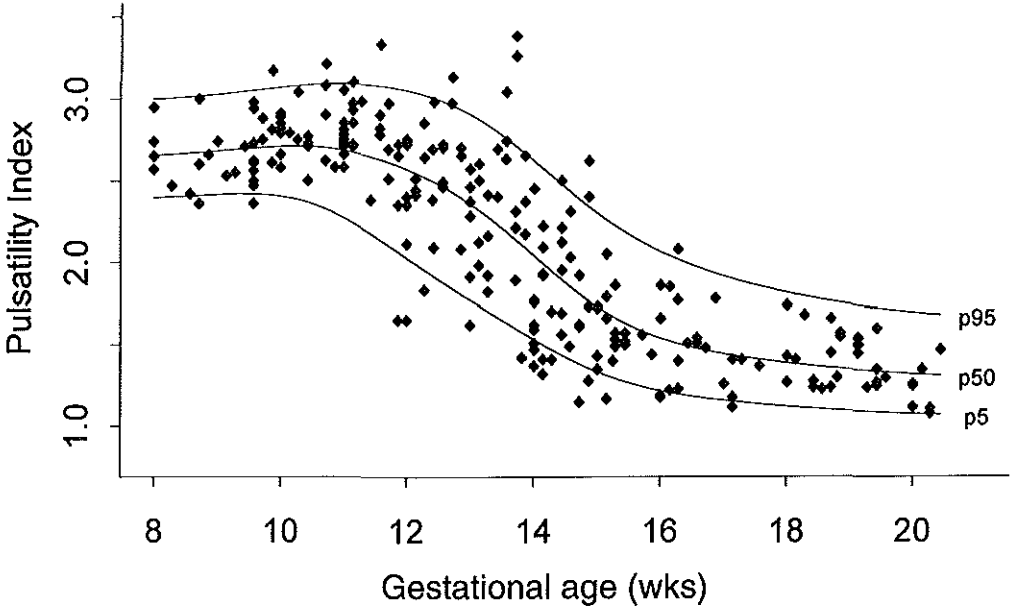

Figure 10 *Individual data and reference ranges (p5, p50, p95) are presented for the pulsatility index (PI) in the umbilical artery relative to gestational age (wks)*

3.2.5 Discussion

We were able to obtain waveform recordings from all three venous vessels as early as 8 weeks of gestation. Apart from the umbilical vein, waveform patterns were not essentially different from those documented later in pregnancy. Flow velocity recordings in the ductus venosus would not be feasible before 8 weeks of gestation, since it is only then that anatomical development of this vessel is completed (Barry, 1963). Equipment related limitations may be responsible for the absence of a separate systolic and diastolic component in the ductus venosus flow velocity profile at 8 weeks of gestation, despite the high resolution ultrasound device used in this study.

An increase in time-averaged velocity was observed with advancing gestational age in all three venous vessels, which was approximately two-fold in the inferior vena cava, three-fold in the umbilical vein and even four-fold in the ductus venosus. The relatively high flow velocities in the ductus venosus are determined by the narrow vessel size which will never exceed 2 mm. In a previous study (Huisman et al., 1993b), within patient coefficients of variation for all venous and arterial flow velocity waveforms were less then 6%. However, between patients coefficients of variation were considerably higher, ranging between 19.8% for the umbilical vein and 31.7% for the inferior vena cava time-averaged velocity. This may explain the rather wide data distribution for venous flow velocities in the present study. Time-averaged velocity times the cross-sectional vessel area equals volume flow in a particular vessel. Exact data about the diameter or cross-sectional area of the three venous vessels at the time of the Doppler flow velocity waveform recording were not available. Comparison of the time-averaged velocity alone between the three venous vessels does not provide any information on venous volume flow. We can, therefore, only speculate that the venous velocity changes observed in the present study may be accounted for by increased volume flow in the developing fetus.

Studies on fetal lambs have demonstrated that the ductus venosus is an important regulator of the fetal venous circulation (Edelstone et al., 1978). Similar to Kiserud et al. (1994) in late pregnancy, we estimated the ductus venosus pressure gradient from umbilical venous and ductus venosus flow velocity waveforms according to a simplified Bernoulli equation between 8 and 20 weeks of gestation. Pressure gradients up to 2 mmHg during ventricular systole and 0.5 mmHg during atrial contraction were established (van Splunder et al., 1995). These data on pressure gradients were lower than those obtained by Kiserud et al. (1994) as a result of higher ductus venosus velocities in the latter study. These differences may be caused by the fact that we measured the ductus venosus in a slightly oblique transection through the fetal abdomen, whereas Kiserud et al. applied a mid-sagittal as well as an oblique transection.

Pulsatility Index for Veins was calculated to allow comparison with data on arterial

downstream impedance. A statistically significant reduction in Pulsatility Index for Veins was established for all three venous vessels relative to gestational age. This reduction may be a reflection of the shift of blood flow from late diastole towards early diastole at atrial level as suggested by the gestational age related increase in transmitral and transtricuspid E/A ratio (Wladimiroff et al., 1992; Tulzer et al., 1994). Whether this can be attributed to a rise in ventricular compliance is not clear. It was recently demonstrated that despite an altered relationship between early and late inflow velocities, the proportion of ventricular filling contributed by atrial contraction, remains constant indicating unchanged ventricular compliance in early pregnancy (Tulzer et al., 1994).

A number of changes in venous flow velocity waveform patterns seems to be completed around 14 weeks of gestation, such as a progressive disappearance of umbilical venous pulsations. This disappearance of pulsations may be explained on a purely mechanical basis, that is reduced conduction of fetal cardiac activity to the extra-abdominal umbilical vein due to increasing anatomical distance between the beating heart and this section of the umbilical vein in the growing fetus. In contrast to Rizzo et al. (1992), in our study the percentage of reverse flow in the inferior vena cava was not related to the presence or absence of umbilical venous pulsations.

Our present results confirm earlier data (Wladimiroff et al., 1991) that well-defined changes also happen on the arterial side with a marked drop in Pulsatility Index in the descending aorta and umbilical artery in the late first and early second trimester of pregnancy, reflecting a reduction in fetoplacental vascular resistance. Whereas this stage of pregnancy is characterized by trophoblast invasion of the spiral arteries (Brosens et al., 1967; de Wolf et al., 1973) and appearance of intervillous blood flow (Jauniaux et al., 1992), the drop in Pulsatility Index in the umbilical artery seems more likely to be determined by the process of angiogenesis which takes place in the developing placenta (Jauniaux et al., 1992). This process is characterized by a progressive increase of the number and surface area occupied by the fetal vessels. No correlation exists between Pulsatility Index for Veins from the three venous vessels and Pulsatility Index in the descending aorta and umbilical artery. The most likely explanation is that the Pulsatility Index for Veins reflects cardiac ventricular preload (deVore et al., 1993), whereas Pulsatility Index values in the arterial vessels reflect downstream impedance at fetal placental level.

The percentage reverse flow in the inferior vena cava is constant up to 14 weeks of gestation, but demonstrates a significant reduction thereafter. Studies during the second half of gestation show a sustained decline in percentage reverse flow to approximately 5 % at term (Reed et al., 1990). Changes in cardiac properties such as myocardial stiffness or rate of ventricular relaxation may play a role in this. Low fetal myocardial compliance has been suggested in late first trimester pregnancies because of low early diastolic filling rates (Wladimiroff et al., 1991).

However, it has also been put forward that ventricular compliance remains unchanged as suggested by a constant contribution of atrial contraction to ventricular filling (Tulzer et al., 1994). Therefore, more data will be needed to understand the underlying mechanisms.

It can be concluded that in the late first and early second trimester of pregnancy fetal hemodynamics is characterized by marked changes in venous and arterial flow velocity waveforms. Time-averaged velocities in the umbilical vein, ductus venosus and inferior vena cava increase with advancing gestational age, whilst umbilical venous pulsations progressively disappear. Data on Pulsatility Index for Veins, reflecting cardiac ventricular preload, undergo a gestational age related reduction. Whether this can be attributed to a change in ventricular compliance is not clear. Changes in Pulsatility Index for Veins take place independently from the reduction in arterial downstream impedance as expressed by the Pulsatility Index in the descending aorta and umbilical artery.

3.3 Fetal pressure gradient estimations across the ductus venosus in early pregnancy using Doppler ultrasonography

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3.3.1 Summary

Doppler ultrasonography was used to estimate the pressure gradient across the ductus venosus at 8-20 weeks of gestation. According to a cross-sectional study design, flow velocity waveform recordings were obtained from the umbilical vein and ductus venosus in 147 uncomplicated singleton pregnancies. Pressure gradients were calculated using the Bernoulli equation.

The pressure gradient was estimated at 0.1-1.9 mmHg during ventricular systole and at 0-0.5 mmHg during atrial contraction. Time-averaged pressure gradients ranged between 0.1 and 1.3 mmHg. No statistically significant correlation could be established between the absence or presence of umbilical venous pulsations and estimated pressure gradient.

Crude estimates of the pressure gradient across the ductus venosus can be established in the late first and early second trimester of pregnancy. The large scatter of data suggests limited accuracy of venous pressure gradient calculation in early gestation. However, it may also indicate that in early gestation venous hemodynamics functions at very low pressures.

3.3.2 Introduction

Lately considerable interest has been expressed in fetal venous flow velocities in early gestation (Huisman et al., 1993a; Rizzo et al., 1992; Wladimiroff et al., 1992). Combined transvaginal and transabdominal Doppler ultrasonography has shown that fetal venous flow velocities undergo marked changes in late first- and early second-trimester pregnancies which may be associated with placental angiogenesis (van Splunder et al., 1996).

Whereas Doppler ultrasonography has revealed a wealth of information on human fetal hemodynamics in general, its non-invasiveness does not allow measurement of pressure and volume

needed for a better understanding of the basic mechanisms responsible for velocity changes under normal and abnormal pregnancy conditions. Kiserud and colleagues (1994) were the first to present estimates of pressure changes at the venous level applying the Bernoulli equation. They provided data on pressure across the fetal ductus venosus during both fetal apnoea and breathing movements in the second half of gestation.

The objective of the present study was to estimate the pressure gradient between the umbilical vein and inferior vena cava in the late first- and early second-trimester fetus according to the method described by Kiserud and colleagues (1994), using combined two-dimensional ultrasound and pulsed Doppler ultrasound.

3.3.3 Methods

Subjects

A total of 200 healthy women consented to participate in the study. Permission for the study was given by the local Ethics Review Board. In each woman, pregnancy duration was established from the measurement of the fetal crown-rump length (8-12 wks) or fetal biparietal diameter (12-20 wks). Pregnancy duration varied between 8 and 20 weeks (median 14 wks). Maternal age ranged between 21 and 41 years (median 33 yrs). Pregnancy was considered uneventful if a normal infant with a birth weight between the 10th and 90th (Kloosterman, 1970) centiles was delivered at term. All women were nonsmokers, and no medication was taken apart from iron tablets. Each woman was included in the study once.

Doppler recordings

Doppler flow velocity measurements were carried out on a Hitachi EUB 450 (Hitachi Medical Corporation, Tokyo, Japan). A combined transvaginal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time) and 6.5 MHz (Doppler) was used at 8-13 weeks of gestation and a combined transabdominal real-time and Doppler system with a carrier frequency of 3.5 MHz (real-time) and 3.0 MHz (Doppler) was used at 14-20 weeks of gestation. The power output was always less than 100 mW/cm2 spatial peak temporal average (SPTA) in imaging and Doppler modes. These output levels are clearly situated in the lower regions for acoustic output of Japanese and American diagnostic equipment (Ide, 1989). All measurements were carried out after the completion of embryonic structural development. Given these statements, there is considerable reason to believe that Doppler recording is safe this early in pregnancy. The total examination time

was limited to 15 minutes in each instance. Doppler recordings were performed by one examiner (IPvS).

Flow velocity waveforms from the umbilical vein and ductus venosus were recorded as previously described (Huisman et al., 1992). Only those waveform recordings were accepted in which the interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30°. Sample volume length for all flow velocity recordings ranged between 0.1 and 0.2 cm. The high pass filter was set at 100 Hz.

All Doppler studies were performed with the women in the semirecumbent position and during fetal apnoea. All flow velocity waveforms were recorded on hard copies. High-quality waveforms representing three consecutive cardiac cycles were used for data analysis. Waveform analysis was performed by one examiner (IPvS), using a microcomputer (Olivetti M24; Olivetti B.V., Leiden, The Netherlands) linked to a graphics tablet. Analysis of the ductus venosus (dv) flow velocity waveforms consisted of calculation of (1) peak systolic velocity (PSV, cm/s); (2) minimum velocity during atrial contraction (cm/s); and (3) time-averaged velocity (TAV, cm/s). Measurements in the umbilical vein (uv) were performed in a straight section of the vessel which included maximum, minimum and time-averaged velocities (cm/s) in the presence of umbilical venous pulsations and only time-averaged velocities from the maximum velocity envelope in the absence of umbilical venous pulsations. In the presence of a flat profile in the umbilical vein, the maximum, minimum and time-averaged velocities were the same.

The pressure gradient across the ductus venosus (ΔP_{dv}) was estimated using the Bernoulli equation (Holen et al., 1976): (1) time-averaged pressure gradient: $\Delta P_{dv} = 4(TAV_{dv}^2 - TAV_{uv}^2)$; (2) peak systolic pressure gradient: $\Delta P_{dv} = 4(PSV_{dv}^2$ - maximum velocity $uv^2)$; (3) minimum pressure gradient: $\Delta P_{dv} = 4$(minimum velocity dv^2 - minimum velocity uv^2).

Data analysis

The Spearman rank correlation test was carried out to assess (1) flow velocity waveform parameters from the ductus venosus and umbilical vein; and (2) estimated pressure gradients relative to gestational age. For the construction of reference centiles, the method described by Royston (1991) was used. The outcome variable, *Y*, was modelled by a straight line regression model with gestational age as predictor. It was tested whether adding the quadratic term was significant. Dependency of the residuals on gestational age was checked. If such dependency was found, straight line regression was used to model the absolute value of the residuals and, from this model, a regression equation for the standard deviation, depending on gestational age, was derived. The two-sample Wilcoxon test, corrected for gestational age by stratification, was used to establish the relationship between absence or presence of umbilical venous pulsations and estimated pressure

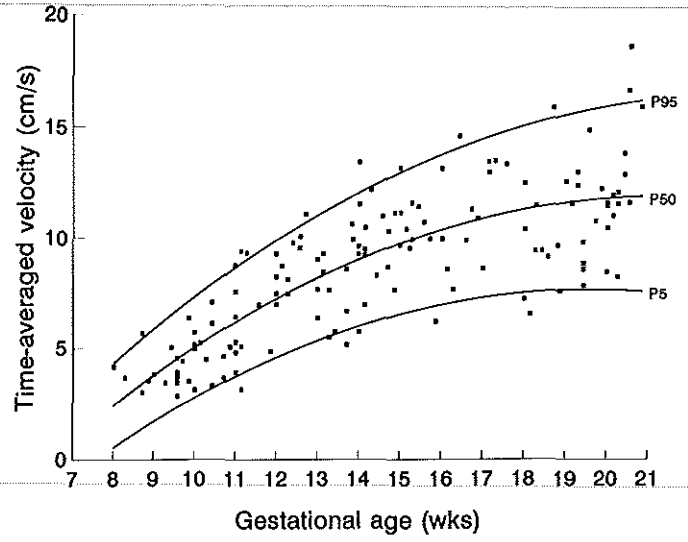

Figure 1 *Individual data and reference ranges (p5, p50, p95) for umbilical venous time-averaged velocity (TAV) relative to gestational age*

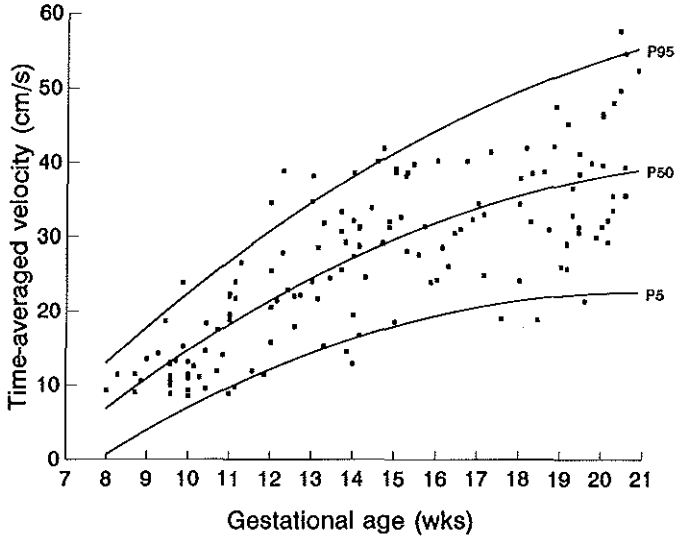

Figure 2 *Individual data and reference ranges (p5, p50, p95) for the ductus venosus time-averaged velocity (TAV) relative to gestational age*

gradients. p-Values of <0.01 were considered statistically significant.

3.3.4 Results

Fifty-three out of 200 women were excluded from the study because of pregnancy pathology (pregnancy-induced hypertension, intrauterine growth retardation) or technically poor-quality Doppler velocity recordings, resulting in 147 women available for data analysis.

Umbilical venous pulsations were present between 8 and 15 weeks of gestation and absent thereafter. A statistically significant increase existed with advancing gestational age for the peak systolic and minimum flow velocity in the ductus venosus ($p<0.001$). The same applied to the time-averaged velocity in the umbilical vein ($p<0.001$; Figure 1) and the ductus venosus ($p<0.001$; Figure 2).

The estimated ΔP_{dv} demonstrates a pressure profile similar to the ductus venosus flow velocity waveforms. The estimated minimum ΔP_{dv} ranged between 0 and 0.5 mmHg (Table 1; Figure 3), the estimated peak systolic ΔP_{dv} between 0.04 and 1.9 mmHg (Table 1; Figure 4) and the time-averaged ΔP_{dv} between 0.02 and 1.3 mmHg (Table 1; Figure 5). A gestational age-related rise was established for all three pressure gradient variables ($p<0.001$).

ΔP_{dv} data relative to the presence (n = 18) or absence (n = 72) of umbilical venous pulsations were studied in 90 women between 8 and 15 weeks of gestation. No statistically significant difference in ΔP_{dv} could be established for the minimum, peak systolic and time-averaged pressure gradients.

Table 1 Minimum, peak systolic and time-averaged pressure gradient (ΔP_{dv})(5th, 50th, 95th centiles) across the ductus venosus at 8-20 weeks of gestation

Gestational age (wks)	*Mimimum ΔP_{dv}*				*Peak systolic ΔP_{dv}*			*Time-averaged ΔP_{dv}*		
	n	*P5*	*P50*	*P95*	*P5*	*P50*	*P95*	*P5*	*P50*	*P95*
8-10	32	0	0.002	0.07	0.04	0.09	0.28	0.02	0.05	0.16
11-12	23	0	0	0.18	0.05	0.29	0.70	0.02	0.15	0.55
13-14	29	0	0	0.01	0.13	0.54	1.10	0.05	0.30	0.63
15-16	19	0	0	0.21	0.21	0.56	1.22	0.10	0.35	0.59
17-18	16	0	0.08	0.22	0.17	0.70	1.35	0.07	0.44	0.88
19-20	28	0	0.16	0.47	0.28	0.69	1.86	0.15	0.46	1.18

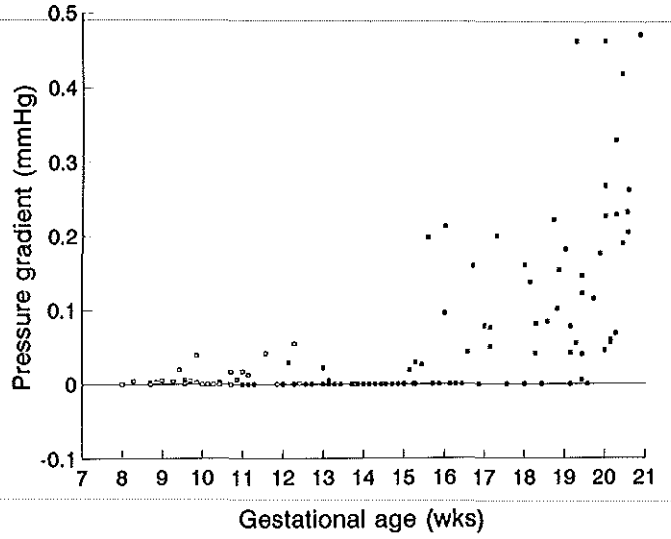

Figure 3 *Individual data for minimum pressure gradient relative to gestational age in the presence (open squares) and absence (filled squares) of umbilical venous pulsations*

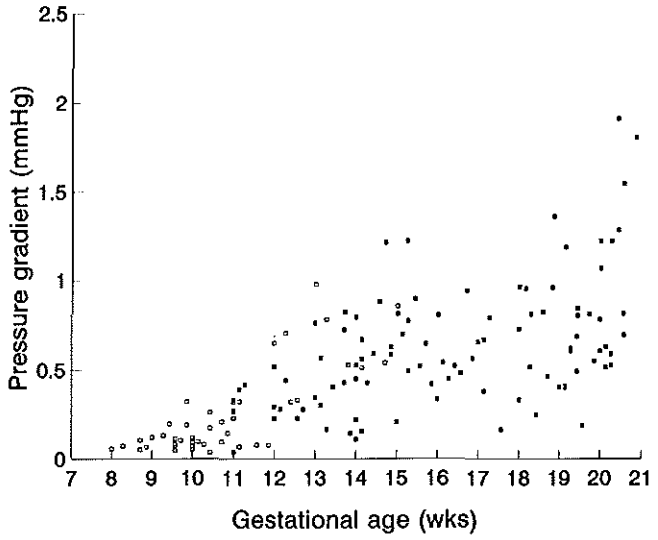

Figure 4 *Individual data for peak systolic pressure gradient relative to gestational age in the presence (open squares) and absence (filled squares) of umbilical venous pulsations*

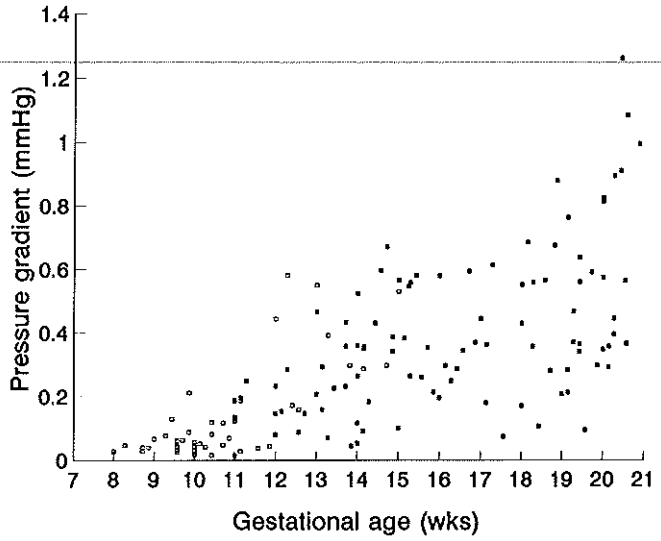

Figure 5 *Individual data for time-averaged pressure gradient relative to gestational age in the presence (open squares) and absence (filled squares) of umbilical venous pulsations*

3.3.5 Discussion

Early fetal circulation is characterized by marked changes at both cardiac and extracardiac level. Characterization of these changes may be helpful in understanding normal and abnormal cardiovascular development.

In the present study, an attempt was made to estimate the pressure gradient between the umbilical vein and inferior vena cava during the late first- and early second trimesters of pregnancy. The Bernoulli equation was applied to the umbilical venous and ductus venosus velocities, as first described by Kiserud and colleagues (1994). The ΔP_{dv} shows a significant increase with gestational age, with maximum values during ventricular systole ranging between 0.4 and 1.9 mmHg, minimum values during atrial contraction varying between 0 and 0.5 mmHg and time-averaged values ranging between 0.02 and 1.3 mmHg. A pressure gradient of zero during atrial contraction may be due to limitations of the Doppler equipment used. Flow velocity measurements may possibly not be sensitive enough to estimate pressure gradients for minimum velocities this early in gestation. Comparison with results obtained by Kiserud and colleagues (1994) was only possible for the gestational age period of 16-20 weeks. We established mean values for peak systolic pressure gradients of 0.6 and 1.0 mmHg, minimum pressure gradients of 0.06 and 0.23 mmHg and time-averaged pressure gradients of 0.36 and 0.68 mmHg at 16 and 20 weeks,

respectively. These data are approximately 1.5-1.8-fold lower than those obtained by Kiserud and colleagues (1994). This appears to be mainly the result of lower ductus venosus velocities measured by us, which may be explained by a different measuring technique. We measured ductus venosus waveform flow velocities in a slightly oblique transection through the fetal abdomen in each instance, whereas Kiserud and colleagues (1994) applied a mid-sagittal as well as an oblique transection.

Umbilical venous flow velocities were not essentially different between the two studies at this stage of gestation, despite the fact that we measured the umbilical venous flow velocities at the extra-abdominal level as opposed to the measurements of Kiserud and colleagues (1994) at the intra-abdominal level. In early pregnancy, flow velocities in the ductus venosus are low, making velocity in the umbilical vein more relevant in pressure gradient calculations than in late gestation. Flow velocity recordings were made in the extra-abdominal part of the umbilical vein, which allows comparison with pressure measurements by cordocentesis. *In vivo* data are only available from 15 weeks of gestation onwards, with mean umbilical venous pressures ranging between 3.0 mmHg at 15 weeks (Nicolini et al., 1989), 4.5 mmHg (range 2.5-8.8 mmHg) at 18 weeks (Ville et al., 1994) and 3.16 mmHg (range 0-6 mmHg) at 19 weeks of gestation (Weiner et al., 1992). To our knowledge, no animal experimental data have been reported on venous pressure gradients in early gestation.

In a recent reproducibility study, it was established that the within-patient coefficient of variation was 3.5% for the time-averaged velocity in both the umbilical vein and the ductus venosus (Huisman et al., 1993b). Whereas this indicates a good reproducibility for each of the flow velocity parameters, it affects accuracy of the Doppler methodology for estimating venous pressure gradients in early gestation. Moreover, a considerable data scatter is demonstrated for the peak systolic and time-averaged pressure gradients. This is determined by the wide data distribution displayed by the individual components of the pressure gradient calculation, the umbilical vein and ductus venosus flow velocity waveforms (see Figures 1 and 2). In an earlier study, it was shown that between-patient coefficient of variation for the time-averaged velocity in the umbilical vein and ductus venosus were as high as 19.8% and 25.3%, respectively (Huisman et al., 1993b). On the other hand, the data scatter may also suggest that fetal venous hemodynamics operate at very low pressure gradients. However, as long as no volume flow and pressure measurements are available, we can only speculate on the underlying mechanisms.

No differences in pressure gradient were observed between pulsating and flat umbilical venous flow velocity waveforms. This is in contrast to normal physiology in which, according to the laws in general fluid mechanisms, fetal cardiac activity is conducted to the venous system on a pressure-related basis. However, it may explain the progressive disappearance of umbilical venous

pulsations after 13 weeks of gestation. Whereas the conduction of cardiac activity to the umbilical vein depends on cardiac pressure changes and the conductivity and compliance of the umbilical vein, an increasing distance to the fetal heart may explain this progressive disappearance of umbilical venous pulsations in the growing fetus.

It can be concluded that non-invasive Doppler recording in the umbilical vein and ductus venosus allows crude estimates to be made of the pressure gradient between the umbilical vein and inferior vena cava during the late first- and early second-trimester of pregnancy. Although these estimates are subject to the reproducibility of the waveforms obtained from the umbilical vein and ductus venosus, this study may indicate that early fetal hemodynamics function at very low pressures.

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Chapter 4

Cardiac flow velocity waveforms in early pregnancy

4.1 Introductory remarks

With the advent of transvaginal ultrasonography, normal and abnormal cardiac morphology can be detected as early as the late first trimester of pregnancy (Gembruch et al., 1993; Achiron et al., 1994).

Heart development is a dynamic process of growth and morphogenesis accompanied by changing hemodynamic function. It has been demonstrated in the chick embryo that cardiac output increases in proportion to embryo weight (Clark and Hu, 1982). Moreover, mean arterial blood pressure increases linearly and vascular resistance decreases geometrically with each embryo stage. In the human fetus, however, little is known about cardiac performance and its relationship with downstream impedance and venous return.

In the chick embryo, induced structural cardiac anomalies are accompanied by marked hemodynamic changes (Broekhuizen, 1996). Within two models, e.g. retinoic acid and venous clip, a spectrum of outflow tract anomalies was induced. Simultaneous dorsal aortic Doppler flow velocity/volume and pressure measurements demonstrated reduced heart rate without compensatory increase of stroke volume suggesting both pacemaker and contractile dysfunction. Thus, in the chick embryo morphological changes in heart development result in altered flow velocity waveform patterns. If a parallel can be drawn to the human fetus, flow velocity waveform recordings obtained by pulsed Doppler ultrasound could serve as an additional diagnostic tool in the detection of congenital heart disease. Therefore, knowledge of normal cardiac function is required to differentiate between normal and abnormal cardiac development. It should be stressed, however, that the additional value of Doppler ultrasound in early abnormal cardiac development is rather hypothetical. Studies will be needed to set out the clinical significance.

In Chapter 4.2 the nature of cardiac flow velocity waveforms and their relationship to gestational age and arterial and venous flow velocity waveforms will be discussed. Systolic and diastolic components of cardiac function relative to gestational age will be presented in Chapter 4.3.

4.2 Fetal atrioventricular flow velocity waveforms and their relation with arterial and venous flow velocity waveforms at 8-20 weeks of gestation

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4.2.1. Summary

Doppler ultrasonography was used to determine the nature and gestational age related changes of human fetal atrioventricular flow velocity waveforms and to establish their relationship with arterial impedance indices and venous flow velocities in normal human fetuses between 8 and 20 weeks of gestation.

Flow velocity waveform recordings were attempted in 318 singleton pregnancies. After the exclusion criteria were applied, data on 214 women were available for further analysis. Differentiation between E-wave and A-wave became possible at 9 weeks, whereas distinction between transmitral and transtricuspid flow velocities was first achieved at 10-11 weeks. A statistically significant nonlinear gestational age-dependent increase was established for all atrioventricular waveform parameters, which became linear when related to logarithmically estimated fetal crown-rump-length. Transtricuspid flow velocities were significantly higher than transmitral flow velocities. Transmitral time-averaged flow velocities were positively correlated with peak diastolic velocities and time velocity integral of late diastolic reverse flow in the inferior vena cava. No correlation existed between atrioventricular time-averaged velocities and arterial impedance indices.

Monophasic atrioventricular flow velocity waveforms can be recorded as early as 8 weeks of gestation and become biphasic as from 9 weeks. They demonstrate a linear increase relative to logarithmically estimated fetal crown-rump-length, suggesting fetal growth-related increase in volume flow to play a role in this velocity rise. Transtricuspid A-wave and E-wave velocities suggest right ventricular predominance as early as the late first trimester of pregnancy. Atrioventricular flow velocities are not related to arterial downstream impedance.

4.2.2 Introduction

Cardiac development is characterized by morphogenesis, growth and changing hemodynamics. In the human fetus, normal or abnormal cardiac anatomy can now be established with reasonable confidence by diagnostic ultrasound as from 18-20 weeks of gestation (Allan et al., 1986; Copel et al., 1987). As a result of further experience in transvaginal ultrasound, some reports have appeared on the sonographic detection of congenital heart disease as early as 12-14 weeks of gestation (Gembruch et al., 1993). Since form and function are interrelated, knowledge of cardiac hemodynamics will be helpful in establishing the prognosis in a particular congenital cardiac anomaly.

Doppler echocardiography does not allow data collection on volume flow, but cardiac velocity recordings would be helpful in providing some insight into the intricate relationship between cardiac and extra-cardiac hemodynamics. Although several reports have appeared on fetal cardiac hemodynamics late in pregnancy (Reed et al., 1986; Kenny et al., 1986; Allan et al., 1987), little information is available on early gestation. Preliminary information shows that cardiac flow velocities can be obtained as early as the first trimester of pregnancy (Wladimiroff et al., 1991; Leiva et al., 1994). Moreover, a profound reduction in arterial downstream impedance has been observed at the fetoplacental level at 12-14 weeks of gestation (Wladimiroff et al., 1992). At the same time, changes occur in venous flow velocity waveforms, notably in the ductus venosus and inferior vena cava (Huisman et al., 1993a). We propose that these extracardiac arterial and venous flow velocity waveform changes are reflected in cardiac hemodynamics.

The present study focuses on cardiac diastolic filling characteristics and their relationship with venous inflow velocities and arterial downstream impedance. The objective of the present study was threefold:

(1) To establish the nature of normal human atrioventricular flow velocity waveforms at 8-20 weeks of gestation;
(2) To determine the gestational age and fetal crown-rump-length related changes in transmitral and transtricuspid flow velocities; and
(3) To relate transmitral and transtricuspid flow velocities to arterial downstream impedance and flow velocities at venous inflow level during this early period of normal fetal development.

4.2.3 Methods

Subjects

Between August 1, 1992 and April 1, 1994, a total of 318 women with a normal singleton pregnancy between 8 and 20 weeks of gestation (median 13 wks) consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Maternal age ranged between 16 and 40 years (median 32 years). Pregnancy duration was estimated from the last menstrual period and confirmed by ultrasound measurement of the fetal crown-rump length (8-12 wks)(Robinson and Fleming, 1975) or biparietal diameter (12-20 wks)(Snijders and Nicolaides, 1994). Each woman was included in the study once.

Only pregnancies that progressed uneventfully resulting in the term delivery of a normal infant with a birth weight between the 10th and 90th percentile corrected for maternal parity and fetal sex (Kloosterman, 1970), were included in the data analysis.

Another 10 uncomplicated pregnancies were investigated both transvaginally and transabdominally at 12 and 13 weeks of gestation to compare fetal atrioventricular flow velocities obtained through both recording techniques.

Doppler recordings

Ultrasound Doppler studies were performed with a Hitachi EUB 450 (Hitachi Medical Corp.). We used a combined transvaginal real-time and pulsed Doppler system (carrier frequencies 3.5 and 6.5 MHz, respectively) at 8-13 weeks of gestation or a combined transabdominal real-time and Doppler system (carrier frequencies 3.5 and 3.0 MHz, respectively) at 14-20 weeks of gestation. The system operates at power outputs of < 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes according to the manufacturer's specification. Doppler recordings were performed by one examiner (IPvS).

Flow velocity waveforms at the fetal atrioventricular level were obtained from the cardiac "four chamber" view. To obtain this view, first a transverse cross-section of the fetal chest at the level of the pulsating heart was obtained. An imaginary line was subsequently drawn from the fetal spine to the anterior chest wall, dividing the fetal chest into two equal parts. At an angle of 45 degrees to the left or right of this imaginary line (depending on fetal position), the "four chamber" view is presented allowing identification of the atrial and ventricular part of the heart and the atrioventricular valves with distinction between the left and right side of the heart and separate identification of the mitral and tricuspid valves depending on gestational age (Figure 1).

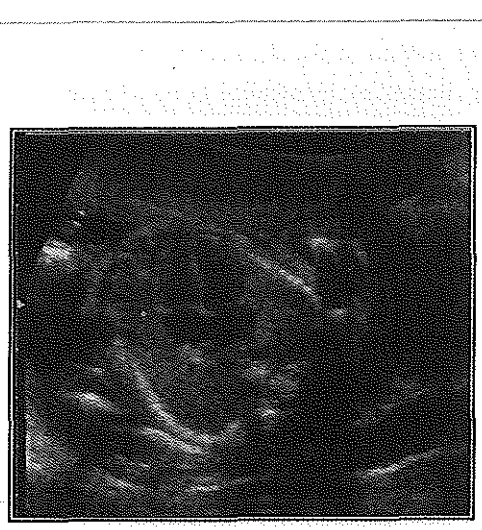

Figure 1 *Left panel: Transverse cross section through the fetal chest demonstrating a normal "four-chamber" view of the fetal heart at 19 weeks of gestation. Right panel: Schematic representation of the same cross section through the fetal heart. Note the angle of 45° between the anteroposterior axis of the fetal chest and the long axis of the fetal heart. The Doppler interrogation angle is approximately 15°. D indicates Doppler transducer; M, maternal vaginal vault (transvaginal scan) or maternal abdominal wall (abdominal scan); L and R, left and right chest; SP, spine; LA and RA, left and right atrium; LV and RV, left and right ventricle; and SV, Doppler sample volume at MV level*

Assuming that atrioventricular blood flow is parallel to this 45 degree axis, the Doppler interrogation beam was positioned as much as possible along this axis and the Doppler sample volume was placed immediately distal to the mitral and tricuspid valve or immediately distal to the atrioventricular valve if distinction between mitral and tricuspid valve was not possible. Only waveforms with angles of insonation less than 30 degrees and consisting of a clear E- and A-wave were accepted. Previous experience (Wladimiroff et al., 1991) has demonstrated that acceptable waveforms can be obtained in the majority of transvaginal examinations before 14 weeks of gestation. Flow velocity waveforms from the umbilical vein and artery were obtained from a straight section of the free-floating loop of the umbilical cord. Flow velocity waveforms from the ductus venosus, inferior vena cava and descending aorta were recorded as previously described (Huisman et al., 1992; Reed et al., 1990; Eik-Nes et al., 1980). The angle of insonation was always less than 30 degrees, and for the descending aorta less than 45 degrees. Sample volume length for all flow velocity waveform recordings ranged between 0.1 and 0.2 cm; the high pass filter was set at 100 Hz. Although the range of motion of the transvaginal probe is

limited, flow velocity waveform recordings could be obtained in most cases because of recurrent changes in fetal position during the examination.

All Doppler studies were performed with the women in the semirecumbent position and during fetal apnea. The total examination time was limited to 15 minutes in each instance. All flow velocity waveforms were recorded on hard copies. Waveform analysis was performed by one examiner (IPvS) using a microcomputer (Olivetti M24; Olivetti B.V., Leiden, the Netherlands) linked to a graphical tablet.

Analysis of the atrioventricular waveforms consisted of calculation of (i) time-averaged velocity (cm/s), (ii) peak velocity (cm/s) of the E-wave (passive atrial filling) and A-wave (atrial contraction) and (iii) E/A ratio. Time-averaged velocity (cm/s) was determined in the umbilical vein. Waveform analysis in the ductus venosus and inferior vena cava consisted of calculation of (i) peak velocity (cm/s) during both systole (S) and diastole (D) and (ii) time-averaged velocity (cm/s). In the inferior vena cava the time-velocity integral of late diastolic reverse flow, which is expressed as a percentage of total forward flow during systole and early diastole, was calculated. The Pulsatility Index (PI) was calculated for the umbilical artery and fetal descending aorta, which is expressed as the difference between the maximal and minimal flow velocity divided by the time-averaged velocity. Fetal heart rate (bpm) was determined from the time interval (m/s) between peak systolic velocities of two successive E-wave or A-wave flow velocities. Three consecutive flow velocity waveforms with the highest velocity and similar appearance were used to calculate the different parameters across the atrioventricular valves and in each vessel. Earlier in our center (Huisman et al., 1993b) acceptable intra-observer reproducibility was established for fetal flow velocity waveforms during the late first and early second trimester of pregnancy. Intra-observer coefficient of variation was less than 6% for all atrioventricular and inferior vena cava (IVC) flow velocity parameters except for time-velocity integral of inferior vena cava late diastolic reverse flow (8%). Intra-observer coefficient of variation was less than 5% for the umbilical artery and descending aorta PI and less than 4% for umbilical venous and ductus venosus velocity parameters. Sonographic measurement of fetal head and upper-abdominal circumference allows a crude approximation of fetal weight in late pregnancy, however, it is unreliable in early gestation. Instead, estimates of fetal crown-rump-length (CRL) may serve as a measure of fetal growth in early pregnancy. CRL measurements can be reliably obtained by ultrasound up to 13 weeks of gestation (Robinson and Fleming, 1975), whereas after that CRL data based on aborted specimen are available (Moore, 1974).

The transvaginal technique of flow velocity waveform recording was validated by comparison of transvaginally and transabdominally collected waveforms at the atrioventricular level in 10 normal singleton pregnancies at 12-13 weeks of gestation. This period of gestational

age was selected, because at that time a transition from transvaginal to transabdominal scanning takes place. In half the women the transvaginal scan preceded the transabdominal scan, in the other half the transabdominal scan preceded the transvaginal scan. The total examination period was limited to 15 minutes.

Data analysis

Correlation coefficients (r_s) were calculated with the Spearman rank correlation test to establish the relationship between gestational age and (i) descending aorta and umbilical artery Pulsatility Index (PI) and (ii) venous flow velocity parameters. Linear regression analysis was used to assess (i) fetal heart rate relative to gestational age and (ii) atrioventricular flow velocity waveform parameters relative to gestational age as well as estimated fetal CRL. In the latter instance logarithmic transformation of the fetal CRL data was carried out since fetal CRL shows a 1.7-fold increase at 10-12 weeks and a 1.1-fold increase at 18-20 weeks of gestation. The difference between the slopes of two regression lines was tested by a simple z test based on the difference of the two estimated slopes and their corresponding standard errors. The paired t test was applied to establish the difference in time-averaged velocity, peak E-wave and peak A-wave velocity and E/A ratio between transmitral and transtricuspid flow velocity waveforms. Multiple regression analysis was used to establish the relationship between atrioventricular flow velocity waveform parameters and fetal heart rate, adjusted for gestational age. Partial correlation coefficients (Altman, 1993) were calculated to assess the relation between atrioventricular flow velocity waveform parameters and (i) descending aorta and umbilical artery Pulsatility Index (PI) and (ii) venous flow velocity waveform parameters. The paired t test was used to establish the difference in arterial, cardiac and venous flow velocity waveforms between the transvaginal and transabdominal approaches at 12-13 weeks of gestation. Limits of agreement between the transvaginal and transabdominal approaches were calculated according to Bland and Altman (1986). Limits of agreement were defined as the range in which approximately 95% of the differences between the transvaginal and transabdominal approach are situated. Data are reported as mean $\pm$ 1SD. Values of $p < 0.01$ were considered statistically significant.

4.2.3 Results

Of the 318 women, who consented to participate in the study, 18 were excluded from analysis because no Doppler signals could be obtained as a result of maternal obesity, fetal

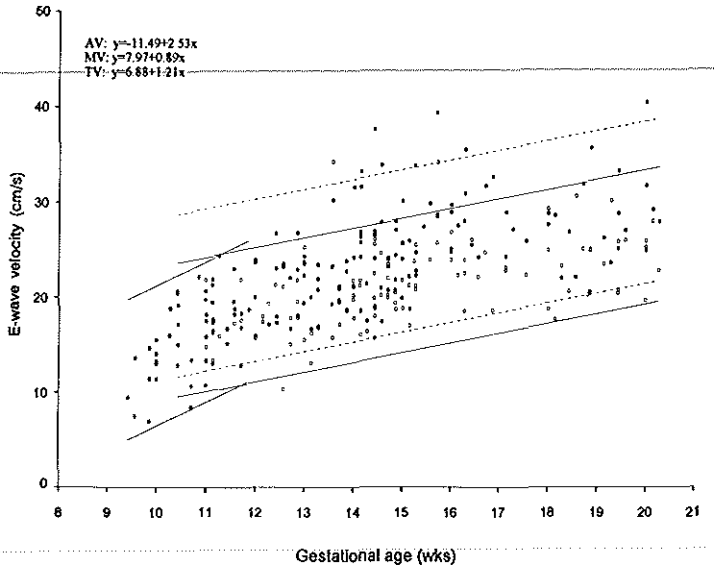

Figure 2 *Individual data and lower (-2SD) and upper (+2SD) normal limits for early diastolic velocity (E-wave, cm/s) in the absence of MV and TV differentiation (*, 9 to 12 weeks; solid line indicates normal limits) and at MV and TV levels (10 to 20 weeks. Open circles, MV; solid line, normal limits, Solid circles, TV; dashed line, normal limits).*

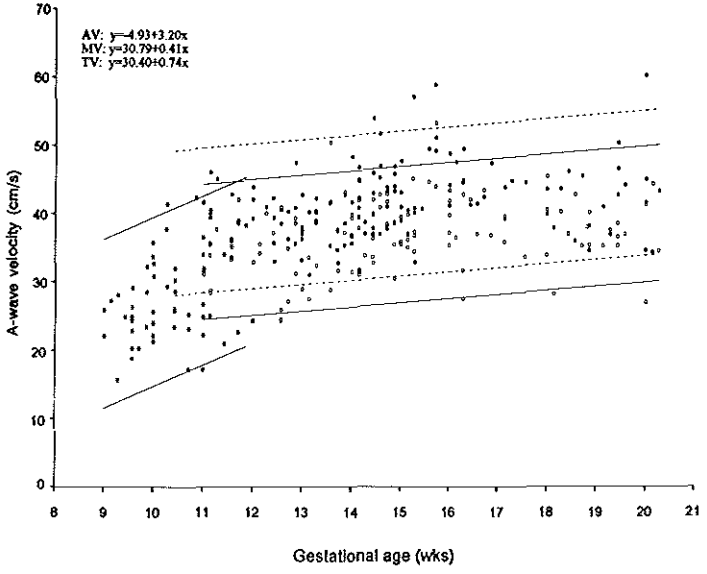

Figure 3 *Individual data and lower (-2SD) and upper (+2SD) normal limits for late diastolic velocity (A-wave, cm/s) in the absence of MV and TV differentiation (*, 9 to 12 weeks; solid line indicates normal limits) and at mitral (MV) and tricuspid (TV) levels (10 to 20 weeks. Open circles, MV; solid line, normal limits, Solid circles, TV; dashed line, normal limits).*

position or fetal body movements. Of these 18 women, 12 were investigated transvaginally and transabdominally. An additional 48 women were excluded independently of the study protocol because of a fetal birth weight below the 10th percentile or above the 90th percentile for gestational age and 38 women subsequently dropped out because of pregnancy abnormalities. These exclusions were made independently of the knowledge obtained from the study protocol. Flow velocity waveform recordings from 214 women were available for further analysis.

Validation of transvaginal flow velocity waveform recordings

Comparison of transvaginal and transabdominal flow velocity waveform recordings at 12-13 weeks revealed no statistically significant difference for the atrioventricular flow velocity parameters (Table 1).

Table 1 Comparison of transvaginal and transabdominal atrioventricular flow velocity recordings at 12 to 13 weeks of gestation

	Mean difference	*P*	*Limits of agreement**
TV E-wave	-0.07	0.91	-1.15 , 1.31
TV A-wave	1.71	0.43	-3.21 , 6.63
TV TAV	0.75	0.18	-0.46 , 1.96
TV E/A ratio	-0.04	0.34	-0.13 , 0.05
MV E-wave	0.98	0.57	-3.01 , 4.97
MV A-wave	-0.53	0.65	-3.26 , 2.20
MV TAV	-0.29	0.56	-1.48 , 0.90
MV E/A ratio	0.04	0.43	-0.08 , 0.16

TAV indicates time-averaged velocity;
*Limits of agreement are defined as the range within which approximately 95% of the differences between transvaginal and transabdominal approaches lie.

Atrioventricular flow velocity waveforms

At 8 weeks of gestation only monophasic atrioventricular (AV) flow velocity waveforms could be obtained. Differentiation between early diastolic filling velocities (E-wave) and late diastolic velocities (A-wave) became feasible in 6 of 17 cases (35.3%) at 9 weeks, in 17 of 20 cases (85%) at 10 weeks, in 13 of 15 cases (86.7%) at 11 weeks and in all cases as from 12 weeks of gestation. Differentiation between transmitral and transtricuspid velocities was not possible at 8-9 weeks, but was achieved in 1 of 21 cases (4.8%) at 10 weeks, in 14 of 29 cases (48.3%) at 11 weeks and in all cases as from 12 weeks of gestation.

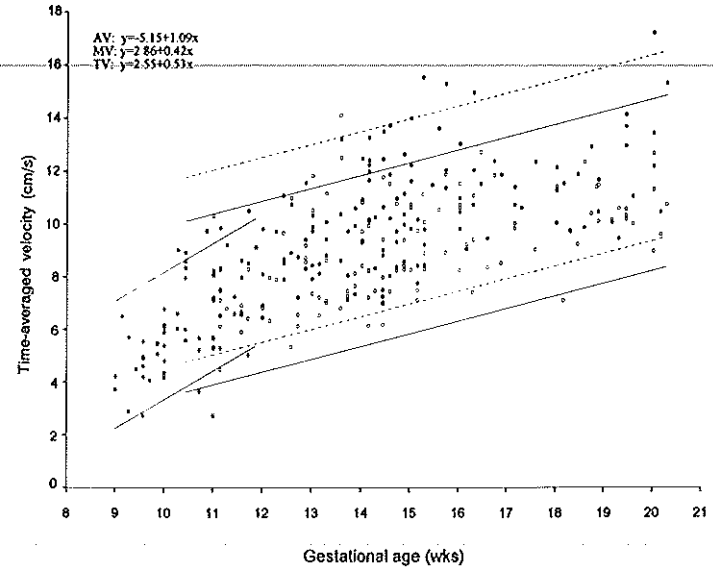

Figure 4 *Individual data and lower (-2SD) and upper (+2SD) normal limits for time-averaged velocity (cm/s) in the absence of MV and TV differentiation (*, 9 to 12 weeks; solid line indicates normal limits) and at MV and TV levels (10 to 20 weeks. Open circles, MV; solid line, normal limits, Solid circles, TV; dashed line, normal limits).*

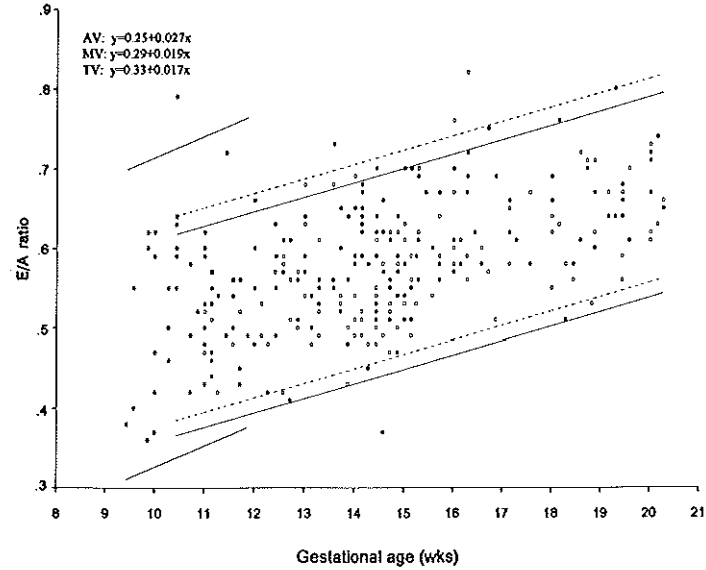

Figure 5 *Individual data and lower (-2SD) and upper (+2SD) normal limits for early/late diastolic ratio (E/A ratio) in the absence of MV and TV differentiation (*, 9 to 12 weeks; solid line indicates normal limits) and at MV and TV levels (10 to 20 weeks. Open circles, MV; solid line, normal limits, Solid circles, TV; dashed line, normal limits).*

Atrioventricular diastolic velocities relative to fetal heart rate, gestational age and crown-rump-length

A statistically significant negative regression coefficient ($r=-0.81$, $p<0.001$) was established for fetal heart rate relative to gestational age with a mean value of 175.0 ± 6.1 bpm at 8 weeks, 158.0 ± 6.4 bpm at 15 weeks and 152.0 ± 5.1 bpm at 20 weeks of gestation. A statistically significant negative regression coefficient ($p<0.001$) was found between fetal heart rate and transmitral (MV) and transtricuspid (TV) flow parameters: (i) E-wave velocity (MV: $r=-0.39$, TV: $r=-0.47$), (ii) time-averaged velocity (MV: $r=-0.42$, TV: $r=-0.48$) and (iii) early/late diastolic (E/A) ratio (MV: $r=-0.47$, TV: $r=-0.42$). However, when adjusted for gestational age, these regression coefficients were no longer significant. A statistically significant linear increase ($p<0.01$) relative to gestational age was established for: early diastolic (E-wave; Figure 2), late diastolic (A-wave; Figure 3) and time-averaged velocities (TAV; Figure 4) as well as E/A ratio (Figure 5) in the absence of mitral and tricuspid valve differentiation (AV: 9-12 wks), at mitral valve level (MV: 10-20 wks) and at tricuspid valve level (TV: 10-20 wks). Reference ranges depicted in figures 2-5 are based on the assumption that transmitral and transtricuspid regression lines run parallel.

Also, the slope for late diastolic (A-wave) and time-averaged velocities in the absence of mitral and tricuspid valve differentiation (9-12 wks) was statistically significantly different from the slope at mitral valve level (10-20 wks; A-wave velocity: $p=0.0003$; TAV: $p=0.003$) and at tricuspid valve level (10-20 wks; A-wave velocity: $p=0.001$; TAV: $p=0.0005$).

A statistically significant positive linear regression coefficient ($p<0.001$) was, however, established for time-averaged velocities (AV: $y=-8.24+9.28\log_{10}x$; MV: $y=-3.59+6.48\log_{10}x$; TV: $y=-5.30+8.07\log_{10}x$; cm/s) relative to logarithmically transformed fetal CRL (mm)(figure 6). The slope for atrioventricular time-averaged velocities at 9-12 weeks (AV) and at 12-20 weeks of gestation (MV, TV) was not statistically significantly different when related to logarithmically transformed fetal CRL.

Transmitral relative to transtricuspid diastolic velocities

Throughout the study period, transtricuspid flow velocities were significantly higher than mitral valve velocities for E-wave velocities (mean difference=-4.67; sd=5.37; $p<0.001$), A-wave velocities (mean difference=-3.69; sd=4.74; $p<0.001$), E/A ratio (mean difference=-0.02; sd=0.08; $p<0.01$) and time-averaged velocities (mean difference=-1.82; sd=1.79; $p<0.001$). In all cases the difference between transmitral and transtricuspid flow velocity waveform parameters was not related to gestational age.

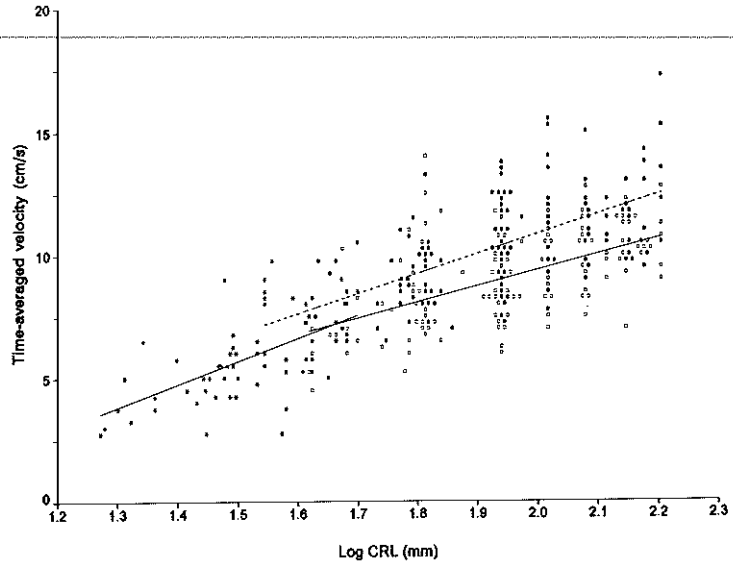

Figure 6 *Individual data for the time-averaged velocity (cm/s) in the absence of mitral and tricuspid differentiation (*, 9 to 12 weeks; solid line indicates normal limits) and at MV and TV levels (10 to 20 weeks. Open circles, MV: $y=-3.59+6.48\log_{10}x$; solid line indicates regression line. Solid circles, TV; $y=-5.30+8.07\log_{10}x$ dashed line, regression line) relative to logarithmically transformed fetal crown-rump-length (mm).*

Atrioventricular flow velocities relative to arterial and venous flow velocity waveform parameters

A statistically significant decrease with gestational age was established for fetal descending aorta PI ($r_s=-0.79$, $p<0.001$) and umbilical artery PI ($r_s=-0.83$, $p<0.001$). The decrease was most pronounced as from 12 weeks of gestation with mean values of 2.72 $\pm$ 0.33 and 2.61 $\pm$ 0.30 at 12 weeks and 1.58 $\pm$ 0.17 and 1.22 $\pm$ 0.10 at 20 weeks. No correlation existed between atrioventricular flow velocities and descending aorta and umbilical artery PI.

A statistically significant increase ($p<0.001$) with gestational age was found for (i) the time-averaged velocity in the umbilical vein and (ii) the peak systolic velocity, peak diastolic velocity and time-averaged velocity in the ductus venosus and in the inferior vena cava. A statistically significant gestational age-related reduction was established for time velocity integral of late diastolic reverse flow in the inferior vena cava ($p<0.001$). The slope for the time-averaged velocity in the umbilical vein and ductus venosus at 8-12 weeks of gestation was sig-

nificantly different from the slope at 13-20 weeks of gestation (umbilical vein: $p<0.001$; ductus venosus: $p<0.01$). After adjustment for gestational age, a statistically significant correlation was established between transmitral time-averaged and peak diastolic velocity ($r_s=+0.48$, $p<0.01$) and time velocity integral of late diastolic reverse flow ($r_s=-0.50$, $p<0.01$) in the inferior vena cava. No correlation existed between atrioventricular waveform velocities and ductus venosus flow velocities.

4.2.4 Discussion

Embryonic and early fetal development is characterized by rapid growth and cardiac morphogenesis. The embryonic heart develops from a smooth-walled cardiac loop into a septated trabecular heart. Characterization of the functional aspects of the embryonic and early human fetal cardiovascular system is important in the eventual understanding of normal and abnormal cardiovascular development. The present article describes diastolic filling characteristics between 8 and 20 weeks of gestation and provides a perspective of the changes in these characteristics including their relationship to venous, descending aortic and umbilical artery flow velocity waveforms. It should be emphasized that non-invasive Doppler studies of the human fetal circulation allow assessment only of flow velocities. The absence of intracardiac and extracardiac volume flow and pressure measurements puts a restriction on the interpretation of our data.

Transvaginal pulsed Doppler ultrasound allows flow velocity waveform analysis as early as 8 weeks of gestation. At that time only monophasic velocities were obtained, as was recently reported by Leiva et al. (1994). This could be the result of increased heart rate with reduced time for early diastolic filling or reduced ventricular compliance relative to older fetuses, with very low, perhaps immeasurable or absent early diastolic filling. Another explanation of the failure to identify separate early diastolic filling (E-wave) and late diastolic atrial contraction (A-wave) velocities at 8 weeks may be the result of limitations in image resolution despite the high quality ultrasound equipment used in this study. As from 9 weeks atrioventricular velocity waveforms increasingly resemble those observed in late pregnancy with a well defined early diastolic E-wave and late diastolic A-wave component. The absence of retrograde flow at the atrioventricular level confirms that atrioventricular cushions function as valves during the cardiac cycle this early in pregnancy.

Differentiation between transmitral and transtricuspid flow velocities was first achieved at 10-11 weeks. As from 12 weeks of gestation, E-wave and A-wave velocities can be recorded

at both mitral and tricuspid valve level in every instance. Transmitral and transtricuspid E-wave and A-wave velocities display a marked rise with advancing gestational age, reflecting an increase in early diastolic filling and atrial contraction and as a result an approximately 1.6-fold rise in time-averaged velocities at the atrioventricular level at 8-20 weeks of gestation, reflecting the larger volume of blood entering the ventricles. The gestational age-dependent rise in E/A ratio suggests a shift of blood flow from late diastole towards early diastole, which may be due to increased ventricular compliance and/or raised ventricular relaxation rate. In the chick embryo, average diastolic ventricular wall stiffness decreases geometrically with development (Hu et al., 1990). Our findings of a gestational age-dependent rise in E/A ratio are in agreement with Tulzer et al. (1994). They demonstrated, however, that despite a changing relation between early and late inflow velocities, the proportion of ventricular filling contributed by atrial contraction, remains constant indicating unchanged ventricular compliance.

Of interest is the significantly steeper slope of increment for time-averaged velocities from data before sonographic differentiation between transmitral and transtricuspid velocity waveforms (9-12 wks) compared with data collected after differentiation became possible (13-20 wks). A similar change in slope of increment was established at around 12 weeks for the time-averaged velocity in the umbilical vein and ductus venosus, but not in the inferior vena cava. These changes are unrelated to the technique of measurement. No difference between transvaginal and transabdominal flow velocity waveforms recordings could be established at 12-13 weeks of gestation. Comparison with fetal crown-rump-length estimates, revealed that atrioventricular, umbilical venous and ductus venosus time-averaged velocities increase parallel to increase in fetal crown-rump-length. This indirectly suggests that fetal growth-determined increase in volume flow plays a part in these gestational age-related flow velocity changes. This is further supported by a study in the chick embryo, in which the increase in cardiac output as represented by dorsal aortic volume flow is comparable to the increase in body weight beyond Hamburger and Hamilton (1951) stage 12 (50 hours of 21-day incubation)(Hu and Clark, 1989). For direct information on atrioventricular volume flow, data on both atrioventricular velocities and valve area are needed. However, the latter can not be reliably measured at this early stage of fetal cardiac development.

Fetal heart rate showed a significant reduction, which has been explained by parasympathetic development (Wladimiroff and Seelen, 1972). With an approximately 1.2-fold drop, the change in fetal heart rate was most pronounced before 15 weeks of gestation. When it was adjusted for gestational age, no correlation between fetal heart rate and atrioventricular diastolic velocities could be established, suggesting independence of these velocities from heart rate at this stage of parasympathetic nerve development. A nearly two-fold reduction in descending

aorta and umbilical artery Pulsatility Index was observed after 12 weeks of gestation, reflecting a marked drop in feto-placental vascular resistance, which may be determined by the process of angiogenesis taking place in the developing placenta (Jauniaux et al., 1992). No relation could be established between atrioventricular flow velocities and Pulsatility Index in the descending aorta and umbilical artery, indicating transmitral and transtricuspid flow velocities to be independent of arterial downstream impedance at the fetal trunk and placental levels.

Animal experimental (Edelstone and Rudolph, 1979) and human fetal studies using color coded Doppler ultrasound (Kiserud et al., 1992) indicate that blood flow from the inferior vena cava is directed primarily through the tricuspid valve to the right ventricle and blood flow from the ductus venosus through the mitral valve to the left ventricle, although some mixture may exist. Diastolic components of venous flow velocities are subject to intrinsic cardiac properties such as the degree of atrial filling and atrial contraction force. However, we found no relationship between ductus venosus and atrioventricular flow velocities, whereas early (forward) and late (reverse) diastolic velocities in the inferior vena cava where related only to transmitral time-averaged velocities. These data suggest that variables other than volume flow such as the pressure gradient across the atrioventricular valves may also be responsible for the observed atrioventricular flow velocity changes with advancing gestational age.

During the entire study period, both E-wave and A-wave velocities are responsible for the higher time-averaged velocities at the tricuspid valve level compared with mitral valve level. Since volume flow is equal to mean velocity multiplied by vessel area, the higher transtricuspid time-averaged velocities may reflect increased right ventricular stroke volume and output. This would be in agreement with observations of right ventricular predominance in normal late pregnancies (Reed et al., 1986). Further support for this was provided by the observation that atrial contribution to ventricular filling was higher at the tricuspid valve than at the mitral valve (Tulzer et al., 1994). It was suggested that the right ventricle might be less compliant than the left ventricle because of a larger right ventricular muscle mass.

It can be concluded that flow velocity waveforms at the atrioventricular level can be recorded as early as 8 weeks of gestation. These waveforms are mostly monophasic before 9 weeks of gestation and biphasic thereafter. Normal late first and early second trimester pregnancies are characterized by marked changes in transmitral and transtricuspid flow velocities. These changes may be mainly determined by increased volume flow in the developing fetus, which would explain the absent relation between atrioventricular flow velocities and arterial downstream impedance at the fetal placental level. Transtricuspid A-wave and E-wave velocities suggest right ventricular predominance as early as the late first and early second trimester of pregnancy.

4.3 Cardiac functional changes in the human fetus in the late first and early second trimesters

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4.3.1 Summary

Fetal cardiac function was studied in 52 women at 10-20 weeks of normal gestation using Doppler ultrasonography. According to a cross-sectional study design, transmitral and ascending aortic flow velocity waveforms were obtained, as well as a simultaneous recording of both mitral and ascending aortic flow, in order to calculate filling and ejection time as well as isovolumic contraction and relaxation time. A statistically significant gestational age dependent increase was established for both trans-mitral and ascending aortic flow velocities. Cardiac cycle length and filling time displayed a statistically significant increase with advancing gestational age, whereas ejection time and isovolumic relaxation time showed a gestational age related decrease. No relationship existed between isovolumic contraction time and gestational age. A statistically significant decrease was demonstrated for atrial contribution to ventricular filling at 10-14 weeks of gestation, with a constant pattern during the remainder of the study period. No relationship existed between the different components of the cardiac cycle and mitral and aortic flow velocity parameters.

The present study shows that the late first and early second trimester of pregnancy are characterized by gestational age-related changes in fetal cardiac function.

4.3.2 Introduction

The introduction of transvaginal color-coded and pulsed Doppler has opened the possibility of investigating the fetal heart as early as the late first trimester of pregnancy (Wladimiroff et al., 1991). Knowledge of normal fetal cardiac performance may provide a tool for surveillance of the human fetus under pathophysiological conditions.

Gestational age-dependent changes in atrioventricular flow velocity waveforms have been described in detail in both early and late gestation (Wladimiroff et al., 1991; Tulzer et al.,

1994; Reed et al., 1986). Tulzer and colleagues (1994) described diastolic function of the fetal heart during the second and third trimester of pregnancy. Preliminary data are available on first trimester fetal cardiac function (Leiva et al., 1994).

The objective of the present study was:

(1) To determine the relationship with gestational age for transmitral and ascending aortic flow velocities and diastolic and systolic components of the cardiac cycle, i.e. filling and ejection time, isovolumic contraction and relaxation time; and
(2) To assess the interrelationship between cardiac variables.

4.3.3. Material and methods

Subjects

Between 1 April and 1 September 1995, a total of 60 women with a normal singleton pregnancy between 10 and 20 weeks of gestation (median 15 wks) consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Maternal age ranged between 16 and 46 years (median 28 years). Pregnancy duration was estimated from the last menstrual period and confirmed by ultrasound measurement of the fetal crown-rump-length (8-12 wks) or biparietal diameter (12-20 wks). Each women was included in the study once. At the time of analysis all pregnancies were progressing uneventfully.

Doppler recordings

Ultrasound Doppler studies were performed with a Toshiba SSH 140A (Toshiba corp., Medical systems Division, Tokyo, Japan). A combined transvaginal real-time and pulsed Doppler system (carrier frequency 6 MHz and 3.5 MHz, respectively) was used at 10-13 weeks of gestation and a combined transabdominal real-time and pulsed Doppler system (carrier frequency 5.0 MHz and 3.5 MHz, respectively) was employed at 14-20 weeks of gestation. The high pass filter was set at 100 Hz. The system operates at power outputs of < 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specification. All Doppler studies were performed with the women in the semirecumbent position and during fetal apnoea. Doppler recordings were performed by one examiner (IPvS).

Previous experience (Wladimiroff et al., 1991) has demonstrated that acceptable cardiac flow velocity waveforms can be obtained in the majority of transvaginal examinations before 14 weeks of gestation. Moreover, in another study, it has been demonstrated that no difference

between transvaginal and transabdominal flow velocity waveform recordings could be established early in gestation (van Splunder et al., 1996a). Earlier in our center (Huisman et al., 1993), acceptable intra-observer reproducibility was established for fetal cardiac flow velocity waveforms during the late first and early second trimester of pregnancy, with coefficient of variation values being less than 6%.

Flow velocity waveforms at mitral level were obtained from the cardiac "four-chamber" view. The Doppler sample volume was placed immediately distal to the mitral valve. Only waveforms consisting of a clear E- and A-wave were accepted. In a previous study, it was demonstrated that differentiation between E- and A-wave was feasible in 85.0% at 10 weeks, 86.7% at 11 weeks and in all cases as from 12 weeks of gestation (van Splunder et al., 1996a).

Flow velocity waveforms from the ascending aorta were obtained from the five-chamber view. The Doppler sample volume was placed immediately distal to the aortic valve. Angles of insonation were kept below 30° at all sampling sites, with the sample volume length ranging between 0.1 and 0.2 cm. Cardiac systole consisted of both isovolumic contraction time and ejection time, whereas cardiac diastole was characterized by isovolumic relaxation time and filling time. All four parameters were measured from a simultaneous recording of the left ventricular inflow and outflow (Figure 1) and expressed as a percentage of the total cardiac cycle length. This was achieved by enlarging the sample volume to 0.3-0.4 cm, to cover the area immediately distal to the aortic and mitral valve. The smallest detectable time-interval of the Doppler equipment used was 1 ms. The angle of insonation was kept below 30°.

The total examination time was limited to 15 minutes in each instance. All flow velocity waveforms were recorded on hard copies. In case of simultaneous recording of transmitral and aortic flow velocity waveforms the scrolling speed was set at 1 cm/s. Waveform analysis was performed by one examiner (IPvS), using a microcomputer (Olivetti M24; Olivetti B.V., Leiden, The Netherlands) linked to a graphics tablet.

Analysis of the atrioventricular waveforms consisted of calculation of (i) time-averaged velocity (cm/s), (ii) peak velocity (cm/s) of early diastolic E-wave and late diastolic A-wave, (iii) E/A ratio, (iv) area of the total time-velocity integral (TVI; cm) and (v) area under E- and A-wave (E-TVI, A-TVI; cm), representing passive atrial filling and active atrial contraction, respectively. Atrial contribution to ventricular filling was calculated by dividing the time-velocity integral under the A-wave (A-TVI) by the total velocity integral (TVI). The analysis of the ascending aorta included calculation of: (i) peak systolic velocity (cm/s), (ii) time-averaged velocity (cm/s), (iii) acceleration time (acc; ms) and (iv) time-velocity integral (TVI_{ao}; cm). The cycle length (ms) was determined by the time interval between the aortic peak systolic velocity of two consecutive cardiac cycles.

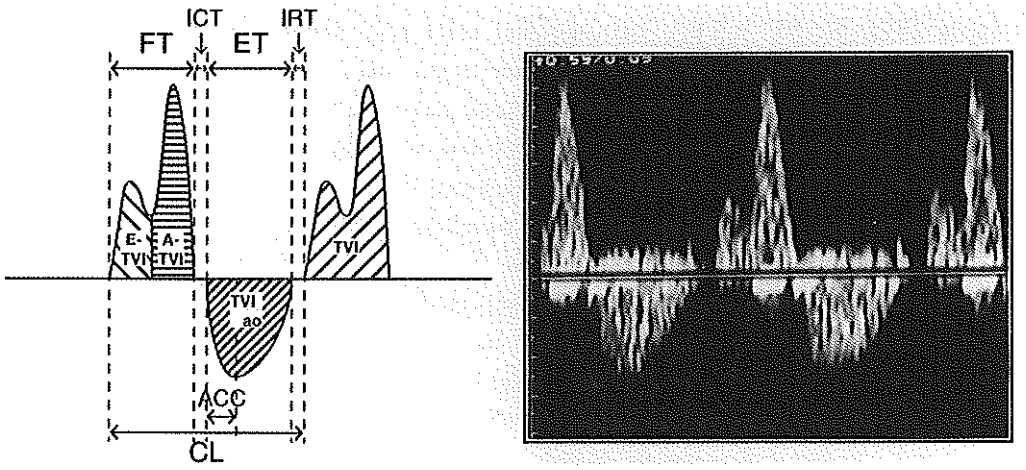

Figure 1 *Left panel: Schematic representation of the simultaneous Doppler recording of transmitral and ascending aortic flow velocities. CL, cycle length (ms); FT, filling time (ms); ICT, isovolumic contraction time (ms); ET, ejection time (ms); IRT, isovolumic relaxation time (ms); E-TVI, total velocity integral (cm) under the transmitral E-wave; A-TVI, total velocity integral (cm) under the transmitral A-wave; TVI, total transmitral velocity integral (cm); TVI_{ao}, total velocity integral (cm) of ascending aortic flow velocity waveform; ACC, acceleration time (ms) in the ascending aorta. Right panel: Doppler flow recording, demonstrating simultaneous recording of transmitral and ascending aortic flow velocity waveforms*

Analysis of the simultaneous recordings of transmitral and aortic flow velocity waveforms included the calculation of (i) filling time (ms) and ejection time (ms), which are defined as the time interval between the beginning and the end of the transmitral and aortic flow velocity waveform, respectively, (ii) isovolumic contraction time (ms), representing the time interval between the end of the transmitral flow velocity waveform and the beginning of the aortic flow velocity waveform, and (iii) the isovolumic relaxation time (ms), which is determined by the time interval between the end of the aortic flow velocity waveform and the beginning of the transmitral flow velocity waveform (Figure 1). All cardiac time intervals were subsequently divided by the cycle length to correct for heart rate and expressed as percentage of cardiac cycle length.

Three consecutive flow velocity waveforms with the highest velocity and similar appearance were used to calculate the different parameters across the mitral valve and in the ascending aorta.

Data analysis

Linear regression analysis was used to establish the relationship between gestational age and (i) mitral E- and A-wave velocity, time-averaged velocity, E/A ratio and time-velocity integrals (TVI, E-TVI, A-TVI), (ii) ascending aorta peak systolic velocity, time-averaged velocity and acceleration time, (iii) cardiac cycle length, and (iv) filling time (%), isovolumic contraction time (%), ejection time (%), isovolumic relaxation time (%) and atrial contribution to ventricular filling. Linear regression analysis was also used to determine the relationship between (i) filling time and transmitral flow velocity waveform parameters and (ii) between ejection time and ascending aorta flow velocity waveform parameters.

For the construction of reference centiles the method described by Royston (1991) was used and, if necessary, the standard deviation was modelled as a function of gestational age as described by Altman (1991). This resulted in the following procedure: the 50th centile was established by modelling the outcome variable Y by a straight line regression model with gestational age as predictor. It was tested whether adding the quadratic term was significant. Next, it was checked if the residuals depended on gestational age. If so, straight line regression was used to model the absolute value of the residuals and from this model a regression equation for the standard deviation, depending on gestational age, was derived. Using this standard deviation, the 5th and 95th centiles were constructed. P-values <0.05 were considered statistically significant.

4.2.4 Results

Of the 60 women participating in the study, no Doppler signals could be obtained in eight women due to maternal obesity, fetal position or fetal body movements. This leaves flow velocity waveform recordings of 52 women for further analysis. Apart from one infant, which was delivered at 27 weeks of gestation as the result of premature labour, all other infants were born between 36 and 41 weeks (mean 39 wks) with birth weights ranging between 2855 and 3835 g (mean 3324 g).

Transmitral flow velocity waveforms

At transmitral level, a statistically significant linear increase ($p<0.001$) relative to gestational age was established for: (i) early diastolic (E-wave) and late diastolic (A-wave) velocity, (ii) time-averaged velocity (TAV), (iii) total time-velocity integral (TVI), (iv) total E-wave time-velocity integral (E-TVI) and (vi) total A-wave time-velocity integral (A-TVI)(Table

1). Also, a statistically significant linear increase ($p<0.01$) was found for mitral E/A ratio relative to gestational age (Table 1).

Arterial flow velocity waveforms

A statistically significant linear increase ($p<0.001$) was established for (i) peak systolic velocity, (ii) time-averaged velocity and (ii) time-velocity integral of the ascending aorta (TVI_{ao}) relative to gestational age (Table 1). No relationship existed between the acceleration time in the ascending aorta and gestational age.

The cardiac cycle

The cardiac cycle length displayed a statistically significant linear increase ($p<0.001$) from 373 ms (50th centile) at 10 weeks of gestation to 406 ms (50th centile) at 20 weeks of gestation. A statistically significant gestational age related linear increase ($y=30.64+ 0.51x$; $p<0.01$) was also established for the filling time (Figure 2). A statistically significant linear decrease existed for (i) the ejection time ($y=48.65-0.42x$; $p<0.01$; Figure 3) and (ii) the isovolumic relaxation time ($y=13.89-0.20x$; $p<0.05$; Figure 4). No relationship could be established between isovolumic contraction time (mean 0.09 $\pm$ 0.02 %) and gestational age. The

Table 1 Transmitral and ascending aorta flow velocity waveform parameters relative to gestational age

	Constant	*Coefficient of linear term*	*Standard error*	*p-value*
Mitral valve				
Early diastolic velocity (E-wave; cm/s)	7.45	1.03	4.48	0.01
Late diastolic velocity (A-wave; cm/s)	22.98	1.23	6.25	<0.001
Time-averaged velocity (TAC; cm/s)	3.43	0.40	1.28	<0.001
Total time velocity integral (TVI)	0.47	0.21	0.56	<0.001
Total E-wave time velocity integral (E-TVI)	-0.27	0.10	0.33	<0.001
Total A-wave time velocity integral (A-TVI)	0.74	0.11	0.34	<0.001
E/A ratio	0.41	0.01	0.08	0.01
Ascending aorta				
Peak systolic velocity (cm/s)	-5.13	2.84	9.22	<0.001
Time-velocity integral (TAV; cm/s)	3.93	0.52	2.62	=0.001
Acceleration time (ms)	39.29		11.94	NS

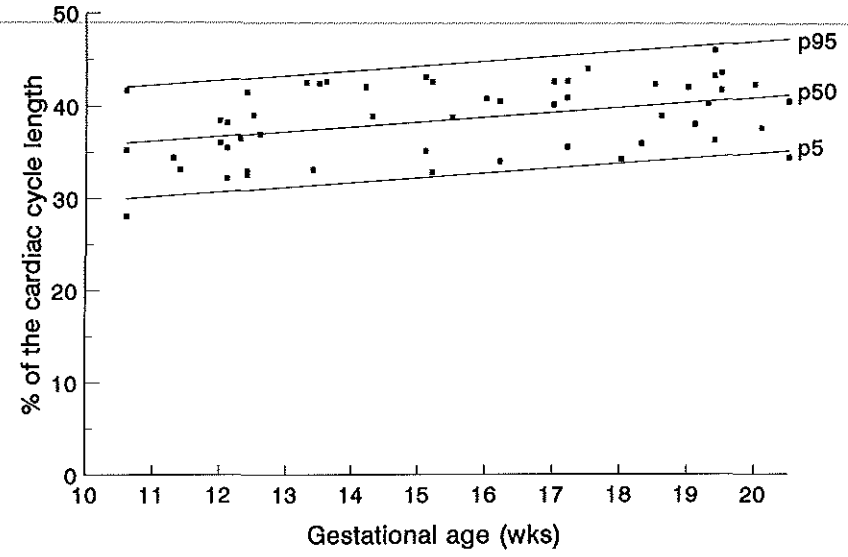

Figure 2 *Individual data and reference ranges (p5, p50, p95) are presented for the filling time (% of the cardiac cycle; y=30.64+0.51x; SD=3.66) relative to gestational age.*

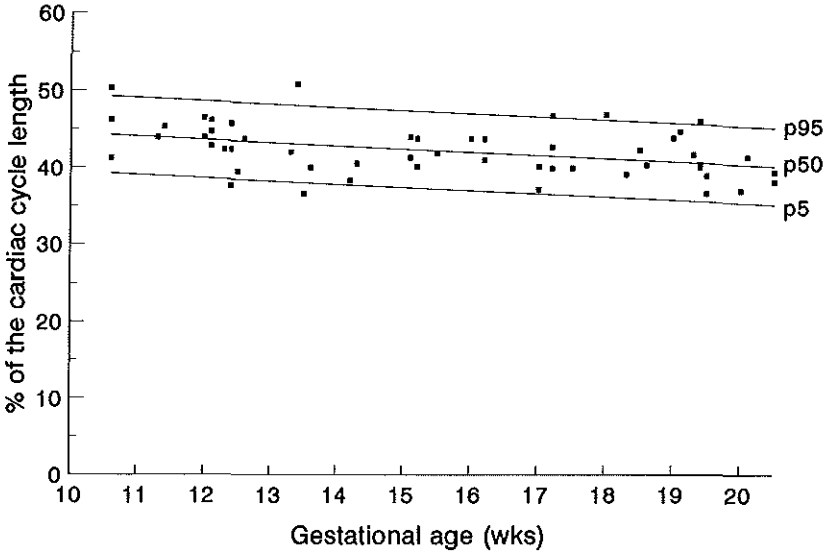

Figure 3 *Individual data and reference ranges (p5, p50, p95) are presented for the ejection time (% of the cardiac cycle; y=48.65-0.42x; SD=3.04) relative to gestational age.*

atrial contribution to ventricular filling decreased significantly ($p<0.01$) between 10-14 weeks of gestation and remained virtually constant during the remainder of the study period (Figure 5). After adjustment for gestational age no relationship existed between mitral and aortic flow velocity parameters and the different components of the cardiac cycle.

4.3.5 Discussion

Data are presented on functional aspects of the fetal heart during the late and early second trimester of pregnancy. The non-invasiveness of the Doppler techniques puts certain restrictions to the interpretation of these data. No information is available on pressure or volume flow.

With advancing gestational age, transmitral E-wave and A-wave velocities undergo a marked increase, reflecting raised early diastolic filling and atrial contraction. Both transmitral and aortic time-averaged velocity indirectly suggest increased transmitral volume flow and left ventricular stroke volume.

The gestational age-dependent rise in E/A ratio suggests a shift of blood flow from late diastole to early diastole, which may result from increased ventricular compliance and/or raised ventricular relaxation rate. A change in ventricular compliance seems unlikely, at least as from 14 weeks onwards. The significant increase in the proportion of ventricular filling contributed by atrial contraction between 10 and 14 weeks of gestation, however, suggest a change in ventricular compliance early in pregnancy.

The cardiac cycle length shows a marked increase with advancing gestational age, likely to be the result of parasympathetic nerve development (Wladimiroff and Seelen, 1972). After adjustment for gestational age, no relationship could be established between transmitral flow velocities and cycle length, which may suggest that mitral flow velocity changes occur independently from parasympathetic nerve development. Cardiac systole consisted of isovolumic contraction time and ejection time, whereas diastole consisted of isovolumic relaxation time and ventricular filling time. Isovolumic contraction time did not change during the study period, occupying 8-9% of the cardiac cycle, which is considerably less than the 20% reported by Leiva and co-workers (1994) up to 12 weeks of gestation. Whereas there is only a overlap of 2 weeks in both studies, hitherto unidentified differences in recording techniques may be responsible for this discrepancy.

The 50th centile of the ejection time decreased from 45.9% at 10 weeks of gestation to 38.9% of the cardiac cycle length at 20 weeks of gestation. It is of interest that in another study

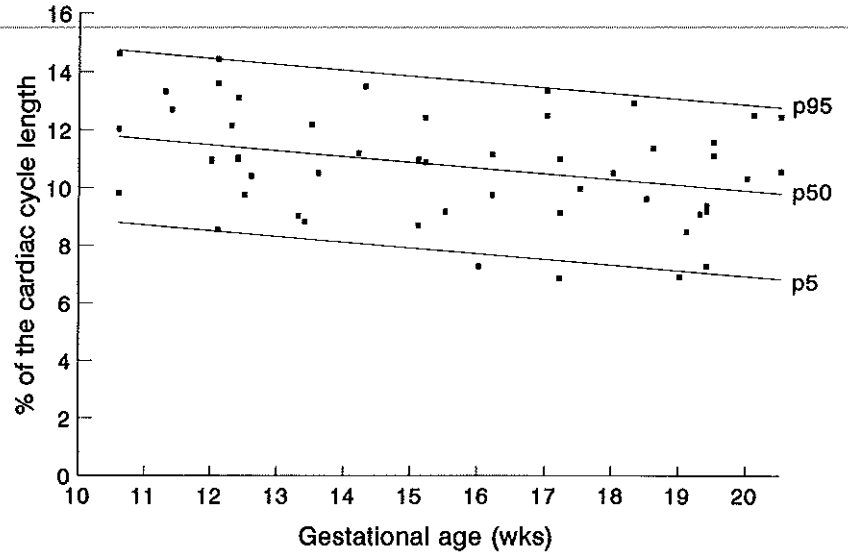

Figure 4 *Individual data and reference ranges (p5, p50, p95) are presented for the isovolumic relaxation time (% of the cardiac cycle; y=13.89-0.20x; SD=0.14) relative to gestational age.*

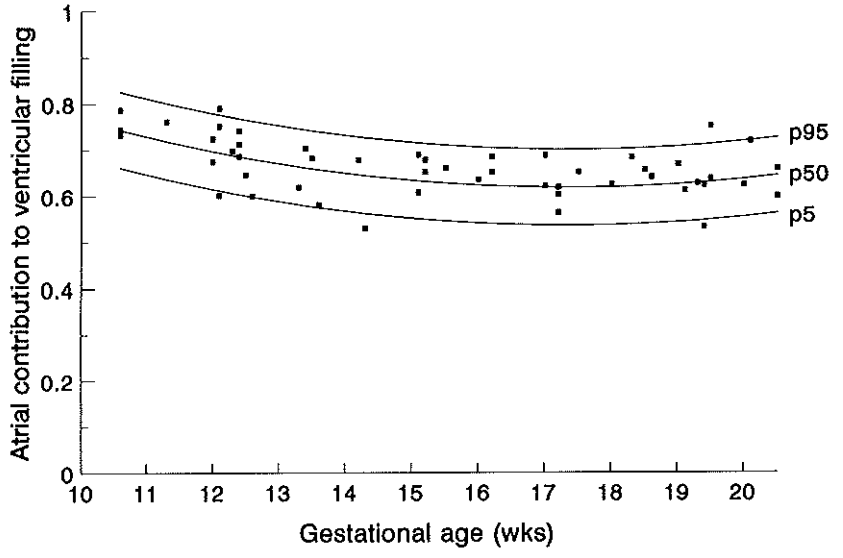

Figure 5 *Individual data and reference ranges (p5, p50, p95) are presented for the atrial contribution to ventricular filling ($y=1.44+0.003x^2-0.09x$; SD=0.05) relative to gestational age.*

(Leiva et al., 1994), ejection time increased approximately two-fold between 5 and 14 weeks of gestation. This is in support of marked changes in myocardial properties in the early developing fetus. The decline in ejection time in the present study may be determined by the drop in afterload as suggested by the marked reduction in umbilical artery pulsatility index values as from 11-12 weeks of gestation (Wladimiroff et al., 1991; van Splunder et al., 1996).

Isovolumic relaxation phase is highly dependent on the complex interaction of inactivation of contraction, loading conditions and nonuniform distribution of load and of inactivation in space and time due to structural, electrical, chemical changes and mechanical feedback regulation (Brutsaert and Sys, 1989). The isovolumic relaxation phase demonstrates a gestational age related decrease in the 50th centile from 12.2% at 10 weeks to 11.5% at 20 weeks of gestation.

In the present study, no information was available on umbilical artery Pulsatility Index. Earlier data show a marked reduction in umbilical artery Pulsatility Index with advancing gestational age (Wladimiroff et al., 1991; van Splunder et al., 1996b). This is most likely the result of the process of placental angiogenesis (Jauniaux et al., 1992), and reflects a reduction in fetoplacental vascular resistance. In small-for-gestational age fetuses during late pregnancy an increase in downstream impedance has been demonstrated, but recently an increase in isovolumic relaxation time was established associated with a raised S/D ratio in the umbilical artery (Tsyvian et al., 1995). Whether the opposite is taking place in normal early pregnancy, needs to be further addressed.

In adults abnormal relaxation may precede inadequate cardiac contraction. If a parallel can be drawn with the fetus, isovolumic relaxation time may provide a tool for early detection of cardiac dysfunction. Also here, a full interpretation of the gestational-age determined changes in isovolumic relaxation time is not possible, due to lack of information on volume flow and pressure changes.

Filling time, as a percentage of the cardiac cycle, shows a gestational age related increase in the 50th centile from 35% at 10 weeks to 38.6% at 20 weeks. No relationship could be established between percentage filling time and transmitral flow velocities, suggesting that factors other than volume, such as ventricular relaxation, left atrial driving pressure and left ventricular compliance rate, play a role in ventricular filling.

It can be concluded that the late first-trimester and early second-trimester fetus is characterized by changing cardiac function, as expressed by an increased filling phase and reduced isovolumic relaxation and ventricular ejection phase of the cardiac cycle.

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Chapter 5

Flow velocity waveforms in late pregnancy

5.1 Introductory remarks

In the human fetus, there is a transition from a high downstream impedance to a low downstream impedance at feto-placental level with advancing gestational age. This is accompanied by marked well-defined changes in flow velocity waveforms at cardiac and venous level. At the same time, umbilical venous pulsations gradually disappear (Rizzo et al., 1991a). Modulation of umbilical venous blood flow by breathing movements has been described in normal late pregnancy (Maršál et al., 1984). In the absence of fetal breathing movements, umbilical venous pulsations in late pregnancy are considered to be associated with fetal compromise. Presence of umbilical venous pulsations has been described in the small-for-gestational age fetus, in fetuses with non-immune hydrops, abnormal fetal heart rates and congenital anomalies of the heart (Gudmundsson et al., 1991; Indik et al., 1991; Nakai et al., 1992; Tulzer et al., 1994; Hecher et al., 1995a). However, mild umbilical venous pulsations have also been observed in normally developing fetuses later in gestation. Data on the existence of venous pulsations at different recording sites and their reproducibility in normal pregnancy are presented in Chapter 5.2.

Whereas normal late pregnancy is characterized by low downstream impedance, the opposite may be observed in the small-for-gestational age fetus (Trudinger et al., 1985; Groenenberg et al., 1989). To maintain optimal oxygen supply to the developing fetus, haemodynamic adjustment takes place, resulting in centralization of the circulation at fetal trunk level as well as a brain-sparing and heart-sparing effect (van den Wijngaard et al., 1989; Noordam et al., 1994; Gembruch and Baschat, 1996). This haemodynamic adjustment, which appears to be brought about by arterial chemoreceptors (Bartelds et al., 1993), has a major impact on arterial, cardiac and venous flow velocity waveforms. The nature of these changes in flow velocity waveforms and their interrelationships are discussed in Chapter 5.3.

5.2 Presence of pulsations and reproducibility of waveform recording in the umbilical and left portal vein in normal pregnancies.

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5.2.1 Summary

Reproducibility and inter-observer variability of intra- and extra-abdominal umbilical venous flow velocity and left portal venous flow velocity as well as heart-synchronous waveform pulsations in these vessels were studied in 23 women at 34-38 weeks of normal pregnancy.

Limited reproducibility, expressed by large intra-patient coefficients and limits of agreement between two observers, was established for all standardized recording sites. Pulsations, defined as negative venous deflections of at least 10% of the mean velocity, were demonstrated at all locations ranging from 19.6 % of the measurements at the free-floating loop of the umbilical vein to 78.2 % of the measurements at the left portal vein.

The present study shows that the limited reproducibility of venous flow velocity waveforms should be taken into consideration, and that presence of pulsations can be demonstrated in normal late pregnancy.

5.2.2 Introduction

An increasing number of reports has appeared on flow velocity waveform recording in the umbilical vein in normal pregnancies as well as in pathological conditions. Waveform velocities have been obtained from either the free-floating loop (Gudmundsson et al., 1991; Indik et al., 1991; Rizzo et al., 1991a; St. John Sutton et al., 1991) or the intra-abdominal part of the umbilical vein (Gill and Kossoff, 1984; van Lierde et al., 1984; Griffin et al., 1985; Erskine and Ritchie 1985; Lingman et al., 1986). Sparse information is available on the reproducibility of umbilical venous flow velocity waveforms. Reproducibility of waveform recordings depends not only on the exact location of the Doppler sample volume, the sample size and interrogation

angle, but also on fetal variables such as breathing movements. Lately, heart-synchronous pulsations have been observed in the umbilical venous flow waveform both in the small-for-gestational age fetus (Gudmundsson et al., 1991) and in fetuses with non-immune hydrops (Indik et al., 1991) in late pregnancy, and in normally developing fetuses during the late first trimester of pregnancy (Rizzo et al., 1991a). In a pilot study in our own center, occasional pulsations have been observed in normal fetuses in the umbilical vein and in its extension, the left portal vein, as late as the third trimester of pregnancy.

The objective of the present study was two-fold:

1. To determine the reproducibility and inter-observer variability of intra- and extra-abdominal umbilical venous flow velocity waveforms and left portal venous flow velocity waveforms; and
2. To investigate the existence of heart-synchronous waveform pulsations relative to these recording levels.

5.2.3 Material and methods

A total of 23 women consented to participate in the study. Gestational age varied between 34 and 38 weeks (mean 36 weeks). Pregnancy duration was determined from the last menstrual period and confirmed by ultrasound measurements of the fetal crown-rump-length or fetal biparietal diameter. All pregnancies were uncomplicated. All women gave birth to a healthy infant with a birth weight between the 10th and 90th centiles (Kloosterman, 1970). Each woman was included in the study once. All participants were non-smokers.

Pulsed wave Doppler ultrasound recordings were obtained using the Hitachi EUB-450, manufactured by Hitachi Medical Corporation, Tokyo, Japan (real-time and Doppler carrier frequency 3.5 MHz; high pass filter 100 Hz).

Doppler studies were performed with the woman in the semirecumbent position and during fetal apnoea, because fetal breathing movements modulate venous blood flow velocity waveforms (Maršál et al., 1984). Sample volume length was between 0.4 and 0.5 cm. Maximal flow velocity waveforms were obtained from four standardized locations:

(1) The free-floating loop of the umbilical cord (location FL-UV);
(2) The intra-abdominal part of the umbilical vein at the entrance into the abdomen (location IA-UV);

(3) The umbilical sinus (location US); and
(4) The left portal vein between the right portal vein and the umbilical sinus (location PV) (Figure 1).

The position of the vessel at location FL-UV and location PV allowed interrogation angles of less than 10°. Recordings at location IA-UV and US were only accepted if the interrogation angle was less than 30°. The examination never exceeded 60 minutes.

All measurements were performed by two investigators in a fixed, standard order:

(1) First measurement by TWAH;
(2) Measurement by IPvS; and
(3) Second measurement by TWAH

Inter-observer variability was defined as the variability between the two measurements by observer 1 and the measurement by observer 2. The intra-patient variability, which depended on the biological variation within the individual patients and the measurement error by observer 1, was defined as the variability in flow velocity between the first and second measurement by observer 1.

Umbilical venous blood flow velocity waveforms were recorded on hard copies. These hard-copies were shuffled in a random order, and the presence or absence of pulsations was

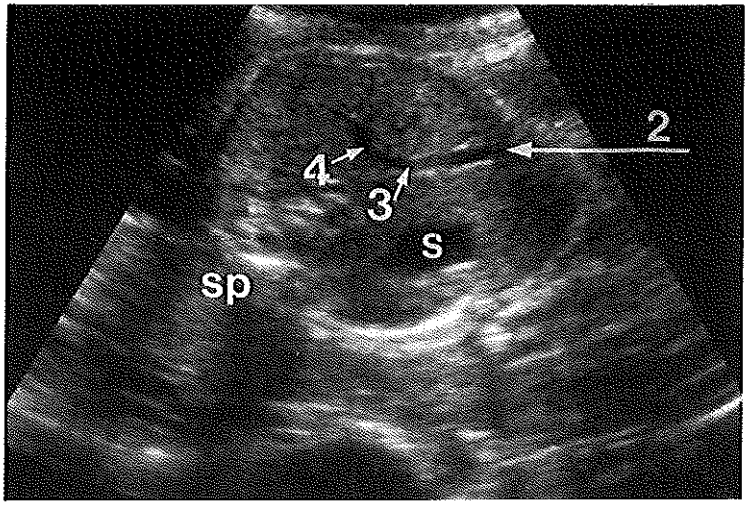

Figure 1 *Ultrasound scan of fetal abdomen illustrating the intra-abdominal recording sites: 2, the intra-abdominal part of the umbilical vein at the entrance into the abdomen; 3, the umbilical sinus; 4, the left portal vein between the right portal vein and the umbilical sinus; s, stomach; sp, spine*

documented independently by the two investigators. Umbilical venous pulsations were defined as at least three consecutive negative deflections of the venous waveform, each comprising at least 10 % of the mean velocity and synchronous with the fetal heart rate (Figure 2). The fetal heart rate was established by correlating time intervals from consecutive umbilical arterial and venous pulsations. The occurrence of umbilical venous pulsations was only accepted if both investigators agreed about its presence. In all recordings displaying pulsations, maximal velocity (cm/s), minimal velocity (cm/s) and mean velocity (cm/s) were determined for three cardiac cycles. In the case of waveforms without pulsations, the mean velocity was analyzed at three different measuring points on the maximum frequency envelope in the continuous flow velocity waveform.

For analysis of the Doppler recordings, a microcomputer (Olivetti M24, Olivetti B.V., Leiden, The Netherlands) was used linked to a graphical tablet. The waveform analysis was performed by one examiner (IPvS).

Statistical analysis

Analysis of variance for repeated measurements was used to assess systematic differences in mean velocities between the three successive measurements. To assess the observer agreement, limits of agreement between the observers were calculated (Bland and Altman, 1986). Limits of agreement were defined as the range in which approximately 95% of the differences between observer 1 and observer 2 were situated. On the basis of the measurements carried out by observer 1, intra- and inter-patient variance components were determined by

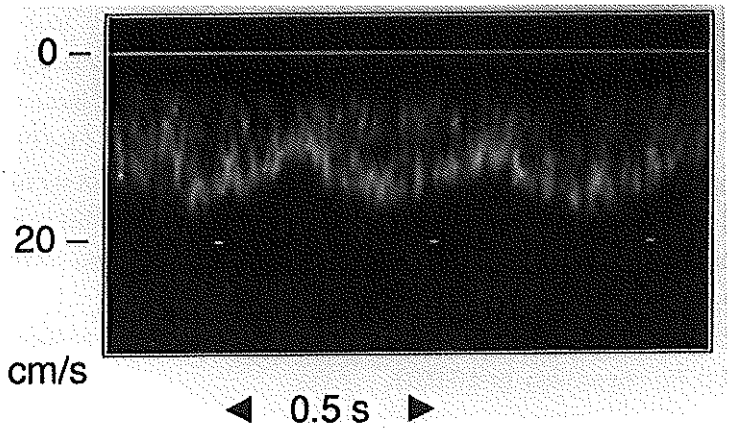

Figure 2 *Venous flow velocity waveform at the umbilical sinus (location US)*

standard analysis of variance. The prevalence of pulsations was compared between the two observers (TWAH 1 vs. IPvS and TWAH 2 vs. IPvS), between the first and second measurement of observer 1 (TWAH 1 vs. TWAH 2) and between all four locations, by McNemar's test.

Fisher's two-tailed exact test was used to assess associations in the presence of pulsations between the different locations. A value of $p<0.05$ was considered statistically significant.

5.2.4 Results

Technically unacceptable flow velocity waveforms were obtained in four women due to persistent fetal breathing or fetal position, leaving data from 19 women for further analysis. Among these 19 women (57 measurements), successful recording of flow velocities was achieved at locations FL-UV and US in 98 % (56/57) and at locations IA-UV and PV in 96 % (55/57).

Mean maximum velocities were significantly higher at location IA-UV as compared with locations FL-UV, US and PV (Table 1). For the mean velocities at location IA-UV and US, the overall test for differences in mean values between the three successive measurements was statistically significant (p = 0.048 and p = 0.013). No such differences could be documented for the mean velocities at locations FL-UV (p = 0.32) and PV (p = 0.59). Table 2 shows the intra-patient variation. Limits of agreement are presented in Table 3. For the analysis of the incidence of pulsations, the data of the three repeated measurements were pooled, and therefore, no adjustment was made for the fact that, from each woman, three measurements were used.

The presence of pulsations was demonstrated at location FL-UV in 19.6% (11/56), at location IA-UV in 32.7% (18/55), at location US in 76.8% (43/56) and at location PV in 78.2 % (42/55) of measurements. This led to significant differences in the incidence of pulsations between locations FL-UV and US (p = 0.002), between locations FL-UV and PV (p = 0.0018), between locations IA-UV and US (p = 0.0039) and between locations IA-UV and PV (p = 0.0034). The Fisher's exact test revealed a significant association between the occurrence of pulsations at locations FL-UV and IA-UV (p = 0.0003) and between locations IA-UV and US (p = 0.0047).

Correlation coefficients between arterial and venous pulsations at location US and PV were 0.71 and 0.74, respectively ($p<0.001$).

Table 1: *Mean maximum velocity ± standard deviation (cm/s) measured by two observers at the four different locations: FL-UV, free-floating loop of the umbilical vein; IA-UV, intra-abdominal part of the umbilical vein at the entrance into abdomen; US, umbilical sinus; PV, left portal vein between the right portal vein and the umbilical sinus*

	FL-UV	*IA-UV*	*US*	*PV*
T.W.A.H. 1	14.4 ± 3.3	18.6 ± 7.0	15.3 ± 2.4	14.0 ± 3.4
I.P.v.S.	15.6 ± 2.8	20.7 ± 5.0	17.3 ± 2.6	14.8 ± 3.1
T.W.A.H. 2	18.8 ± 2.9	17.9 ± 5.3	17.2 ± 3.4	14.1 ± 2.5
p value	$p = 0.32$	$p = 0.048$	$p = 0.013$	$p = 0.59$

Table 2 *Intra-patient variation relative to the four different recording sites: FL-UV, free-floating loop of the umbilical vein; IA-UV, intra-abdominal part of the umbilical vein at the entrance into the abdomen; US, umbilical vein; PV, left portal vein between the right portal vein and the umbilical sinus*

Location	*Mean*	*SD*	*Coefficient of variation (%)*
FL-UV	15.1	3.5	23.2
IA-UV	18.3	3.6	19.7
US	16.3	2.3	14.2
PV	14.1	2.2	15.6

Table 3 *Mean difference and limits of agreement (the range within which approximately 95% of the differences between observer 1 and observer 2 lie) relative to the four locations; FL-UV, free-floating loop of the umbilical vein; IA-UV, intra-abdominal part of the umbilical vein at the entrance into the abdomen; US, umbilical vein; PV, left portal vein between the right portal vein and the umbilical sinus*

Location	*Mean difference*	*p value*	*Limits of agreement*
FL-UV	1.18	0.03	-5.05 , 7.34
IA-UV	2.06	0.01	-7.99 , 12.13
US	1.88	0.04	-3.28 , 7.05
PV	0.67	0.47	-7.74 , 9.08

5.2.5 Discussion

In most studies Doppler flow velocity waveforms were obtained from the free-floating loop of the umbilical vein and no account was taken of the waveform reproducibility at this or any other location along the umbilical vein.

Our data suggest differences in flow velocity at different standardized recording locations. Data from the intra-abdominal part of the umbilical vein at the entrance into the abdomen are similar to those reported by van Lierde and colleagues (1984), but lower than those collected by Griffin and co-workers (1985) and Erskine and associates (1985) with velocities ranging between 20 and 50 cm/s. This may be due to the higher insonation angle (30°- 60°) and variable Doppler sample positioning in the latter studies.

Measurement of umbilical venous flow velocities just inside the fetal abdomen (location IA-UV) may not be ideal since the waveform patterns at this location are less consistent as a result of the cranial-to-caudal course of the vessel. Moreover, the acquisition of waveforms at this location may be difficult as a result of obstruction of the Doppler beam by the lower limbs. There is no clear explanation for the systematic differences in flow velocity at location US. It is unlikely that the systematic differences in mean velocity at both locations IA-UV and US resulted from fetal movements, since these movements occur at random.

The higher mean flow velocity at the intra-abdominal location of the umbilical vein in comparison with the free-floating loop and the umbilical sinus may be explained by a difference in vessel diameter at the entrance of the umbilical vein into the abdomen. To our knowledge, no data are available on vessel diameter at this level.

Large coefficients of variation for recordings were established at all four measuring points. Since a systematic variation could be demonstrated for obtaining Doppler flow velocities at locations IA-UV and US, coefficients of variation from these locations should not be interpreted. For location FL-UV, large coefficients of variation were also reflected by the wide range of variation in data from both observers. This is an important finding, for this measurement is often performed and is so easy to obtain. Apparently, standardization of sample volume placement in this study was not precise enough. A large intra-patient variance may also be attributed to the normal biological variation of umbilical blood flow.

Location PV seems to be the most reliable recording site for obtaining venous flow velocity waveforms. The clinical significance, however, has not yet been established.

The presence of pulsations in the umbilical vein in the absence of fetal breathing is considered to be abnormal (Gudmundsson et al., 1991; Indik et al., 1991), except in early pregnancies (Rizzo et al., 1991a). Umbilical venous pulsations have been observed in small-for-

gestational age fetuses and during fetal bradycardia and tachycardia (Indik et al., 1991) as well as in non-immune hydrops (Gudmundsson et al., 1991). These findings have been attributed to an increased reverse flow into the inferior vena cava during atrial contraction. In fetal lambs, umbilical vein pulsations have been established following cord occlusion (Hasaart and de Haan, 1986; Abitbol et al., 1992). It has been suggested that in normal conditions the pulsations in the venae cavae, which are modulated by cardiac cycle length and respiratory movements, are not large enough to be propagated via the ductus venosus to the umbilical vein. However, in our study, umbilical venous pulsations were demonstrated in normal late pregnancies. This is supported by studies in normal fetal sheep, in which minimal flow pulsations have been observed in the umbilical vein as well as increased pulsatility under conditions which modulate the amplitude of phasic flow pattern in the inferior vena cava (Reuss et al., 1983).

Our study demonstrated umbilical venous and left portal venous pulsations in normal pregnancies. The venous pulsations at locations US and PV were shown to be synchronous to fetal heart rate. The incidence of venous pulsations were more or less equal for the umbilical sinus and left portal vein. This is in contrast with a recent report (Nimrod et al., 1992) in which a monophasic continuous flow pattern in the umbilical vein, as well as in the portal venous system, has been described. Under normal circulatory conditions, most of the veins are compressed by surrounding tissues. This compression causes resistance to damp out the pulsations. Backward transmission of pulses occurs to some extent in the normal circulation. Pulsatile flow patterns have been reported for the ductus venosus and inferior vena cava resulting from right atrial contraction and relaxation (Huisman et al., 1991). It seems plausible that pulsations in venous vessels further from the heart, such as the umbilical sinus and left portal vein, are caused by the same mechanism.

The fact that no association existed between the presence of pulsations at locations US and PV is probably due to the variability in propagation of the pulsations. It is our impression, therefore, that the significant associations between locations FL-UV and IA-UV and between locations IA-UV and US are probably coincidental.

It can be concluded that the occurrence of umbilical venous pulsations should be interpreted with caution. We demonstrated that umbilical venous and left portal venous pulsations even occur in normal late pregnancy. Difficulty in standardizing the recording site as well as the individual variations in umbilical venous flow velocity may be responsible for the large intrapatient coefficients of variation and limits of agreement between observers. The left portal vein seems to be the most reliable recording site for obtaining flow velocity waveforms. In future studies the limited reproducibility of umbilical venous blood flow velocity waveforms should be taken into consideration.

5.3 Atrioventricular, venous and arterial flow velocity waveforms in the small-for-gestational age fetus.

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5.3.1 Summary

Arterial, venous and intracardiac Doppler flow velocity waveforms were studied in 35 SGA fetuses and normal controls matched for gestational age and maternal parity according to a cross-sectional study design.

Statistically significant differences in baseline characteristics were found between the two subsets. The Pulsatility Index in the umbilical artery and descending aorta was significantly higher in the SGA fetus, but lower in the middle cerebral artery. At atrioventricular and venous level (umbilical vein, ductus venosus and inferior vena cava) reduced time-averaged velocities were established in the SGA fetus. In both subsets, transtricuspid flow velocity waveforms were significantly higher than at transmitral level. The Pulsatility Index for Veins in all three venous vessels showed a statistically significant increase in the SGA fetus, when compared to normal controls. No relation could be established between arterial downstream impedance and (i) atrioventricular flow velocities and (ii) Pulsatility Index for Veins in all three venous vessels. No relationship existed between flow velocity waveforms and pregnancy-induced hypertension and admission to the Neonatal Intensive Care Unit. Umbilical venous pulsations and absent/reverse flow in the umbi-lical artery were associated with a high intrauterine mortality rate and low birth weights. Umbilical artery PI and middle cerebral artery/descending aorta PI ratio were most predictive for SGA.

In the SGA fetus, marked changes in arterial, atrioventricular and venous flow velocity waveforms are established. Atrioventricular and venous flow velocity waveforms change independently from arterial downstream impedance, indicating that other factors, such as reduced volume flow, may play a role in the observed changes.

5.3.2 Introduction

Doppler ultrasonography has shown increased downstream impedance at placental and fetal trunk level (Trudinger et al., 1985; Groenenberg et al., 1989) in the small-for-gestational age (SGA) fetus, whereas a brainsparing effect has been demonstrated at the level of the internal carotid and middle cerebral artery (van den Wijngaard et al., 1989; Noordam et al., 1994). Also, a fall in cardiac output and alterations in left ventricular function have been described (Reed et al., 1987; Rizzo and Arduini, 1991). Recently, fetal coronary blood flow has been suggested to be a possible indicator of severe compromise of the SGA fetus (Bembruch and Baschat, 1996). Changes have also been described for venous flow velocity waveforms. Increased reverse flow in the inferior vena cava during atrial contraction has been reported (Rizzo et al., 1992), suggesting changes in cardiac function. Normal ductus venosus peak systolic velocities have been found in association with increased pulsatility index values in the umbilical artery (Kiserud et al., 1994), suggesting maintenance of preferential bloodstreaming through the ductus venosus during placental haemodynamic compromise. It can be concluded that there is a large body of information on the separate components of the abnormal circulation in the SGA fetus. However, only a few studies are available, which combine flow velocity waveforms recordings at arterial, cardiac and venous level (Hecher et al., 1995b). Insight into the intricate relationship between flow velocity waveform changes at different locations of the circulation in the SGA fetus may aid in the understanding of underlying mecha-nisms responsible for these changes.

We, therefore, set out in a cross-sectional study design, to establish the relationship between arterial, cardiac and venous flow velocity waveforms in the SGA fetus and normal controls; to compare these waveforms between both subsets; to relate flow velocity waveforms to pregnancy-induced hypertension and pregnancy outcome; and to determine the significance of flow velocity waveforms in the prediction of the SGA fetus.

5.3.3 Methods

Subjects

This study was performed over a period of 18 months in the Department of Obstetrics and Gynaecology of the University Hospital Rotterdam-Dijkzigt, which serves as a tertiary referral centre for cases of fetal growth retardation. It consisted of 45 women with a singleton pregnancy, who all consented to participate in the study. The study protocol was approved by

the Hospital Ethics Committee. SGA was defined as a sonographic fetal upper abdominal circumference below the 5th centile for gestational age (Snijders and Nicolaides, 1994). A detailed anomaly scan revealed no structural abnormalities. In 35 cases SGA was confirmed by the delivery of an infant below the 5th centile for gestational age according to the Kloosterman's tables corrected for parity and fetal sex (Kloosterman, 1970). The remaining 10 infants with a birth weight above the 5th centile were removed from the study. All infants were structurally normal. Gestational age at entering into the study ranged between 21 and 34 weeks of gestation (mean 29 wks) and maternal age varied between 17 and 34 years (mean 26 yrs). Thirty-three women were nulliparous.

Thirty-five singleton pregnancies studied within the same time frame, displaying a fetal abdominal circumference between the 10th and 90th centiles for gestational age and a birth weight between 10th and 90th centile for gestational age according to Kloosterman's tables (1970) served as matched controls. These women were selected from out-patients of the Department of Obstetrics and Gynaecology of the University Hospital Rotterdam-Dijkzigt. Matching took place with respect to gestational age and maternal parity.

Pregnancy duration was determined from the last reliable menstrual period and confirmed by ultrasonic measurement of the crown-rump length (8-12 wks) or biparietal diameter (12-20 wks). Pregnancy-induced hypertension was defined as a diastolic blood pressure of 90 mmHg or more during the second half of pregnancy in a previously normotensive woman. An abnormal fetal heart rate tracing was defined as the presence of late decelerations and a heart rate band width of less than 10 bpm. Each woman was included in the study only once. Baseline characteristics of all pregnancies are provided in Table 1.

An abnormal heart rate tracing at delivery was established in 19 out of 27 (70%) SGA fetuses versus 1 out of 35 (3%) normal controls. Caesarian section was carried out in 23 (66%) SGA fetuses because of an abnormal heart rate tracing, and in 5 (14%) controls because of abnormal heart rate tracing (n=4) or previous fibroid resection (n=1). Pregnancy-induced hypertension was present at the time of the Doppler study in 19 (54%) SGA fetuses, whereas 3 (8%) developed hypertension at a later stage. Twenty (57%) out of 35 SGA fetuses were admitted to a Neonatal Intensive Care Unit versus none in the normal control group. Eight cases (23%) from the SGA subset ended in intrauterine death between 21 and 31 weeks of gestation. Twenty-four (69%) SGA fetuses had a birth weight <2.3 centile corrected for parity and fetal sex. Fetal outcome according to the umbilical artery pH and Base Excess was not essentially different for the two subsets.

Doppler recordings

Ultrasound Doppler studies were performed using a Hitachi EUB 450 combined transabdominal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time) and 3.0 MHz (Doppler)(Hitachi Medical Corp., Tokyo, Japan). The system operates at power outputs of less than 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. Doppler recordings were performed by one examiner (IPvS). Doppler data were blinded to the obstetric staff of the referring hospital.

At arterial level flow velocity waveforms were obtained from the descending aorta, middle cerebral artery and umbilical artery. Flow velocity waveforms from the thoracic part of the descending aorta were recorded from a sagittal cross-section through the fetal trunk, displaying a major section of the fetal spine (Eik-Nes at al., 1980). Middle cerebral artery flow velocity waveforms were obtained from a transverse section through the lower part of the fetal cerebrum. The middle cerebral artery can be required as a major branch of the circle of Willis running anterolaterally towards the edge of the orbit (Wladimiroff et al., 1986). Umbilical artery flow velocity waveforms were obtained from a straight section of the free-floating loop of the umbilical cord.

Flow velocity waveforms at atrioventricular level were obtained from the cardiac "four chamber" view. Cardiac anomalies were ruled out. The Doppler sample volume was placed immediately distal to the mitral and tricuspid valve. Blood flow velocity recordings through the foramen ovale were made either from a "four-chamber" view or a modified short-axis view (van Eyck et al., 1990). The sample volume was placed across the septal opening.

At venous level flow velocity waveform recordings were obtained from the extra-abdominal umbilical vein, ductus venosus and inferior vena cava. Flow velocity waveforms from the umbilical vein were collected from a free-floating loop of the umbilical cord. The sample volume was placed over a straight section of the cord. The fetal ductus venosus is localized in the liver, approximately between the right and left liver lobe. Its course is from caudal to cranial, from ventral to dorsal and slightly oblique to the left. It originates from the ventral side of the umbi-lical sinus and joins the inferior vena cava close to the right atrium. The sample volume was placed immediately above the umbilical sinus, visualised in a transverse cross-sectional view (Huisman et al., 1992). Inferior vena cava flow velocity flow velocity waveforms were recorded in a sagittal view, which included the fetal right atrium, right ventricle and ascending aorta (Reed et al., 1990).

The angle of insonation for the descending aorta was less than 45 degrees, for the middle cerebral artery, atrioventricular valves and venous vessels less than 30 degrees and for the foramen ovale less than 20 degrees. Sample volume length for all flow velocity waveform

recordings ranged between 0.2 and 0.4 cm; the high pass filter was set at 100 Hz. All Doppler studies were performed with the women in the semirecumbent position and during fetal apnoea, since the latter may modulate flow velocity waveforms (Maršàl et al., 1984). The total examination time was limited to 20 minutes in each instance. All flow velocity waveforms were recorded on hard copies. Waveform analysis was performed by one examiner (IPvS) using a microcomputer (Olivetti M24; Olivetti B.V., Leiden, The Netherlands) linked to a graphics tablet.

The degree of pulsatility in the descending aorta, the umbilical artery and middle cerebral artery was expressed by the Pulsatility Index (PI) as calculated according to Gosling et al. (1975). Peak systolic (PSV; cm/s), end-diastolic (EDV; cm/s) and time-averaged velocities (TAV; cm/s) were determined in the descending aorta and middle cerebral artery.

Analysis of the atrioventricular waveforms consisted of calculation of (i) time-averaged velocity (cm/s), (ii) peak velocity (cm/s) of E-wave (passive atrial filling) and A-wave (atrial contraction) and (iii) E/A ratio. The foramen ovale waveform consists of two components: (i) peak systolic velocity and (ii) peak diastolic velocity coinciding with passive atrial filling (van Eyck et al., 1990). Flow velocity decreases to zero during atrial contraction. Extra-abdominal umbilical venous pulsations were defined as at least three consecutive negative deflections of the venous waveform each comprising at least 10% of the time-averaged velocity and synchronous to fetal heart rate. In all recordings displaying umbilical venous pulsations, maximal velocity (cm/s), minimal or late diastolic velocity coinciding with atrial contraction (a; cm/s), and time-averaged velocity (cm/s) were determined for three consecutive cardiac cycles from the maximum frequency envelop. In case of umbilical venous waveforms without pulsations, the time-averaged velocity was analyzed at three different measuring points on the maximum frequency envelop in the continuous flow velocity waveform. Waveform analysis in the ductus venosus and the inferior vena cava consisted of calculation of (i) peak velocity (cm/s) during both systole (S) and diastole (D) and (ii) time-averaged velocity (TAV; cm/s). Moreover, the late diastolic flow velocity component coinciding with atrial contraction, was determined in the ductus venosus as minimal forward velocity (a; cm/s) and in the inferior vena cava as peak reverse velocity (a; cm/s). In the inferior vena cava time-velocity integral as expressed by the percentage of total forward flow was calculated. The degree of pulsatility in all three venous vessels, reflecting preload at venous level, was determined according to the following equation: PIV=(S-a)/TAV, in which PIV = Pulsatility Index for Veins, S = peak systolic velocity, a = late diastolic velocity and TAV = time-averaged velocity (Hecher et al., 1995b). Three consecutive flow velocity waveforms with the highest velocity and similar appearance were used to calculate the different parameters in each vessel.

Data analysis

Partial correlation coefficients were calculated to assess in both subsets the for gestational age adjusted relationship between the pulsatility index in the umbilical artery and descending aorta and (i) atrioventricular flow velocity waveform parameters and (ii) flow velocity waveform recordings in the umbilical vein, ductus venosus and inferior vena cava. Partial correlation coefficients were calculated to determine the interrelationship between the Pulsatility Index for Veins in (i) the umbilical vein and ductus venosus and (ii) in the ductus venosus and inferior vena cava. For comparison between SGA fetuses and normal controls, the paired *t*-test and Mc Nemar's test were used for continuous and dichotomous variables, respectively.
Student's *t*-test and the Fisher exact test were used to compare independent groups for continuous and dichotomous variables, respectively. Logistic regression was used to estimate within the SGA fetus the association between flow velocity waveform parameters and the dependent variables: pregnancy-induced hypertension, intra-uterine death, caesarian section rate and admission to the Neonatal Intensive Care Unit. Taking a cut-off level of 14 days for relating velocity Doppler data to fetal heart rate tracings from SGA fetuses, the number of abnormal tracings was too small (n=5) for statistical analysis. Relating flow velocity data to the mode of delivery was also not possible due to the small number of vaginal deliveries (n=4) in this subset.

All Doppler parameters were converted into standard deviations scores (SD-scores). This score was obtained by taking the difference between the observed value and the predicted value according to gestational age and dividing the result by the standard deviation of the normal control values. Receiver Operating Characteristics (ROC) curves, graphically depicting the sensitivity versus the false positive rate for various SD cut-off levels, were constructed.

Data are presented as mean $\pm$ 1 SD. Statistical significance was tested at the level of 0.05.

5.3.4 Results

Statistically significant differences were found between SGA fetuses and normal controls for incidence of pregnancy-induced hypertension, abnormal fetal heart rate tracing at Doppler survey and delivery, caesarian section rate, gestational age at delivery, birth weight, Apgar score at 1 minute, placental weight and admission to the Neonatal Intensive Care Unit (Table 1). In five normal controls umbilical artery PI at delivery was below 7.18 and the base excess below -10 mEq/l as a result of prolonged labour without previous signs of placental insufficiency. When excluding these five cases from the analysis, a statistically significant difference was

Table 1 Baseline characteristics of small-for-gestational age (SGA) fetuses and normal controls

	SGA (n=35)			Normal (n=35)					
	Mean	SD	Range	Mean	SD	Range	Significance of difference (*p*)	Paired difference	95% CI
Gestational age at survey (wks)	29	3.13	21-34	29	2.94	21-34	NS		
Gestational age at delivery (wks)	31	3.88	21-38	39	1.80	34-42	=0.001	-7.5	[-9.4 , -5.5]
Lag-time between survey and delivery (wks)	2	2.18	1 day-7 wks	10	3.69	3-16 wks	<0.001	-7.5	[-9.4 , -5.6]
Birth weight (g)	926	490	140-2420	3120	537	2250-4005	<0.001	-2214	[-2471 , -1808]
Apgar at 1 minute	6	2.39	1-9	8	1.38	3-9	0.04	-1.2	[-2.3 , -0.0]
5 minutes	8	1.08	6-10	9	0.84	7-10	NS		
10 minutes	9	0.62	8-10	9	0.55	8-10	NS		
Umbilical artery pH	7.20	0.09	7.00-7.35	7.21	0.14	6.88-7.39*	NS		
Umbilical artery base excess (mEq/l)	-6.16	3.54	-14.00-0	-8.99	6.31	-24.8-(-1.1)*	NS		
Placental weight (g)	238	96	100-490	581	312	350-780	<0.001	-356	[-445 , -267]
Maternal age (yrs)	26	4.22	17-34	26	5.55	17-39	NS		

	Ceasarian section rate		Pregnancy-induced hypertension		Abnormal fetal heart rate trace at survey		Abnormal fetal heart rate trace at delivery		Admission to Neonatal Intensive Care Unit (NICU)	
	n	*p*-value	n	*p*-value	n	*p*-value	n	*p*-value	n	*p*-value
SGA	23	<0.001	19	<0.001	5	<0.001	19	<0.001	20	<0.001
Normal control subjects	5		3		0		1		0	

95% CI = 95% Confidence Interval

* 5 cases of prolonged labour presented with umbilical artery base excess < -10 mEq/l and pH ≤ 7.18

established between SGA fetuses and normal controls for pH (7.20 ± 0.09 vs. 7.26 ± 0.04; p-=0.005) and Base Excess (-6.16 ± 3.54 mEq/l vs. -1.96 ± 2.79 mEq/l; $p<0.001$).

Relationship between arterial, venous and atrioventricular flow velocity waveforms in the SGA fetus and normal controls (Tables 2-4)

Both in SGA fetuses and normal controls, no significant correlation could be established between the umbilical artery and descending aorta pulsatility index and atrioventricular and foramen ovale flow velocities, when adjusted for gestational age.

In normal controls, transtricuspid flow velocities were significantly higher than transmitral flow velocities for E-wave (mean difference -4.70, SD 5.53, $p<0.001$) and time-averaged velocities (mean difference -2.31, SD 5.52, $p=0.03$). No such relationship could be established for A-wave velocity and E/A ratio. In the SGA fetuses, transtricuspid flow velocities were significantly higher than transmitral flow velocities for A-wave velocity (mean difference -3.26, SD 7.33, $p=0.02$) and time-averaged velocity (mean difference -1.06, SD 2.83, $p<0.05$). No relationship existed for E-wave velocity and E/A ratio.

There was no significant correlation between arterial flow velocity waveforms and venous inflow parameters as expressed by umbilical venous, ductus venosus and inferior vena cava pulsatility index for veins in both SGA fetuses and normal controls. Umbilical venous pulsations were present in 17 (45%) out of 45 SGA fetuses. After adjustment for gestational age, a statistically significant positive correlation was established between the PIV in the ductus venosus and inferior vena cava in SGA fetuses ($r=+0.74$; $p<0.001$) and in normal controls ($r=+0.43$; $p<0.05$). In the SGA fetus also, a statistically significant correlation was found between the PIV in the ductus venosus and umbilical vein ($r=+0.72$; $p=0.006$).

When dividing umbilical artery end-diastolic velocities into present and absent (including 11 cases of reverse flow), a statistically significant difference was established for flow velocity parameters from the descending aorta, inferior vena cava and umbilical vein (Table 5). Similarly, when dividing umbilical venous pulsations into present and absent, a statistically significant difference was observed for umbilical artery PI and inferior vena cava velocity parameters (Table 6).

Comparison of flow velocity waveforms between SGA fetuses and normal controls (Tables 2-4)

A statistically significant difference was established for all flow velocity waveform parameters, except for (i) peak systolic velocity in the middle cerebral artery, (ii) all foramen ovale parameters, (iii) transmitral and transtricuspid E/A ratio, (iv) mean difference in time-averaged velocity between transmitral and transtricuspid flow velocity waveforms, (v) PIV, peak systolic

Table 2 Arterial flow velocity waveform parameters in SGA fetuses and normal controls

	SGA (n=35)			Normal (n=35)					
	Mean	SD	Range	Mean	SD	Range	Significance of difference (*p*)	Paired difference	95% CI
Umbilical artery (UA)									
PI	2.44	1.18	1.15-6.72	1.11	0.20	0.77-1.41	<0.001	1.33	[0.92 , 1.75]
Descending aorta (Ao)									
PI	2.49	0.99	1.51-5.65	1.71	0.23	1.37-2.33	<0.001	0.81	[0.41 , 1.20]
PSV (cm/s)	48.23	12.13	29.52-81.98	62.57	16.11	16.43-91.13	=0.001	-14.34	[-22.48 , -6.20]
TAV (cm/s)	20.79	6.96	8.42-42.56	31.33	7.92	10.77-46.93	<0.001	-10.53	[-13.94 , -7.13]
EDV (cm/s)	5.24	8.61	0-40.84	11.96	4.77	5.24-32.08	0.002	-6.28	[-9.98 , -2.58]
Middle cerebral artery (MCA)									
PI	1.20	0.27	0.86-1.65	1.84	0.38	1.21-2.42	<0.001	-0.59	[-0.81 , -0.38]
PSV (cm/s)	34.17	9.33	20.32-54.13	30.16	8.78	14.11-41.79	NS		
TAV (cm/s)	20.10	5.36	12.76-33.71	14.10	3.52	7.49-17.86	0.003	6.27	[2.51 , 10.03]
EDV (cm/s)	10.15	3.33	4.90-19.31	5.59	2.38	1.54-12.80	0.003	4.55	[1.85 , 7.25]
Ratio Ao/UA PI	1.10	0.35	0.69-2.08	1.58	0.31	0.98-2.36	<0.001	-0.47	[-0.65 , -0.30]
Ratio MCA/Ao PI	0.56	0.21	0.32-0.45	1.10	0.24	0.72-1.45	<0.001	-0.53	[0.41 , 0.65]
Ratio MCA/UA PI	0.55	0.24	0.26-1.04	1.72	0.56	1.01-2.94	<0.001	-1.13	[-1.40 , -0.86]

CI = conficence interval; PI = Pulsatility Index; PSV = peak systolic velocity; TAV = time-averaged velocity; EDV = end-diastolic velocity

and peak diastolic velocity in the inferior vena cava. Statistical analysis of the PIV from the extra-abdominal umbilical vein was not possible due to the small number (n = 1) of normal controls with umbilical venous pulsations. Reverse flow in the ductus venosus was demonstrated in two SGA fetuses.

Comparison of flow velocity waveforms between SGA fetuses and normal controls was not essentially different when taking into account the pregnancy period before and after 32 weeks of gestation.

Flow velocity waveform parameters in SGA fetuses relative to pregnancy-induced hypertension and fetal outcome

Within the subset of 35 SGA fetuses, there was no relationship between fetal velocity waveforms and pregnancy-induced hypertension (n=19) or admission to the Neonatal Intensive Care Unit (n=20). Of the 11 cases of umbilical artery reverse flow, five were diagnosed as intrauterine death (45%) within 2 to 35 days following Doppler measurement (median 10 days). A statistically significant difference between umbilical artery end-diastolic flow velocities present and absent, including reverse flow) was established for (i) gestational age at delivery (34 ± 2.8 wks vs. 29 ± 2.9 wks; $p<0.001$), (ii) birth weight (1279 ± 485 g vs. 661 ± 292 g; $p<0.001$) and (iii) Apgar score at 1 minute (6 ± 2.2 vs. 4 ± 2.5 vs; $p=0.02$). A statistically significant difference between umbilical venous pulsations present and absent was observed for: (i) gestational age at delivery (29 ± 3.6 wks vs. 33 ± 3.2 wks; $p=0.002$) and (ii) birth weight (698 ± 366 g vs. 1212 ± 517 g; $p=0.003$). Of all 17 fetuses with umbilical venous pulsations, 44% died in utero within 2 to 35 days following Doppler measurement (median 13 days), whereas there was 100 % fetal survival without umbilical venous pulsations.

There were two cases of reverse flow in the ductus venosus, both resulting in intrauterine death. The percentage reverse flow in the inferior vena cava was significantly higher ($p=0.03$) in fetuses associated with intrauterine death (mean 23.34 ± 12.87%), when compared with fetal survival (mean 12.37 ± 4.33%).

Flow velocity waveforms in the prediction of the SGA fetus

Figure 1 displays ROC-curves for the five most sensitive flow velocity parameters for the prediction of SGA in this study. Umbilical artery PI displays a sensitivity and specificity of 97% and 89% at +1 SD score, and of 80% and 97% at +2 SD score. For the middle cerebral artery PI a sensitivity and specificity of 67% and 79% was found at -1 SD score and of 33% and 100% at -2 SD score. For late diastolic velocity in the ductus venosus, a sensitivity and specificity was established of 74% and 78% at -1 SD score and of 37% and 92% at -2 SD

score. A sensitivity and specificity was established for the ratio (i) between the middle cerebral artery and descending aorta PI of 85% and 81% at +1 SD score and of 69% and 100% at +2 SD score and (ii) between the middle cerebral artery and umbilical artery PI of 60% and 82% at +1SD score and of 0% and 100% at +2 SD score.

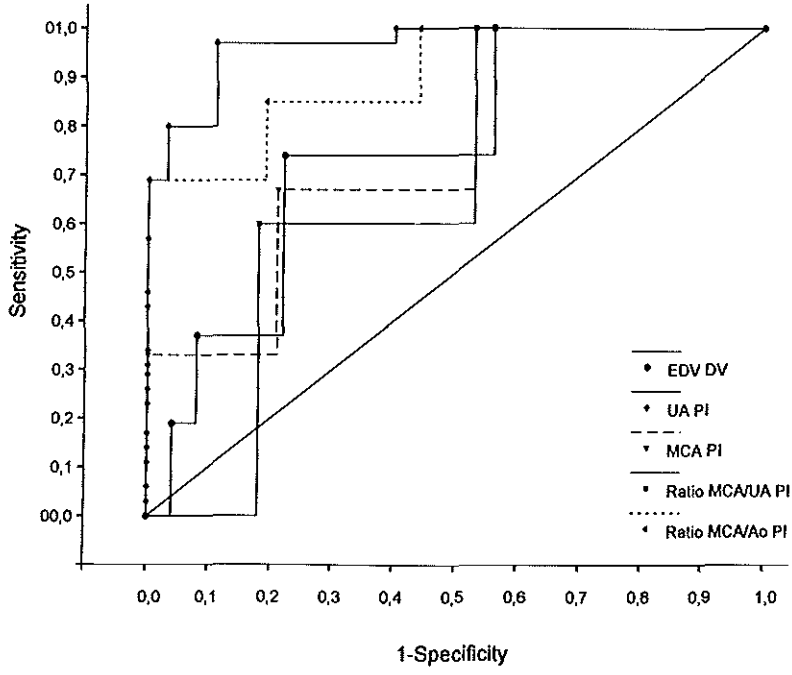

Figure 1 *Receiver Operating Characteristics (ROC) curves of the umbilical artery pulsatility index (UA PI), middle cerebral artery pulsatility index (MCA PI), ratio between MCA PI and UA PI (ratio MCA/UA), ratio between MCA PI and descending aorta pulsatility index (ratio MCA/Ao) and end-diastolic velocity in the ductus venosus (EDV). The diagonal line represents an imaginary test which has no discriminative power.*

Table 3 Atrioventricular and foramen ovale flow velocity waveform values in SGA fetuses and normal controls

	SGA (n=35)			Normal (n=35)					
	Mean	SD	Range	Mean	SD	Range	Significance of difference (p)	Paired difference	95% CI
Mitral valve									
E wave (cm/s)	29.00	5.54	18.72-41.86	35.41	6.64	21.72-50.00	<0.001	-6.43	[-9.53 , -3.32]
A wave (cm/s)	37.23	6.11	25.88-48.74	46.42	7.06	32.74-62.12	<0.001	-9.18	[-13.05 , -5.32]
TAV (cm/s)	12.49	2.96	7.99-19.82	14.96	2.10	10.50-19.54	0.001	-2.47	[-3.80 , -1.14]
E/A ratio	0.76	0.06	0.62-0.87	0.76	0.08	0.57-0.89	NS		
Tricuspid valve									
E wave (cm/s)	31.70	6.58	22.29-48.31	40.39	6.77	25.34-60.42	<0.001	-8.68	[-11.26 , -6.11]
A wave (cm/s)	40.55	7.31	29.55-58.49	50.24	11.01	26.27-75.55	<0.001	-9.18	[-13.60 , -5.77]
TAV (cm/s)	13.49	3.14	8.96-20.48	16.30	2.20	10.04-23.01	<0.001	-2.80	[-3.96 , -1.67]
E/A ratio	0.78	0.07	0.61-0.90	0.77	0.05	0.67-0.89	NS		
Foramen ovale									
PSV (cm/s)	28.44	6.38	14.87-38.11	27.10	3.80	17.84-31.42	NS		
PDV (cm/s)	19.75	6.23	10.22-29.94	16.62	3.47	12.32-23.07	NS		
TAV (cm/s)	16.11	4.84	8.25-28.47	16.14	2.78	11.52-21.22	NS		

CI = confidence interval; PSV = peak systolic velocity; PDV = peak diastolic velocity; TAV = time-averaged velocity

Table 4 Venous flow velocity waveform values in SGA fetuses and normal controls

	SGA (n=35)			Normal (n=35)					
	Mean	SD	Range	Mean	SD	Range	Significance of difference (p)	Paired difference	95% CI
Umbilical vein TAV (cm/s)									
extra-abdominal	10.84	3.23	5.91-21.06	12.61	2.82	7.02-21.27	0.03	-1.81	[-3.41 , -0.21]
PIV (only SGA: n = 17)	0.35	0.31	0.10-1.42						
Inferior vena cava									
PSV (cm/s)	34.41	9.22	20.67-60.95	38.27	7.34	19.50-52.15	NS		
PDV (cm/s)	21.11	7.86	10.22-43.82	23.53	5.73	12.45-36.49	NS		
TAV (cm/s)	18.66	5.53	10.50-32.97	21.96	4.97	10.89-31.66	0.03	-3.30	[-6.24 , -0.36]
% reverse flow	15.11	8.64	5.0-15.1	7.77	3.41	3.5-14.9	<0.001	7.65	[4.44 , 10.85]
PIV	2.70	0.49	2.03-4.05	2.34	0.32	1.82-3.04	0.003	0.36	[0.13 , 0.59]
Ductus venosus									
PSV (S: cm/s)	51.76	17.64	17.64-87.47	62.07	12.68	36.35-82.27	0.03	-10.18	[-18.95 , -1.41]
PDV (D: cm/s)	44.55	16.37	14.24-82.09	56.17	11.84	30.04-77.62	0.007	-12.16	[-20.64 , -3.68]
TAV (cm/s)	38.98	14.60	11.29-71.57	52.13	11.25	26.31-71.77	0.001	-13.67	[-21.15 , -6.20]
EDV (cm/s)	18.60	12.18	0-44.32	33.99	8.94	13.69-51.58	<0.001	-15.68	[-22.12 , -9.24]
PIV	0.98	0.48	0.44-2.24	0.52	0.16	0.16-0.86	<0.001	0.41	[0.22 , 0.59]

CI = confidence interval; PSV = peak systolic velocity; PDV = peak diastolic velocity; TAV = time-averaged velocity; EDV = end-diastolic velocity; PIV = Pulsatility Index for Veins

Table 5 End-diastolic velocity in the umbilical artery relative to other flow velocity parameters in SGA fetuses

	EDV - (n=20)*		*EDV+ (n=15)*		
	Mean	*SD*	*Mean*	*SD*	*p-value*
Descending aorta PI	2.91	1.10	1.92	0.38	0.002
Inferior vena cava					
PSV (cm/s)	30.79	7.11	39.68	9.65	0.005
PDV (cm/s)	18.38	7.08	25.09	7.45	0.02
TAV (cm/s)	16.30	4.69	22.10	4.93	0.002
Umbilical vein					
TAV (cm/s)	9.50	2.31	12.69	3.50	0.005

EDV = end-diastolic velocity; PSV = peak systolic velocity; PDV = peak diastolic velocity; TAV = time-averaged velocity

* including 11 cases of end-diastolic reverse flow

Table 6 Extra-abdominal umbilical venous pulsations relative to other flow velocity parameters in SGA fetuses

	Present (n=17)		*Absent (n=14)*		
	Mean	*SD*	*Mean*	*SD*	*p-value*
Umbilical artery PI	3.14	1.30	1.76	0.50	0.001
Inferior vena cava					
PSV (cm/s)	31.61	9.32	39.24	6.70	0.03
PDV (cm/s)	17.56	5.11	26.64	8.02	0.001
TAV (cm/s)	16.61	4.55	22.65	5.20	0.003

5.3.5 Discussion

Second and early third trimester data are presented from a cross-sectional study of flow velocity waveforms at arterial, intracardiac and venous level in normally developing and small-for-gestational age fetuses. Characterization of functional aspects of the fetal cardiovascular system is of importance in the eventual understanding of normal and abnormal fetal hemodynamics. However, the contribution of Doppler flow velocity waveforms to our knowledge of fetal hemodynamics has its limitations, since no information is available on pressure or volume flow. Moreover, measuring cross-sectional vessel areas, particular in pulsating arteries, puts a restriction on the implication of Doppler ultrasound. Nevertheless, both angle independent and angle dependent Doppler assessment of flow velocity waveforms provide useful information on circulatory changes in the developing fetus.

Normal fetal development is characterized by a low feto-placental vascular resistance with the objective to maintain optimal supply of oxygen and nutrients to the fetus. At cardiac level, flow velocities across the atrioventricular valves are higher during atrial contraction (A-wave) than during early diastolic filling (E-wave). Also, time-averaged velocities at tricuspid valve level are significantly higher than at mitral valve level. Since volume flow is equal to time-averaged velocity times cross-sectional vessel area, these data suggest right ventricular predominance during normal pregnancy. Throughout the cardiac cycle, right to left flow is present at the foramen ovale with time-averaged velocities slightly higher than at atrioventricular level.

Preferential streaming of highly oxygenated blood takes place from the placenta through the umbilical vein, ductus venosus and foramen ovale into the left heart ensuring optimal oxygen supply to the brain and myocard, whereas blood from the inferior vena cava is mainly directed to the right heart. In the fetal lamb, the ductus venosus acts as an important regulator of the venous circulation (Edelstone et al., 1978). In the present study of normal controls, mean time-averaged velocity in the ductus venosus (52.1 cm/s) is more than two-fold of that in the inferior vena cava (22.0 cm/s) and four-fold of that in the extra-abdominal umbilical vein (12.7 cm/s). The relatively high velocities in the ductus venosus are determined by the narrow vessel size which will never exceed 2 mm. From the pulsatility index for veins an estimate of cardiac preload can be obtained, reflecting ventricular end-diastolic pressure. The positive correlation between the Pulsatility Index for Veins in the ductus venosus and inferior vena cava in both subsets is explained by the equal effect of right ventricular end-diastolic pressure changes on flow in these two vessels in the presence of a closed foramen ovale (van Eyck et al., 1990). The increase in Pulsatility Index for Veins in the SGA fetus may be attributed to the marked

reduction in flow velocity during atrial contraction in the presence of relatively high peak systolic and peak diastolic flow velocities, suggesting increased end-diastolic ventricular pressure. In fetal hypoxia increased downstream impedance would result in increased ventricular afterload and ventricular end-diastolic pressure. However, in the present study, the Pulsatility Index for Veins in all three venous vessels appears to be independent of arterial downstream impedance as expressed by descending aorta and umbilical artery PI, suggesting other factors to play a role in changes in cardiac preload.

Comparing small-for-gestational age fetuses and normal controls, a difference was established in incidence of abnormal maternal conditions such as pre-eclamptic toxaemia, mode of delivery and fetal outcome as expressed by fetal heart rate tracings at delivery, Apgar score at 1 minute and admission to the Neonatal Intensive Care Unit. In the small-for-gestational age fetus, increased resistance to flow is demonstrated in the umbilical arteries and descending aorta, but a reduced resistance to flow is found in the middle cerebral artery, suggesting brain-sparing. Also, time-averaged and end-diastolic velocities were raised in the latter vessel as opposed to reduced velocities in the descending aorta, reflecting centralization of the fetal circulation, which is supposed to be mediated by arterial chemoreceptors (Bartelds et al., 1993).

Reduced transmitral and transtricuspid flow velocities were observed in the small-for-gestational age fetus which is consistent with other studies (Reed et al., 1986; Stoddard et al., 1989) and are similar to earlier data on flow velocities from the ascending aorta, pulmonary artery and ductus arteriosus (Groenenberg et al., 1989). There are several explanations for the reduced atrioventricular and cardiac outflow tract velocities in fetal growth retardation. Firstly, a decrease in time-averaged velocity may be secondary to a decrease in volume flow. Secondly, a change in cardiac ventricular contractility could result in changes in time-averaged velocities. Another factor is arterial afterload which is determined by blood pressure and resistance. However, no relationship exists between atrioventricular flow velocities and downstream impedance as expressed by descending aorta and umbilical artery PI. Both arterial volume flow and blood pressure may change in parallel or opposite directions and may, therefore, result in alterations in transmitral and transtricuspid flow velocity waveform. Moreover, atrioventricular flow velocity waveforms may not change with afterload if other factors change simultaneously.

Our data suggest that right heart predominance is also present in fetal growth retardation. This is based on the time-averaged velocity relationship between mitral and tricuspid valves, which is not different from normal controls. This is further supported by the presence of normal flow velocities across the foramen ovale. This observation of right ventricular predominance is at variance with other authors (Reed et al., 1987; Rizzo et al., 1991b) who reported a shift of cardiac output in favour of the left heart in the small-for-gestational age fetus. A diffe-

rent hypoxemic state of the small-for-gestational age fetus at the time of Doppler investigation may explain this discrepancy. Whereas our cross-sectional study design does not allow information on serial flow velocity waveform changes, the present study demonstrates that centralization of the circulation may occur before changes in cardiac right/left relationship become evident. On the other hand, both absent or reverse end-diastolic flow velocities in the umbilical artery and pulsatile umbilical venous velocities, reflecting advanced fetal hypoxemia (Hecher et al., 1995c), are not associated with a shift to left heart predominance. No difference could be found in E/A ratios between small-for-gestational age and normally developing fetuses, indicating that E- and A-wave velocities are subject to a similar reduction in the presence of fetal growth retardation.

Reduced time-averaged velocities are shown in all three venous vessels in the small-for-gestational age fetus. Studies in normal late first and early second trimester pregnancies suggest that gestational age-related changes in flow velocities are mainly determined by volume changes associated with fetal growth (van Splunder et al., 1996). It is speculated, therefore, that the observed reduction in time-averaged velocities at venous, arterial and atrioventricular level in fetal growth retardation indirectly reflects a growth-related reduction in volume flow. This is further supported by the virtually unaltered time-averaged velocity relationship between the three venous vessels, when compared with normal controls. In contrast to the inferior vena cava, the pulsatility index for veins in the ductus venosus of the SGA fetus, displays a significant reduction when compared to normal controls, reflecting reduced preload in this vessel. This is at variance with the consistent time-averaged velocity relationship between the three venous vessels, described earlier. Direct volume flow and pressure data are needed to resolve this issue. It has been proposed that high placental resistance and vascular constriction at fetal trunk level will result in increased cardiac ventricular residual volume and end-diastolic pressure (Hecher et al., 1995c). To what extent the observed reduction in late diastolic velocities in the ductus venosus and increased reverse flow velocities in the inferior vena cava are due to these intracardiac changes and/or increased arterial downstream impedance is not yet clear. Also in fetal growth retardation no correlation could be established between arterial downstream impedance and cardiac preload, as expressed by umbilical artery and descending aorta PI and Pulsatility Index for Veins.

Absent or even reverse end-diastolic flow in the umbilical artery is accompanied by a further reduction in inferior vena cava and umbilical venous flow velocities. Fetal birth weight in this subgroup is approximately half of that in the presence of end-diastolic flow velocities even though a mean gestational age difference of 5 weeks may be responsible for most of this weight difference. Also, the Apgar score at 1 minute was lower in cases with absent or reverse

end-diastolic velocities, indicating fetal hypoxemia. One may speculate that next to diminished fetal growth, reduced myocardial contraction force associated with fetal hypoxemia may be responsible for the further deterioration of venous flow velocities. Intrauterine death occurred in nearly half of the cases with end-diastolic reverse flow in the umbilical artery, although in one instance the time-interval between Doppler recording of reverse flow and intrauterine death was as long as 35 days. Similar findings were done in the presence of umbilical venous pulsations. The high intrauterine mortality rate (44%) confirms results form other studies on umbilical venous pulsations in small-for-gestational age fetuses (Indik et al., 1991; Arduini et al., 1993; Hecher et al., 1995c).

The degree of hemodynamic adaptation to chronic hypoxemia as seen in intrauterine growth retardation (Hecher et al., 1995c) is related to fetal maturity, e.g. gestational age. However, in the present study velocity differences between small-for-gestational age fetuses and normal controls were not essentially different when comparing the pregnancy period before and after 32 weeks.

Our study design does not allow direct assessment of fetal compromise by Doppler flow velocity waveform investigation. Prediction of fetal growth retardation was, however, possible from the different fetal flow velocity waveforms. Following umbilical artery PI, middle cerebral artery/descending aorta PI ratio appears to display the highest sensitivity and specificity for detecting intrauterine growth retardation, emphasising the process of centralization of the circulation and brainsparing associated with fetal growth retardation. The predictive value of the end-diastolic ductus venosus flow velocity waveform with a sensitivity of only 37% at -2SD score is disappointing.

It can be concluded that marked cardiovascular changes occur in the small-for-gestational age fetus. Whereas there is a change from a low uteroplacental vascular resistance to a high vascular resistance at placental and fetal trunk level, redistribution of blood flow takes place in favour of the fetal brain. Flow velocity waveforms at cardiac and venous level change independently from downstream impedance suggesting other factors to play a role in these changes. Longitudinal studies will be needed to elucidate the natural history of cardiovascular changes in the small-for-gestational age fetus.

5.4 References

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Chapter 6

General conclusions

In this thesis the human fetal circulation was studied with combined two-dimensional real-time and pulsed Doppler ultrasound in early and late pregnancy, with emphasis on the impact of changing arterial downstream impedance on atrioventricular and venous flow velocity waveforms.

The late first and early second trimester of pregnancy

Transvaginal Doppler ultrasonography allows detailed information on flow velocity waveforms as early as 8 weeks of gestation. The late first trimester of pregnancy is characterized by absence of end-diastolic velocities in the umbilical artery and descending aorta, indicating high downstream impedance. As from 11 weeks of gestation end-diastolic velocities gradually appear, which may result from the process of angiogenesis in the developing placenta. At the same time, umbilical venous pulsations gradually disappear, which may be explained on a purely mechanical basis.

An increase in time-averaged velocities with advancing gestational age was observed for the umbilical vein, ductus venosus and inferior vena cava. Also, at atrioventricular level an increase was established for transmitral and transtricuspid flow velocity waveforms. A statistically significant relationship between logarithmically transformed crown-rump-length and transmitral and transtricuspid time-averaged velocities, suggests that an increase in volume flow in the early developing fetus may play a role in the observed increase in atrioventricular time-averaged velocities.

The Pulsatility Index for Veins reflects cardiac preload, whereas the Pulsatility Index in the umbilical artery and descending aorta reflects downstream impedance at fetal trunk and placental level. The absence of a relationship between these two pulsatility indices suggests that cardiac preload changes independently from arterial downstream impedance.

Doppler ultrasonography does not allow direct information on volume flow and pressure measurements. However, crude estimates on the pressure gradient across the ductus venosus can be made using the Bernoulli equation. Although displaying a rather wide data distribution, estimates on the pressure gradients may indicate that early fetal hemodynamics function at very low pressures.

Time-averaged velocities at mitral and tricuspid valve level increase with advancing gestational age. During the entire study period, transtricuspid flow velocity waveforms are higher than transmitral flow velocity waveforms, which may reflect right ventricular predominance as early as the late first and early second trimester of pregnancy. Also, the E/A ratio at

both mitral and tricuspid valve level shows a gestational age-related increase, suggesting a shift of blood flow from late diastole towards early diastole. The latter may result from increased ventricular compliance and/or raised ventricular relaxation rate. A change in ventricular compliance is supported by the reduction in atrial contribution to ventricular filling, at least between 10 and 14 weeks of gestation. As from 14 weeks of gestation atrial contribution to ventricular filling remains rather constant, suggesting that other factors than ventricular compliance play a role in the increase in E/A ratio. Further studies before 10 weeks of gestation are needed to elucidate the development in ventricular compliance in the human fetus.

Marked gestational age dependent changes are not only observed for atrioventricular flow velocity waveforms, but also for fetal cardiac function. The filling phase is increased and a reduction in isovolumic relaxation and ventricular ejection phase are established. To determine the significance of these systolic and diastolic cardiac changes, more data are needed relative to the intracardiac parameters such as atrioventricular and outflow tract velocities, arterial afterload and venous preload.

Knowledge on normal fetal hemodynamics may be helpful in the detection and surveillance of pathophysiological conditions. In the chick embryo it has been demonstrated that a structurally abnormal heart may be accompanied by an impaired contraction force, resulting in well-defined changes in flow velocity waveforms. It is speculated that also in human fetuses impaired cardiac function may be detected as early as the late first trimester of pregnancy. Although no direct information is available on volume flow and pressure measurements, sufficient information is available on normal flow velocity waveforms in the early and second trimester of pregnancy. Future studies will have to be focused on pregnancies, which are at increased risk of pregnancy-related pathology such as pregnancy-induced hypertension or intrauterine growth retardation or increased risk of congenital heart defects. Only then the clinical significance of Doppler ultrasonography may be properly established.

Late pregnancy

Late pregnancy is characterized by low downstream impedance at fetal trunk and placental level. Although umbilical venous pulsations are considered to be associated with fetal compromise, mild umbilical venous pulsations are observed in the normal late pregnancy. The left portal vein seems to be the most reliable recording site for obtaining venous flow velocity waveforms. However, its clinical relevance is yet to be determined.

Optimal supply of oxygen and nutrients is of major importance to the growth restricted

fetus. The increase in Pulsatility Index in the umbilical artery and descending aorta is accompanied by a reduction in Pulsatility Index in the middle cerebral artery, indicating hemodynamic adjustment (brain-sparing) in the developing fetus.

Reduced transmitral and transtricuspid flow velocity waveforms may result from a reduction in volume flow, impairment of cardiac contractility and/or a raised afterload. With respect to the absence of a relationship between umbilical artery and descending aorta Pulsatility Index and atrioventricular flow velocity waveforms, a raised afterload seems not to be responsible for the observed changes in atrioventricular flow velocity waveforms. Instead, these changes may result from reduced volume flow, since in the late first and early second trimester of pregnancy the opposite was established. Transtricuspid flow velocity waveforms are higher than transmitral flow velocity waveforms, indicating right ventricular predominance.

The reduction in venous flow velocity waveforms in the small-for-gestational age fetus may also be determined by a reduction in volume flow. The reduction in end-diastolic velocities in the ductus venosus and increased percentage reverse flow in the inferior vena cava may result from intracardiac changes and/or increased arterial downstream impedance. However, this could not be effectuated in the present study. Absent or even reverse flow in the umbilical artery and umbilical venous pulsations are associated with adverse neonatal outcome.

From the present study, it appears that the Pulsatility Index in the umbilical artery is still the best predictor for a small-for-gestational age fetus. This is followed by the ratio between the middle cerebral artery and descending aorta Pulsatility Index which emphasises the process of centralization in fetal growth retardation.

Unfortunately, the present study does not allow assessment of fetal compromise by Doppler ultrasonography. Longitudinal studies will be needed to elucidate the time sequence of hemodynamic changes, which will provide more insight into the underlying mechanisms.

Chapter 1

In human fetuses a shift has been demonstrated from a high feto-placental vascular resistance to a low feto-placental vascular resistance with advancing gestational age. However, the opposite is observed in the small-for-gestational age fetus. The objectives of the present thesis are focused on the effect of arterial downstream impedance changes on atrioventricular and venous flow velocities in early normal and late abnormal pregnancies. It should be stressed, however, that the lack of volume flow and pressure measurements puts a restriction on the interpretation of our data.

Chapter 2

A literature survey is presented on arterial, intracardiac and venous flow velocity waveforms in the late first and early second trimester normal fetus and in the small-for-gestational age fetus. Both subsets are characterized by changing downstream impedance with marked changes at atrioventricular and venous level.

Chapter 3

Venous flow velocity waveforms can be obtained as from 8 weeks of gestation. Whereas, fetal lamb and human fetal studies have provided useful information on venous flow velocities in late pregnancy, little information is available on venous flow velocity waveforms in the late first and early second trimester of pregnancy.

In sub-chapter 3.2 the nature and gestational age dependency of fetal venous flow velocity waveforms and their relationship with arterial waveforms are established in the late first and early second trimester of pregnancy. Downstream impedance, as expressed by the pulsatility index in the umbilical artery and descending aorta, shows a marked reduction with advancing gestational age, whereas time-averaged velocities in the umbilical vein, ductus venosus and inferior vena cava increase with gestational age. Umbilical venous pulsations progressively disappear during the same time period. Also, a gestational age-dependent reduction in pulsatility index for veins is established, which reflects cardiac ventricular preload. This reduction in pulsatility index for veins takes place independently from the reduction in downstream impedance as expressed by the umbilical artery and descending aorta pulsatility

index.

Whereas Doppler ultrasonography does not allow direct information on volume flow and pressure measurements, an attempt was made to estimate the pressure gradient across the ductus venosus by using the Bernoulli equation. Insight into pressure gradients would aid in the understanding of the importance of the ductus venosus in the early developing fetus. In subchapter 3.3 attention is focused on the assessment of estimates of the pressure gradient across the ductus venosus. It is demonstrated that Doppler ultrasonography does allow crude estimates of the pressure gradient between the umbilical vein and inferior vena cava. This study indicates that early fetal hemodynamics appears to function at low pressure.

Chapter 4

In animal experimental work, it has been demonstrated that cardiac anomalies may be accompanied by marked hemodynamic changes. In order, to interpret flow velocity waveform data in the early developing human fetus and allow detection of congenital heart disease, knowledge of normal cardiac function is needed.

In subchapter 4.2 atrioventricular flow velocity waveforms are documented between 8 and 20 weeks of gestation and their relation with arterial and venous flow velocity waveforms is established. Both transmitral and transtricuspid flow velocity waveforms show a marked increase with advancing gestational age. Higher transtricuspid flow velocity waveforms suggest right ventricular predominance as early as the late first and early second trimester of pregnancy. Whereas no relationship could be determined between changing downstream impedance as expressed by the pulsatility index in the umbilical artery and descending aorta, and atrioventricular flow velocity waveforms, a statistically significant relationship exists between logarithmically transformed crown-rump-length and atrioventricular flow velocity waveforms. This suggests that the observed changes in atrioventricular flow velocity waveforms may be determined by increased volume flow in the developing fetus.

In subchapter 4.3 fetal cardiac function relative to gestational age is discussed. Cardiac cycle length and filling time displayed a statistically significant increase with advancing gestational age, whereas ejection time and isovolumic relaxation time showed a gestational age related decrease. The gestational age-dependent rise in E/A ratio suggest a shift of blood flow from late diastole to early diastole. This may be explained by the increase in the proportion of ventricular filling contributed by atrial contraction between 10 and 14 weeks of gestation, suggesting a change in ventricular compliance early in gestation.

Chapter 5

In normal late pregnancy, umbilical venous pulsations are considered to be associated with fetal compromise. However, mild umbilical venous pulsations have been observed in normal late pregnancy. In Chapter 5.2 data on the existence of umbilical venous pulsations at different recording sites and their reproducibility in normal pregnancy is discussed. Umbilical venous and left portal venous pulsations are demonstrated in normal pregnancies. Large intra-patient coefficients of variation and limits of agreement between observers are established, which are probably due to the difficulty in standardizing the recording site as well as the individual variation in umbilical venous flow velocity. The left portal vein seems to be the most reliable recording site for obtaining flow velocity waveforms.

Normal late pregnancy is characterized by low downstream impedance at fetal trunk and placenta level. The opposite can be observed in the small-for-gestational age fetus. As a consequence of this changing downstream impedance, well-defined changes take place at arterial, atrioventricular and venous level. The latter changes are discussed in Chapter 5.3. A reduction in middle cerebral artery pulsatility index is observed, indicating fetal brain-sparing. Reduced flow velocities are also established at transmitral and transtricuspid level, with transtricuspid flow velocity waveforms being higher than transmitral flow velocity waveforms. The latter suggests some degree of right ventricular predominance. At venous level, reduced flow velocity waveforms are documented, which may result from reduced volume flow. Increased pulsatility index for veins suggest an increase in end-diastolic ventricular pressure. The occurrence of intrauterine death is associated with absent or reverse flow in the umbilical artery and umbilical venous pulsations. No relationship could be established between atrioventricular and venous flow velocity waveforms and the pulsatility index in the umbilical artery and descending aorta, suggesting that other factors than downstream impedance may play a role in the observed flow velocity changes. The pulsatility index in the umbilical artery is the best predictor of a small-for-gestational age fetus, followed by the middle cerebral artery/descending aorta PI ratio. It can be concluded that in the small-for-gestational age fetuses marked changes take place at arterial, atrioventricular and venous level, which suggest hemodynamic adjustment.

Hoofdstuk 1

In de humane foetus vindt met het vorderen van de zwangerschap een verschuiving plaats van een hoge naar een lage foetale en placentaire vaatweerstand. In het geval van intrauteriene groeivertraging treedt echter het tegenovergestelde op. De doelstellingen van dit proefschrift concentreren zich op het effect van deze veranderingen in arteriële vaatweerstand op cardiale en veneuze bloedstroomsnelheden in de vroege normale zwangerschap en in de gecompliceerde late zwangerschap. Opgemerkt dient te worden dat conclusies met een zekere voorzichtigheid betracht dienen te worden door de afwezigheid van volume en drukmetingen.

Hoofdstuk 2

In dit hoofdstuk wordt een literatuuroverzicht gegeven over foetale arteriële, intracardiale en veneuze bloedstroomsnelheden in het late eerste en vroege tweede zwangerschapstrimester en in de groeivertraagde foetus. Beide groepen worden gekarakteriseerd door een verandering in de vaatweerstand op foetaal en placentair niveau, hetgeen tevens gepaard gaat met duidelijke veranderingen op atrioventriculair en veneus niveau.

Hoofdstuk 3

Vanaf 8 weken zwangerschapsduur kunnen veneuze bloedstroomsnelheidsprofielen verkregen worden. Door studies in het foetale lam en in de humane foetus is er kennis beschikbaar over de veneuze circulatie laat in de zwangerschap. Er is echter weinig bekend over de veneuze circulatie in het eerste en vroeg tweede trimester van de zwangerschap.

In hoofdstuk 3.2 wordt de aard van foetale veneuze bloedstroomsnelheidsprofielen besproken alsmede de relatie tot de zwangerschapsduur en de arteriële vaatweerstand. De vaatweerstand, uitgedrukt als de pulsatiliteits index in de arteria umbilicalis en aorta descendens, vertoont een uitgesproken afname met het vorderen van de zwangerschapsduur. De gemiddelde snelheid in de vena umbilicalis, ductus venosus en vena cava inferior toont echter een toename met het vorderen van de zwangerschap. In dezelfde periode verdwijnen heel geleidelijk de pulsaties in de vena umbilicalis. Een van de zwangerschapsduur afhankelijke afname in de pulsatiliteits index voor venen kan worden waargenomen, hetgeen een maat is voor de cardiale ventriculaire "preload". Deze afname in de pulsatiliteits index voor venen vindt

plaats onafhankelijk van de afname in de vaatweerstand, zoals weergegeven door de pulsatiliteits index in de arteria umbilicalis en aorta descendens.

Doppler ultrageluid verschaft geen directe informatie over volume en drukmetingen. Door middel van de Bernoulli vergelijking kan er echter een schatting gemaakt worden van de drukgradient over de ductus venosus. Kennis hierover kan meer inzicht verschaffen over de functie van de ductus venosus in de zich ontwikkelende humane foetus. In hoofdstuk 3.3 wordt aandacht besteed aan de schatting van deze drukgradient. De resultaten van deze studie tonen aan dat een ruwe schatting van het drukverschil tussen de vena umbilicalis en inferior vena cava gemaakt kan worden en suggereren dat de vroege hemodynamiek in de humane foetus op zeer lage drukken functioneert.

Hoofdstuk 4

Dierexperimenteel onderzoek heeft aangetoond dat hartafwijkingen gepaard kunnen gaan met welomschreven hemodynamische veranderingen. Om gegevens van pathologische omstandigheden te kunnen interpreteren is kennis van de normale cardiale functie onontbeerlijk.

In het eerste artikel worden de atrioventriculaire bloedstroomsnelheidsprofielen beschreven tussen 8 en 20 weken zwangerschapsduur. Tevens wordt aandacht besteed aan de relatie met arteriële en veneuze bloedstroomsnelheidsprofielen. Zowel de bloedstroomsnelheidsprofielen op mitraal als tricuspidaal niveau vertonen een toename met het vorderen van de zwangerschapsduur. De hogere snelheden over de tricuspidalis kleppen suggereren een rechts-dominantie van het foetale hart vroeg in de zwangerschap. De afwezigheid van een relatie tussen de arteriële vaatweerstand, uitgedrukt als de pulsatiliteits index in de arteria umbilicalis en aorta descendens, en atrioventriculaire bloedstroomsnelheden lijkt er op te wijzen dat andere factoren dan de arteriële vaatweerstand een rol spelen bij de veranderingen op cardiaal niveau. De relatie tussen de logaritmisch getransformeerde kruin-romp-lengte en atrioventriculaire bloedstroomsnelheden suggereert dat de veranderingen op atrioventriculair niveau bepaald zouden kunnen zijn door een toename in circulerend volume in de zich ontwikkelende humane foetus.

Het tweede artikel beschrijft de cardiale functie in relatie tot de zwangerschapsduur. De hart cyclus en de vullingstijd vertonen een toename met de zwangerschapsduur, terwijl de ejectie tijd en de isovolemische relaxatie tijd een afname vertonen. De toename in E/A ratio suggereert een verschuiving van bloedstroom van de late naar de vroege diastole. Dit zou verklaard kunnen worden door de toename in de bijdrage van de atriale contractie aan de ventrikel vulling, hetgeen een verandering in ventriculaire compliantie betekent.

Hoofdstuk 5

Pulsaties in de vena umbilicalis worden in de late zwangerschap beschouwd als een teken van foetale nood. Milde pulsaties in de vena umbilicalis zijn echter ook in de normale late zwangerschap gezien. In hoofdstuk 5.2 worden de aanwezigheid van deze pulsaties en de reproduceerbaarheid beschreven. Grote intrapatient variatie en "limits of agreement" worden gevonden, hetgeen hoogst waarschijnlijk bepaald wordt door de moeilijkheid om de meetplaats te standaardiseren en door de variatie in veneuze bloedstroomsnelheden binnen de foetus. De vena porta sinistra lijkt de meest betrouwbare meetplaats te zijn.

De normale tweede helft van de zwangerschap wordt gekarakteriseerd door een lage foetale en placentaire vaatweerstand. Het tegenovergestelde kan waargenomen worden in de groeivertraagde foetus. Als gevolg hiervan, vinden er welomschreven veranderingen plaats op arterieel, atrioventriculair en veneus niveau. Deze veranderingen worden in hoofdstuk 5.3 beschreven. De pulsatiliteits index in de arteria cerebri media neemt af, hetgeen wijst op een "hersen-sparend effect". Afgenomen bloedstroomsnelheden zijn tevens waargenomen op het niveau van de mitralis en tricuspidalis kleppen, waarbij de bloedstroomsnelheden over de tricuspidalis kleppen hoger zijn dan over de mitralis kleppen. Dit laatste suggereert een rechts-dominantie van het hart. Op veneus niveau zijn eveneens afgenomen bloedstroomsnelheden gemeten, die mogelijk het gevolg zijn van een afgenomen circulerend bloedvolume. De toegenomen pulsatiliteits index in de venen zou een uitting kunnen zijn van een toegenomen eind-diastolische duk in de rechter ventrikel. Intra-uterien overlijden is geassocieerd met pulsaties in de vena umbilicalis en met afwezige of zelfs omgekeerde eind-diastolische bloedstroom in de arteria umbilicalis. Er kan geen relatie gevonden worden tussen bloedstroom-snelheden op het niveau van de atrioventriculaire kleppen en veneuze vaten en de pulsatiliteits index in de arteria umbilicalis. Andere factoren dan de arteriële vaatweerstand lijken dus een rol te spelen bij de geobserveerde veranderingen op cardiaal en veneus niveau. De pulsatiliteits index in de arteria umbilicalis is het best in staat om een groeivertraging te voorspellen, gevolgd door de ratio tussen de pulsatiliteits index in de arteria cerebri media en aorta descendens. Er kan geconcludeerd worden dat er in de groeivertraagde foetus markante veranderingen plaats vinden op arterieel, cardiaal en veneus niveau, die wijzen op hemodynamische adaptatie.

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