BLOOD FLOW IN THE HUMAN FETAL DESCENDING AORTA
A PULSED DOPPLER STUDY

BLOEDDOORSTROMING IN DE AORTA DESCENDENS VAN DE HUMANE FOETUS
EEN ONDERZOEK MET GEPULSDE DOPPLER

PROEFSCHRIFT

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to Erna
to Leendert en Frederike
to the memory of my father
to my mother

CONTENTS

Chapter 1

INTRODUCTORY REMARKS AND DEFINITION OF OBJECTIVES OF THE PRESENT STUDY

In 1628 William Harvey introduced his concept of the human circulation. Although a lot of studies concerning the fetal circulation were done before it was not until the 1930s that Barcroft (1934, 1939) and associates performed radiographic studies on the fetal goat and lamb to establish the fetal circulation. Later in 1964 Lind, Stern and Wegelius used cine-angiographic studies to describe the human fetal circulation.

Volume flow measurements were already carried out in 1884 by Cohnstein and Zuntz using a stromuhr in an umbilical artery. In 1949 Cooper, Greenfield and Huggett made their measurements of the umbilical blood flow at different gestational ages in the fetal sheep using a venous plethysmograph. A variety of methods followed each other, such as density flowmeter, the velodyne flowmeter, the cannulated type of electromagnetic flowmeter and the cuff electromagnetic flowmeter. All these methods had several disadvantages. The major ones are exteriorisation of the fetus and the acute character of the flow measurements. Therefore, because of these disadvantages, techniques were developed with the possibility to study the fetus in chronic preparations after recovery from surgery (Berman et al, 1975). These chronic experiments however, may still not be indicative of the normal physiological state.

The introduction of ultrasonic Doppler techniques opened the possibility to measure blood flow non-invasively. Satomura (1959) published the first report on the use of ultrasonic Doppler equipment for the detection of human blood flow velocity. Since then the interest in the non-invasive detection of human blood flow has been overwhelming. Nevertheless it took until the end of the seventies before the first reports appeared on the detection of human fetal blood flow. FitzGerald et al (1977) introduced a method for measurement of human umbilical blood flow using continuous wave Doppler. A few years later pulsed Doppler was introduced for the measurement of umbilical venous blood flow (Gill et al, 1978) and blood flow in the fetal descending aorta (Eik-Nes et al, 1980). Blood flow in the fetal descending aorta reflects cardiovascular function which in itself is an important source of information about fetal well-being. To appreciate correctly the data obtained from these non-invasive flow measurements it is important to establish their reproducibility and to study the possible effects of internal and external stimuli since the latter may lead to misinterpretation of the results.

The objectives of the present study were:

1. to analyse the pitfalls related to the pulsed Doppler flow velocity measurement in the lower thoracic part of the fetal descending aorta.

2. to establish the reproducibility and normal values for blood flow velocity, vessel diameter and volume flow in the lower thoracic part of the fetal descending aorta during the third trimester of pregnancy.
3. to analyse the influence of external stimuli e.g. smoking and short term moderate exercise on these parameters.
4. to develop a more precise method of recording of the vessel diameter changes in the lower thoracic part of the fetal descending aorta.

References

Barcroft, J., L.B. Flexner, T. Mc.Clurkin. The output of the fetal heart in the goat. Physiology: 82, 498-508, 1934.

Barcroft, J., J.A. Kennedy, N.F. Mason. The direct determination of the oxygen consumption of fetal sheep. Physiology: 95, 269-275, 1939.

Berman, W., R.C. Goodlin, M.D. Heymann, A.M. Rudolph. Measurement of umbilical blood flow in fetal lambs in utero. J. Appl. Physiol.: 39, 1056-1059, 1975.

Cohnstein, J., N. Zuntz. Untersuchungen über das Blut, den Kreislauf und die Athmung beim Säugethier Fötus. Pflüger's Arch. ges. Physiol.: 34, 173-233, 1884.

Cooper, K.E., A.D.M. Greenfield, A.St.G. Huggett. The umbilical blood flow in the fetal sheep. J. Physiol.: 108, 160-166, 1949.

Eik-Nes, S.H., A.O. Brubakk, M.K. Ulstein. Measurement of human fetal blood flow. Br. Med. J.: 1, 283-284, 1980.

FitzGerald, D.E., J.E. Drumm. Non-invasive measurement of the fetal circulation using ultrasound. Br. Med. J.: 2, 1450-1451, 1977.

Gill, R.W. Quantitative blood flow measurement in deep lying vessels using pulsed Doppler with the Octoson. Ultrasound in Medicine: 4, 341-348, 1978. Ed.: White, D.N., New York, Plenum Press.

Harvey, W. Exercitatio anatomica de motu cordis et sanguinis in animalibus. Franoforti, Sumptibus Guilelmi Fitzeri, 1628.

Lind, J., L. Stern, C. Wegelius. Human fetal and neonatal circulation. Ed.: Anderson, J.A., Charles C. Thomas Publisher, Springfield, Illinois, U.S.A., 1964.

Satomura, A. Study of the flow pattern in peripheral arteries by ultrasonics. J. Acoustic. Soc. Japan.: 15, 151-158, 1959.

Chapter 2

PRINCIPLES OF DOPPLER VELOCITY MEASUREMENTS

2.1. History

Johann Christian Doppler (1805-1853) published in 1843, as professor of elementary mathematics and practical geometry in Prague, his famous paper entitled "Uber das farbige Licht der Doppelsterne under einiger anderer Gestirne des Himmels". In this paper Doppler recapitulates the wave theory of light and explains that the colour perceived by the eye varies with the frequency. He also postulates that this frequency will increase if the observer is moving towards the source and will decrease if he is moving away from the source.

Buys Ballot (1817-1890) decided in 1844 to verify in an experimental set up with sound waves the theory of Doppler. In 1845 he persuaded the Dutch Government to loan him a locomotive and a flat car. He placed one trumpet player on the flat car and one to either side of a station, where an observer with the ability to appreciate absolute pitch found the sound of the trumpet from the car half a note higher in comparison with the stationary trumpet as the train approached him at a speed of 65 km/hour and half a note lower after it passed.

This was the first verification of the Doppler theory for acoustic waves. The demonstration of the optical Doppler shift was more difficult and it was the beginning of the twentieth century before Belopolski (1900) succeeded in this. It was not until the years after World War II, that as a result of an increasing interest in ultrasonic techniques, the first practical application of the acoustic Doppler effect took place. From that moment on it was possible to generate acoustic energy with a narrow frequency bandwidth and to detect and measure the frequency of a reflected signal.

2.2. Doppler-principle

When ultrasound is transmitted through a medium (for example the human body) then not only will the intensity of the ultrasound diminish because of diffraction, but also it will be reflected at boundaries between media that are of different acoustical impedancies. When a reflector is stationary in relation to the ultrasound source, then the reflected ultrasound is of similar frequency to the transmitted ultrasound waves. On the other hand if the reflector is moving with a velocity V towards the ultrasound source the frequency of the reflected waves is higher than that of the transmitted ultrasound.

The frequency shift f_D is calculated using the formula:

$$f_D = 2 f_0 \cdot \frac{V \cdot \cos \alpha}{c}$$

f_D = frequency shift
f_0 = frequency of the transmitted ultrasound
c = propagation velocity of ultrasound in the medium
α = angle between the direction of the moving reflection and the ultrasonic source

A reflection that moves towards the ultrasonic source results in a positive frequency shift. A reflection that moves away results in a negative frequency shift.

2.3. **Continuous-wave Doppler systems**

The Doppler ultrasound frequencies that are used for diagnostic purposes lie between 1-10 MHz. The transducer consists of piezo-electric crystals that are able to convert electrical energy into mechanical energy and vice versa. The transducer of a continuous wave Doppler system consists of two crystals lying next to each other. One is for transmitting and the other is for receiving ultrasound waves (fig. 2.1., C.W.). Demodulation involves comparing the frequency of the received waveform with a replica of the transmitted waveform. The purpose of this demodulation is to extract the Doppler information contained as frequency shifts in the reflected signal. The demodulated frequencies are in the audible range. All moving structures that lie along the ultrasonic beam will produce changes in Doppler shift. It cannot distinguish signals that arise from different moving structures in the beam path. Therefore it has no depth resolution.

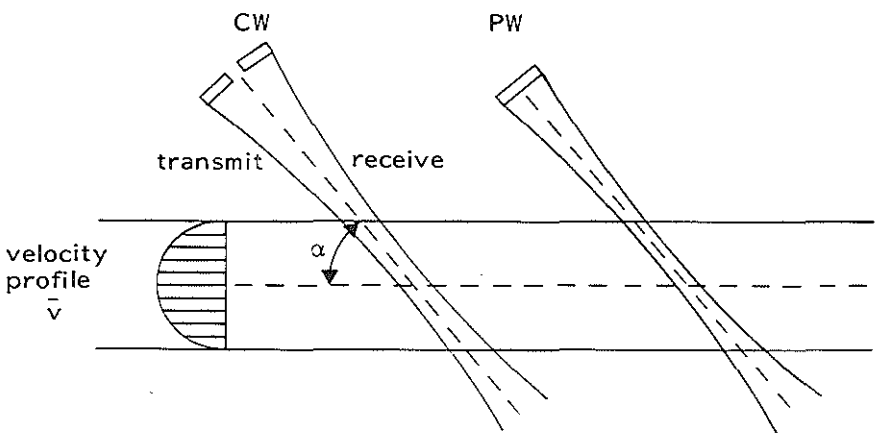


Fig. 2.1. Principles of continuous-wave (C.W) and pulsed-wave (P.W.) Doppler systems.

2.4. Pulsed Doppler systems

In a pulsed Doppler system short pulses of ultrasound are transmitted into the body by one transducer which intermittently acts as transmitter and as receiver (fig. 2.1., P.W.). Depth resolution is obtained by sampling the reflected signal after a certain time delay relative to the transmitted pulse. Assuming a constant propagation velocity in the human body, the reflections under consideration are originating from a depth which is related to the time-delay of the transmitted and received pulse. The axial resolution is determined by the pulse length of the transmitted ultrasound wave. The lateral resolution is determined by the beam width.

The rate at which the pulses are transmitted is called the pulse repetition-frequency. After one ultrasound wave pulse has been transmitted, a second cannot be sent out until the reflected echo of the structure of interest has generated an echo signal on the receiver. There it follows that the maximum detectable frequency, i.e. the maximum measurable velocity for a given propagation velocity and a given transmitting frequency is dependent on the depth. This can be expressed by the formula

$$V_m = \frac{c^2}{8 . f_0 . R}$$

V_m = maximum measurable velocity
c = propagation velocity of ultrasound in the medium
f_0 = frequency of the transmitted ultrasound
R = depth at which the measurement is carried out.

Fig. 2.2. shows the relationship between the maximum measurable velocity and the depth, assuming a propagation velocity of ultrasound of 1500 m/sec. As one can see from figure 2.2. the maximum detectable velocity for an angle of zero degrees was 1.8 m/sec between 2 and 8.5 cm depth and 1.3 m/sec between 8.5 and 10.5 cm depth and for an angle of 45 degrees was 2.5 m/sec between 2 and 8 cm and 1.8 m/sec under a transmitting frequency of 2 MHz. In the lower thoracic part of the fetal descending aorta peak velocities higher than 1.8 m/sec are not found (Griffin et al, 1983). Therefore we assumed that aliasing did not occur in our fetal measurements.

2.5. Doppler frequency spectrum

In the previous subchapters we described the Doppler effect of reflection with a constant velocity. However the reflections originating from blood are mainly caused by erythrocytes. Erythrocytes generally move with different velocities.

Therefore the Doppler frequency shift is composed of different frequency components, the Doppler frequency spectrum.

If we consider a long straight liquid filled tube and a constant pressure is applied

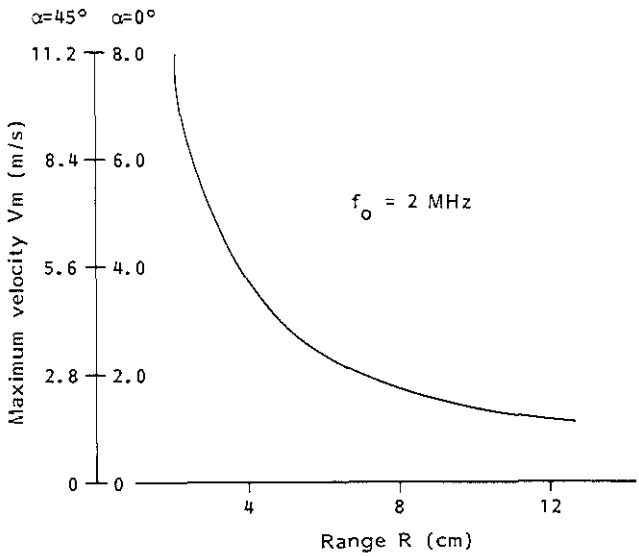


Fig. 2.2. Relationship between the maximum measurable velocity and the range (R), at which the measurement is carried out, for an angle of zero and 45° degrees assuming a propagation velocity of 1500 m/sec and an ultrasound frequency of 2 MHz.

to the liquid this will result in a constant rate of flow. In this case the cross-sectional velocity profile has a parabolic shape. Then all velocities are equally present resulting in a flat Doppler spectrum up to the maximum frequency (McDonald, 1974).

However if the applied rate of flow is increased above a certain critical point than liquid is no longer moving regularly in the line of flow but is following more or less random paths across the tube. The flow is then defined as being turbulent. In the human body parabolic velocity profiles are found, as well as virtual flat profiles in condition of high acceleration (Hatle and Angelsen, 1982; fig. 2.3). The mean frequency can be calculated from the Doppler power spectrum as follows

$$f_D = \frac{\int_{-\infty}^{\infty} f \cdot P(f)\, df}{\int_{-\infty}^{\infty} P(f)\, df}$$

f_D = mean Doppler frequency shift
P(f) = Power spectrum

Finally, various processing methods are available to determine the mean frequency. In recent apparatus the Fast-Fourier method is used to register from the received signal the whole spectrum and as a consequence all velocity components.

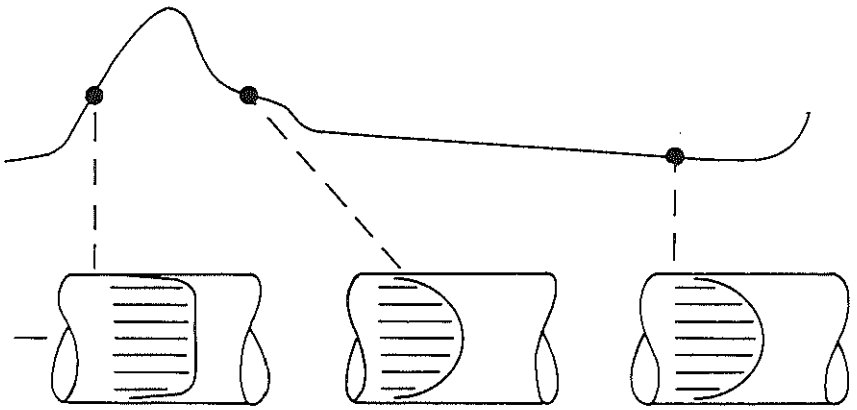


Fig. 2.3. Flow velocity profiles during the acceleration, deceleration and end-diastolic phase of the cardiac cycle.

References

Belopolski, A.A. Opyt issledovania printsipa Dopplera — Fizo ne pribegaya k kosmicheskin skorostyam. Izvest. Imperator Adad. Nauk. 13, 461-474, 1900.

Buys Ballot, C.H.D. Akustische Versuche auf der Niederlandischen Eisenbahn nebst gelegentlichen Bemerkungen zur Theorie des Hrn Prof. Doppler. Pogg. Ann B 66, 321-351, 1845.

Doppler, J.C. Uber das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels. Abhandl. d. Konigl. Bohmischen Gesellschaft der Wissenschaften. Sers. 2, 465-482, 1843.

Griffin, D., T. Cohen-Overbeek, S. Campbell. Fetal and uteroplacental blood flow. In: Clinics in Obstetrics and Gynecology. Ed: Campbell S., London Saunders Company, pp. 565-602, 1983.

Hatle, L., B.A.J. Angelsen. Doppler ultrasound in cardiology. Philadelphia, Lea and Febinger, 1982.

McDonald, D.A. Blood flow in arteries. 2nd Edition, London, Edward Arnold Publish. Limited 1974.

Chapter 3

DESCRIPTION OF THE ULTRASONIC EQUIPMENT USED IN OUR OWN BLOOD FLOW STUDIES

Combined use of 2D-real-time echography and pulsed wave Doppler systems enabled us to carry out non-invasive measurements of fetal blood flow. Real-time 2D-echography is used for localisation of the vessel of interest, while the Doppler system was used to measure blood flow velocity. Vessel size is obtained from the combined use of 2D-real-time echography and M-mode technique or Time Distance (T.D.) recording.

3.1. Description of 2D-real-time equipment

A real-time 2D-apparatus based on the linear-array principle was used. The transducer of such a system consists of a number of small acoustical elements in a row. For each scanline a subarray of adjacent elements was used. The transducer in our set up contained 51 elements, each scanline is formed from 12 elements. As a result a picture of 40 scanlines is built up. The interelement spacing is 2.05 mm which means that the distances between two scanlines is about 2 mm. With a scan depth of 16 cm the scan plane will be 8×16 cm. The used apparatus has dynamic focusing. The emission frequency of the transducer is 3.5 MHz. The axial resolution is in the order of 1 mm, while the lateral resolution is around 3 mm.

3.2. Description of the pulsed Doppler system

The Pedof (Pulsed Echo Doppler Flow velocity meter) is an ultrasonic instrument developed by Angelsen and Brubakk (1976) to measure blood flow velocity transcutaneously. The equipment may be used both in pulsed and continuous mode (fig. 3.1.). In our set up the pulsed mode was used. The frequency of the ultrasound source is 2 MHz. The pulse length is 10 μ seconds. Two pulse repetition frequencies are used, i.e. 8.93 and 5.95 kHz. At an angle of zero degrees velocities up to 1.8 m/sec can be measured at a maximum depth of 8.5 with the higher pulse repetition frequency. Using the lower repetition frequency the maximum measurable velocity is 1.3 m/sec at a depth ranging from 8.5-10.5 cm. In transmission the pulses ar amplified in a power amplifier and are then transformed into ultrasonic energy by a transducer. A schematic diagram of the instrument is shown in fig. 3.2. The received signal is separated into the so-called quadrature components. This method serves to contain the formation in the signal which is caused by forward or

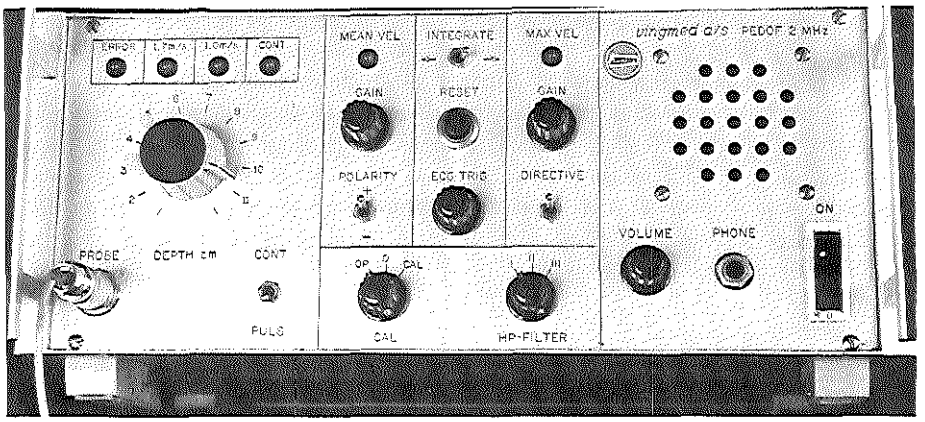


Fig. 3.1. The front panel of the Pedof equipment.

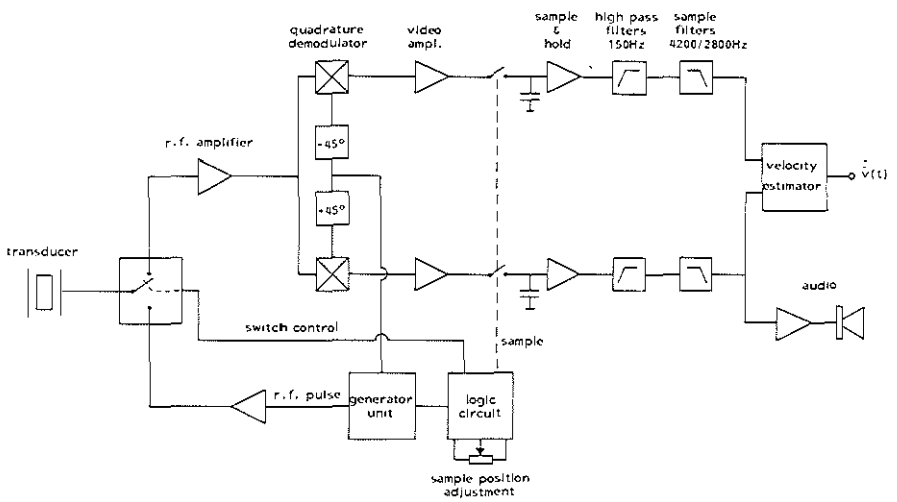


Fig. 3.2. Schematic presentation of the Pedof apparatus.

backward flow. Without quadrature demodulation it is impossible to separate the flow direction.

After passing the sample and hold circuits the signal passes through band pass filters. These band pass filters consist of high pass filters and low pass filters. The high pass filters remove low frequency high intensity Doppler signals produced by the vessel wall movements. This is why in many clinical registrations low velocity

values as observed during the end-diastolic phase of the cardiac cycles fade away. In our set up we select a high pass filter with a cut-off frequency of 150 Hz. Thereafter the low pass filter removes the high frequency components introduced in the sampling. The cut-off frequency of the low pass filter is 4200 Hz at a pulse repetition frequency of 8.93 kHz which automatically switches to 2800 Hz at a pulse repetition frequency of 5.95 kHz above a depth adjustment of 8.5 cm. The signals from the band pass filters are fed to the mean velocity estimator. The principle of this mean velocity estimator is described by Angelsen in his thesis (Angelsen, 1975). The output of the mean velocity estimator is proportional to the mean velocity in the sample volume.

3.3. Combined use of 2D real-time and pulsed Doppler equipment for blood flow velocity measurements

The imaging equipment and the pulsed Doppler velocity meter are combined as follows: a transducer clamp was constructed in which the Doppler velocity probe is attached to the linear array transducer under an angle of 45° (fig. 3.3.).

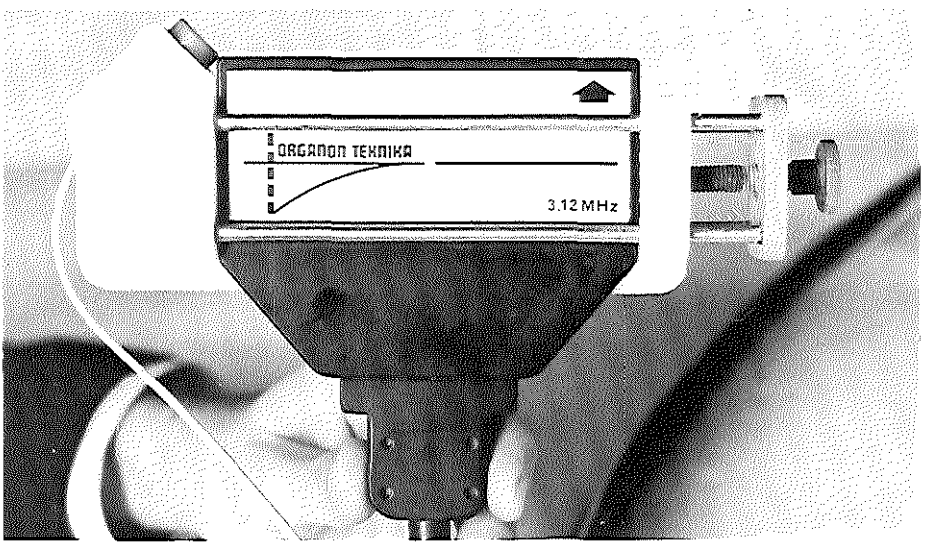


Fig. 3.3. The transducer clamp in which the Doppler velocity probe is attached to the linear array transducer under an angle of 45° degrees.

One of the problems when performing blood flow velocity measurements is the unacceptable interference which results from simultaneous emissions of sound pulses from the 2D real-time transducer and the pulsed Doppler probe. This was overcome by introduction of an electronic interface system between the ultrasonic

real-time scanner and Doppler velocity meter (Wladimiroff et al, 1981). The real-time transducer produces 50 images per second, i.e. one image per 20 milliseconds. The interface reduces the image presentation from 50 images to one image per second by switching off the real-time scanner during a period of 980 milliseconds. During this 980 milliseconds blood flow velocity in the vessel under investigation can be measured. During the remaining 20 milliseconds the last measured flow velocity is contained by means of hold circuits. In the 2D-image a marker is generated which is electronically coupled with the depth of the Doppler flow velocity meter. This marker indicates the centre of the sample volume (fig. 3.4.). This system allows easy selection of the sample volume relative to the vessel lumen. In this way more accurate blood flow measurements can be obtained.

Fig. 3.4. Positioning of the sample volume in the centre of the vessel lumen of the lower thoracic part of the fetal descending aorta as indicated by an asterix.

3.4. Description of the techniques used for measurement of the vessel size

The measurement of the vessel size is necessary for quantitative calculation of volume flow (Q). In our first studies vessel size was calculated from the vessel diameter which was measured using the M-mode technique. Later on the T.D. recording method was used.

The M-mode technique yields information with a high sampling rate along a single sound beam. First, the real-time image of the required longitudinal cross-section of the fetal descending aorta is obtained. A line is subsequently selected in the 2D real-time image which runs perpendicular to the proximal and distal vessel wall at the level of the lower thoracic part of the fetal descending aorta at which the flow velocity measurement is carried out. Then, a M-mode recording of the aortic vessel wall movements is made on light-sensitive paper (fig. 3.5.). As a final step callipers are placed on the leading edges of the proximal and distal vessel wall registration at the end-diastolic and end-systolic phase of the cardiac cycle.

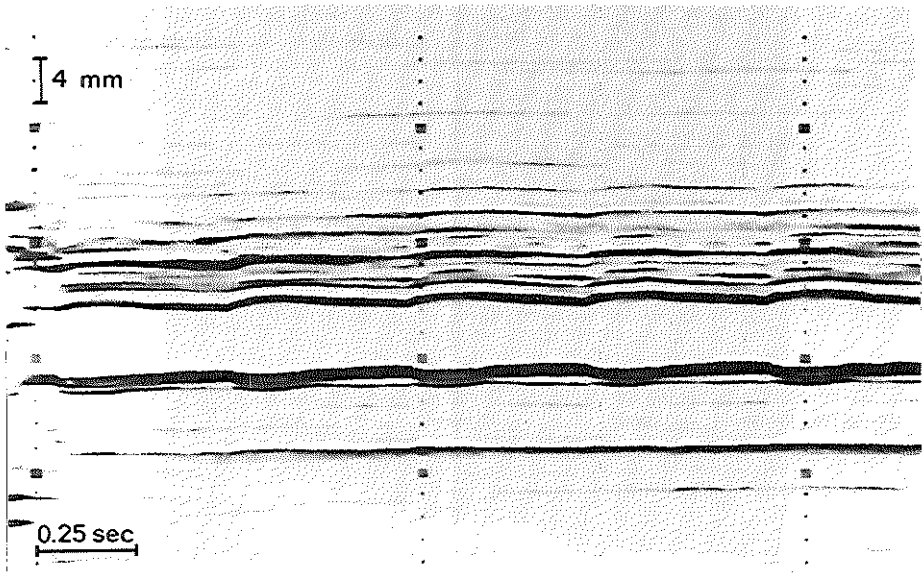


Fig. 3.5. M-mode recording of the lower thoracic part of the fetal descending aorta.

In our later studies (see also Chapter 9) the T.D. recording method was used. An instrument (Blom, Cardiovascular Research Department Rotterdam) was developed which has the capability to follow two preselected echoes. The markers of the T.D. recorder were positioned on the onset of the deflections of an A-mode presentation of the proximal and distal vessel wall. A continuous recording of the vessel diameter was possibly in this way (fig. 3.6.).

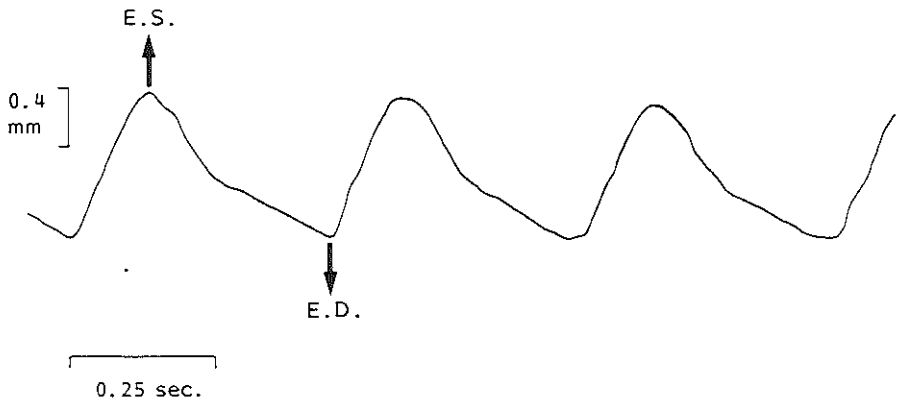


Fig. 3.6. T.D. recording of the lower thoracic part of the fetal descending aorta. E.D. = end-diastolic phase and E.S. = end-systolic phase of the cardiac cycle.

3.5. Data analysis

The analogue mean velocity signal was stored on a 14 channel magnetic tape-recorder (RACAL-STORE 14) for further computer analysis. Signals were digitalized using an 11/34 mini-computer (under RT-11) equiped with a LPS-11 (Laboratory Peripheral System) extension containing a 12-bit A/D converter and a real-time clock. The mean velocity was sampled with a frequency of 25 Hz.

Signals were digitalized for a period of 50 minutes and the resulting data files were stored on a RLØ1 hard disk. Analysis was performed on a PDP 11/70 mini-computer (under RSX- 11M plus). Programs used were written in Fortran IV plus. Statistical data analysis was carried out on a DEC 20 computer (under Tops-20) using the Statistical Package for Social Sciences.

References

Angelsen, B.A.J. Transcutaneous measurement of aortic blood velocity by ultrasound. A theoretical and experimental approach. Report 75-78-W. Division of Engineering Cybernetics, the Norwegian Institute of Technology, the University of Trondheim, 1975.

Angelsen, B.A.J., A.O. Brubakk. Transcutaneous measurement of blood flow velocity in the human aorta. Cardiovascular Research 10, 368-379, 1976.

Wladimiroff, J.W., R.P.L. Vosters, J.S. McGhie, P.C. Struijk. Human fetal cardiovascular dynamics during the last trimester of pregnancy and first 48 hours following delivery. In: Recent advances in ultrasound diagnosis III. Ed: Kurjak, A., A.A. Kratochwil. Amsterdam, Excerpta Medica: 203-208, 1981.

Chapter 4

MEASUREMENT OF FETAL BLOOD FLOW VELOCITY; TECHNIQUE AND POTENTIAL ERRORS

4.1. Description of the scan technique

2D real-time ultrasound enables us to localize the aorta descendens of the fetus. In order to measure blood flow velocity it is essential that the longitudinal axis of the fetal descending aorta lies in the scanning plane. The position, in which the proximal and distal vessel wall of the fetal descending aorta are visible as distinct lines with maximum reflection, is chosen. Due to the beam width of the ultrasound wave there is no real plane. This is of practical importance for correct positioning of the transducer. A thin thread under tension in a watertank which intersects the scanning plane is represented on the 2D image as a line instead of a dot. For this reason, it is essential that the scanning plane is positioned in such a way to ensure maximum visualisation of the aorta. In doing so it is possible to position the transducer in such a way that the longitudinal axis of the aorta is entirely situated within the scanning plane. The angle between the Doppler and the 2D real-time transducer is fixed at 45 degrees. The angle of insonation in only 45 degrees if the position of the transducer is parallel to the longitudinal axis of the aorta. Therefore the transducer must be selectively lifted or tilted until this position is achieved. Sometimes the distance between the Doppler transducer and fetal descending aorta is so great that measurement of blood flow velocity cannot be achieved. When this is the case the Doppler transducer can be repositioned in an attempt to reduce this distance. In the 2D image a marker, representing the centre of the Doppler sample volume, can be positioned at the site where the blood flow velocity is to be measured. The marker must be positioned in the centre of the fetal descending aorta in order to cover the velocity of all the red blood cells. By means of a foot switch the blood velocity sampling is started and by means of an interface the image frequency is reduced from 50 images per sec. to one image per sec. This enables fine adjustment of the Doppler sample volume so that the maximum Doppler signal can be heard. During the time of optimal blood velocity measurement a second footswitch is pressed which generates an electrical signal which is recorded on magnetic tape to indicate the parts of the tape which should be used for analysis.

4.2. Potential errors in the measurement of blood flow velocity

4.2.1. *The insonation angle*

There are two potential angle errors
a. the longitudinal axis of the fetal descending aorta intersects the scanning plane.
b. the longitudinal axis of the fetal descending aorta does not lie perpendicular to scanning lines, but is located in the scanning plane.

Fig. 4.1. and 4.2. are schematic presentations of the situations a. and b. The range of errors as presented in fig. 4.1. is estimated. Assuming an angle error (angle β in fig. 4.1.) of 10 degrees, with a given lateral resolution of 3 mm, a maximum length of about 17 mm of the fetal descending aorta will be represented on the 2D image. In all our measurements a longer position of the fetal descending aorta was seen, implying that the angle β was less than 10 degrees. This was confirmed in an in vitro study using a water tank and a thin thread. It can be seen from figure 4.1. that an error in angle β will also affect angle α. In triangle AOC, $\cos \alpha = OC/OA$, in triangle BOC $OC = OB \cos \beta$ and in triangle AOB, $OA = a\sqrt{2}$. It can be calculated that $\cos \alpha = \cos \beta/\sqrt{2}$. When the angle β is 10 degrees, angle α will be 45 degrees, 52 minutes. The resulting error in blood flow velocity measurement is less than 1.5% and thus can be considered as very small.

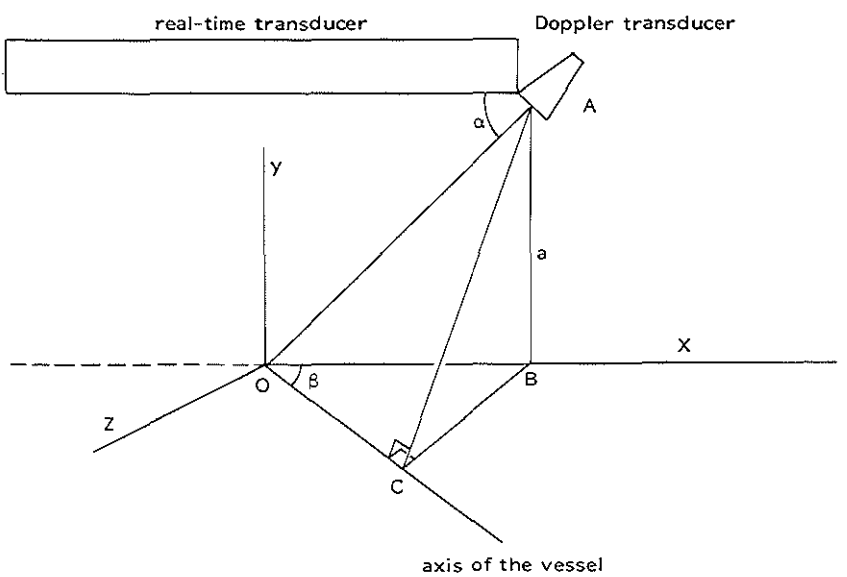


Fig. 4.1. Schematic presentation of the situation in which the longitudinal axis of the fetal descending aorta intersects the scanning plane.

The range of errors as presented in figure 4.2. was investigated in a study, in which the qualitative blood flow velocity was recorded in association with a polaroid photograph of the 2D-image. With the aid of a protractor the angle between the scanlines and the axis of the fetal descending aorta was measured. In the ideal situation the scanlines are perpendicular to the fetal descending aorta. This is when the angle of insonation is 45 degrees. The effects of this error on the blood flow velocity measurement were studied in three pregnant subjects at a gestational age of 36 weeks. Blood flow velocity was recorded ten times in each patient. The error in the angle of insonation was subsequently calculated and varied between –4 and +5 degrees. This implies that the angle between the Doppler ultrasound beam and the direction of the velocity of the erythrocytes in the fetal descending aorta must lie between 42 and 48 degrees. When the angle is 45 degrees the angle correction factor $1/\cos \alpha = 1.41$. In the presence of the measured angle error the correction factor lies between 1.35 and 1.49. This results in a possible error in the blood flow velocity measurement of less than 4.5%.

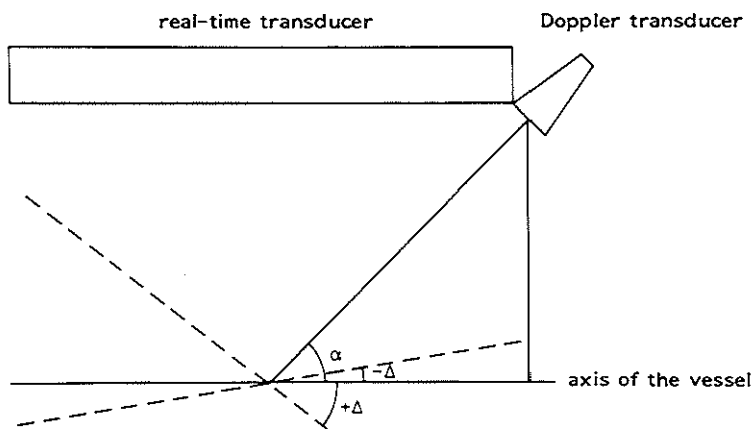


Fig. 4.2. Schematic presentation of the situation in which the longitudinal axis of the fetal descending aorta does not lie perpendicular to scanning lines, but is located in the scanning plane.

4.2.2. *The sample volume*

The Doppler sample volume must cover the entire lumen of the fetal descending aorta in order to ensure uniform scattering of all moving particles. The diameter of the sample volume must therefore be larger than the maximum diameter of the fetal descending aorta in which the blood flow velocity will be measured. The length of the sample volume in the axial direction is determined by the pulse length of the transmitted and received ultrasound. In our system the length of the sample volume is 8 mm according to the factory specification. The dimension of the sample volume

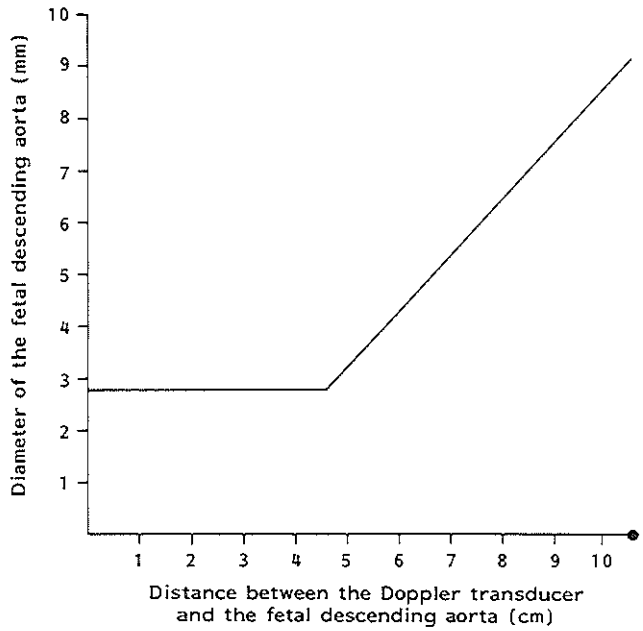


Fig. 4.3. Relationship between the maximum measurable diameter of the fetal descending aorta and the distance between the Doppler transducer and the fetal descending aorta under conditions of uniform scattering.

in the lateral direction is determined by the beam width. In the near field the diameter is similar to that of the transducer element. In the far field the ultrasound beam diverges. The beam divergence can be calculated using the formula:

$$D = \frac{f_0 . r^2}{c} \quad \text{(Wells, 1969).}$$

D = point of divergence
f_0 = frequency of the transmitted ultrasound
c = propagation velocity of ultrasound in the medium
r = radius of the transducer element.

For our transducer the beam divergence begins at 47 mm. The angle at which the ultrasound beam diverges is angle γ. This angle can be calculated using the formula:

$$\sin \gamma = \frac{0.61 . c}{f_0 . r} .$$

For our Doppler instrument the angle is known to be 4°5'.

The fetal descending aorta generally lies more than 5 cm from the real-time transducer. The distance between the Doppler transducer and the fetal descending aorta will therefore be more than 6.3 cm. The maximum depth at which blood flow velocity measurement can be carried out is 10.5 cm. In fig. 4.3. the maximum

measurable diameter of the fetal descending aorta related to the distance between the Doppler transducer and the fetal descending aorta under conditions of uniform scattering is shown. It can be seen from figure 4.3. that at a distance of 6.3 cm between the fetal descending aorta and the Doppler transducer uniform scattering occurs if the diameter of the fetal descending aorta is 4.6 mm or less and at a distance of 10.5 cm if the diameter is 9.2 mm or less.

References

Wells, P.N.T. Physical principles of Ultrasonic Diagnosis. Academic Press, New York, 1969.

Chapter 5

NON-INVASIVE BLOOD FLOW MEASUREMENTS IN THE HUMAN FETUS; AN OVERVIEW

Doppler flow measurements in the human fetus have been mainly carried out in the intra-abdominal part of the umbilical vein, the umbilical arteries, the inferior vena cava and the lower thoracic part of the descending aorta. Reports have appeared on flow measurements both under physiological and pathophysiological circumstances. For a correct interpretation of recorded data, it is of importance to establish the effect of internal (breathing movements) and external stimuli (maternal smoking and exercise) on the fetal circulation.

In the next subchapters, published data on Doppler flow measurements in the fetus will be presented and discussed.

5.1. Arterial measurements

Blood flow velocity signals have been obtained from the umbilical arteries and vein using continuous-wave (FitzGerald and Drumm, 1977; Stuart et al, 1980, 1981; FitzGerald et al, 1984) and pulsed wave Doppler systems (Gill and Kossoff, 1979; Gill et al, 1981; Kurjak and Rajhvajn, 1982; Jouppila et al, 1984a, 1984b; Gill et al, 1984; Reuwer et al, 1984a, 1984b) and from the lower thoracic part of the descending aorta using pulsed-wave Doppler systems only (Eik-Nes et al, 1980a, 1982a; Wladimiroff et al, 1981; Fendel et al, 1983; Griffin et al, 1983a, 1983b; Marsal et al, 1984).

5.1.1. *Qualitative analysis of Doppler signals*

Figures 5.1. and 5.2. represent blood flow velocity waveforms from the lower thoracic part of the descending aorta and umbilical arteries. The following parameters are essential in the analysis of these waveforms:

- the acceleration slope, which reflects the rate of acceleration of blood through the vessel and depends on the density of blood, the elasticity of the vessel wall and the pressure gradient propelling the blood forward (McDonald, 1974).
- the systolic flow velocity, which is governed by the capacitance of the vessels.
- the diastolic flow velocity, which reflects placental resistance.

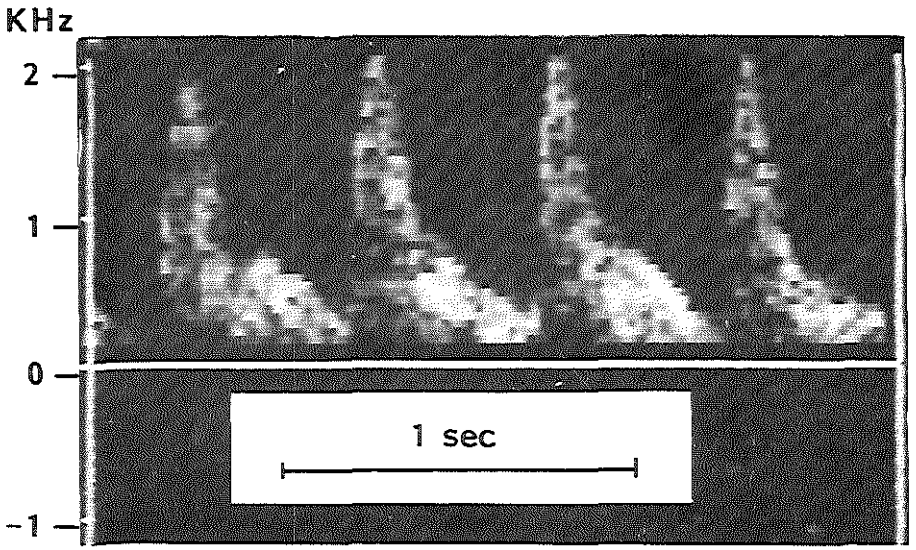


Fig. 5.1. Flow velocity wave profile in the lower thoracic part of the fetal descending aorta at a gestational age of 30 weeks.

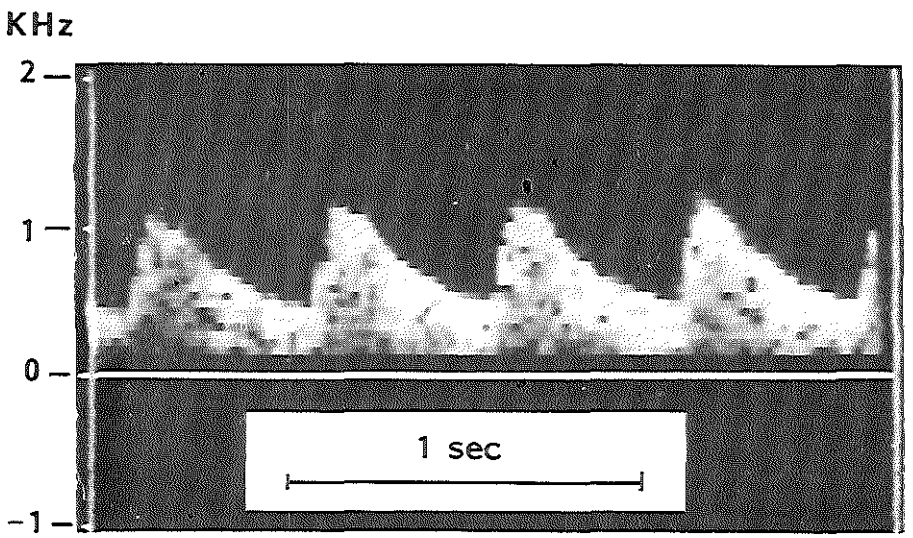
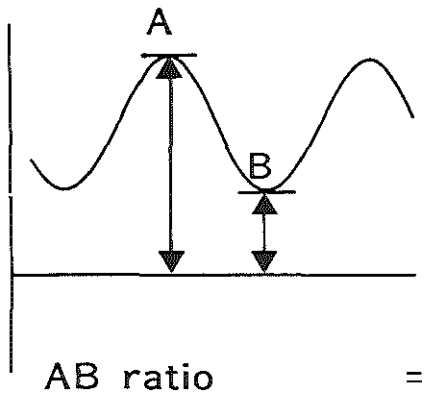


Fig. 5.2. Flow velocity wave profile in the umbilical arteries at a gestational age of 30 weeks.

Particularly in umbilical arteries most studies have concentrated on angle-independent parameters (Fig. 5.3) such as:

- *Resistance Index* (Planiol and Pourcelot, 1975), which is derived by dividing the result of the systolic flow velocity (A) minus the diastolic flow velocity (B) by the systolic flow velocity (A).
- *Pulsatility Index* (Gosling and Kind, 1975), which is derived by dividing the peak-to-peak height of the velocity waveform by the mean flow velocity.
- *A/B Ratio* (Stuart et al, 1980), which is determined by dividing systolic flow velocity (A) by diastolic flow velocity (B).



$$\text{AB ratio} = A/B$$

$$\text{Resistance index} = \frac{A-B}{A}$$

$$\text{Pulsatility index} = \frac{A-B}{\text{mean}}$$

Fig. 5.3. Schematic presentation of angle-independent parameters, respectively Resistance Index, Pulsatility Index and A/B ratio.

5.1.1.1. Clinical findings

The acceleration slope does not change significantly during normal pregnancy (Stuart et al, 1980), but rises significantly in advanced cases of Rh-isoimmunisation with developing fetal hydrops. This rise is most likely determined by fetal anaemia (FitzGerald et al, 1984). All studies on blood flow velocity both in the lower thoracic part of the descending aorta and umbilical arteries demonstrate that systolic forward flow is not overcome by placental resistance so that there is forward flow throughout the cardiac cycle with the velocity waveform remaining elevated above the baseline (figs. 5.1 and 5.2.). In the umbilical arteries the Resistance Index, Pulsatility Index and A/B ratio show a progressive decline with advancing gestational age indicating a progressive reduction in placental vascular

resistance (Stuart et al, 1980; Reuwer et al, 1984a; Schulman et al, 1984). In the same arterial vessels, an increase in these three parameters as determined by reduced or even absent flow velocity in diastole has been observed in severe fetal growth retardation during the 3rd trimester of pregnancy (Trudinger and Cook, 1982; Trudinger et al, 1983; Lingman et al, 1983; Griffin et al, 1983a, 1983b; FitzGerald et al, 1984; Reuwer et al, 1984b). Counting of the number of small muscular arteries in the tertiary stem villi, Giles and coworkers (Giles et al, 1983) revealed that a raised A/B ratio was associated with a significantly lower small arterial count when compared with a normal group. The ratio also correlated with fetal morbidity as expressed by the Apgarscore at 5 minutes (Trudinger et al, 1983). All these parameters have also been studied under pathological circumstances other than fetal growth retardation. A raised Pulsatility Index in the umbilical arteries has been found in a very small number ($n = 4$) of patiens with insulin dependent diabetes mellitus (McCallum et al, 1978) and oligohydramnios (Maulik et al, 1982). Normal Resistance Index values were observed during hypertension (FitzGerald et al, 1984).

Finally, analysis of umbilical artery waveforms during uncomplicated labour revealed no measurable changes by uterine contractions, artificial rupture of the membranes, infusion of oxytocin or administration of analgesia (Stuart et al, 1980; FitzGerald et al, 1984).

5.1.1.2. Comments

Correct determination of the angle between the insonating ultrasonic beam and the direction of the erythrocyte movement is often not possible due to coiling of the umbilical cord. It is therefore that attention has mainly been focused on angle independent parameters such as Resistance Index, Pulsatility Index and A/B ratio. As pointed out earlier by Planiol and Pourcelot (1975) and by Gosling and King (1975) both indices reflect the degree of pulse waveform dampening and have been found indicative for downstream impedance. This also holds true for the A/B ratio as defined by Stuart et al (1980). In all three indices there is a gradual decrease with advancing gestational age reflecting a decline in placental resistance. This has also been established in animal experimental studies (Dawes, 1968; Clapp et al, 1980) and is supposed to result from the continuous growth of arteriovenous anastomoses in the placental villi (Hamilton and Boyd, 1970).

In a number of cases of severe fetal growth retardation a significant rise in Resistance Index, Pulsatility Index and A/B ratio was found (Trudinger and Cook, 1982; FitzGerald, 1984; Reuwer et al, 1984b). The reduced arterial count in the tertiary stem villi is in agreement with the increased Pulsatility Index following the embolisation of the umbilical circulation in sheep (Clapp et al, 1980). Preliminary data even suggest that impaired placental circulation may be reflected by a raised Pulsatility Index several weeks before establishing reduced fetal growth by the ultrasonic indices. Further studies are needed to evaluate the time relationship between changes in placental resistance and fetal growth retardation.

5.1.2. *Quantitative analysis of Doppler signals*

Quantitative examinations on arterial blood flow have been restricted to the lower thoracic level of the descending aorta and include measurements of aortic size in an effort to estimate volume flow. In most studies calculations are based upon the assumption that flow in major vessels studied is laminar. Dependent from the fact whether the flow profile is parabolic or plug the mean blood flow velocity is equal to half the maximum blood flow velocity or even equal to the maximum blood flow velocity.

Recently, Griffin et al (1983b) pointed out that the lower thoracic part of the descending aorta depicts a plug profile during systolic acceleration and a parabolic profile during diastole. Aortic size is derived from the aortic diameter which has been calculated from B-mode images, M-mode or Time-Distance recordings. Volume flow (ml/min) is calculated from the following formula:

$$Q = \tfrac{1}{4}\,\pi \cdot d^2 \cdot V$$

whereby V = mean blood flow velocity (cm/sec) and d = vessel diameter (mm). Calculations of volume flow in ml/min/kg fetal body weight have been based on fetal birth weights when flow measurements were carried-out within 7 days of delivery and on estimated weights from ultrasonic measurements of abdominal circumference (Campbell and Wilkin, 1975) or a combination of BPD and abdominal transverse diameter (Eik-Nes et al, 1982b) when flow measurements were carried out more than one week before delivery.

5.1.2.1. Clinical findings

Normal data are presented in Table I. All examinations have been carried out during the last trimester of pregnancy and all data are cross-sectional. Flow velocity data are presented as mean blood flow velocity or peak mean blood flow velocity. Calculations generally included 10 or more cardiac cycles, except in one study (Griffin et al, 1983b). Mean blood flow velocity in the lower thoracic part of the descending aorta demonstrates a fairly constant pattern during the 3rd trimester of pregnancy. Aortic vessel diameter was nearly always obtained from B-mode images or M-mode recordings. Although the Time-Distance recorder as a means of measuring vessel size was already mentioned by Eik-Nes in 1980 (Eik-Nes et al, 1980b), clinical data obtained with this system are only available from a recent study by Tonge et al (1983). In all studies a significant increase in vessel diameter can be observed. Although from recent reports there seems to be an agreement on the rise of volume flow in the lower thoracic part of the descending aorta during the 3rd trimester of pregnancy, there is a wide distribution of individual data resulting in large SD values. The reduction of volume flow reported in small-for-dates is mainly determined by the associated reduced vessel size (Wladimiroff et al, 1980; Jouppila et al, 1981).

Table 1. Normal data for blood flow velocity, vessel diameter and volume flow in the lower thoracic part of the fetal descending aorta during the third trimester of pregnancy as reported from different centers.

authors	number of patients studied	gestational age (weeks)	number of cardiac cycles studied	mean blood flow velocity (cm/sec)	peak mean blood flow velocity (cm/sec)	method of vessel measurement	vessel diameter (mm)	volume flow (ml/min	volume flow/ fetal weight (ml/min/kg)
Eik-Nes et al (1980)	26	32-41	10	range 19-26.0	—	B-mode	—		$\bar{x} \pm$ SEM 191.0 ± 126
Wladimiroff (1980)	11	29-31		$\bar{x} \pm$ SD 22.1 ± 4.6			$\bar{x} \pm$ SD 5.2 ± 0.5	$\bar{x} \pm$ SD 250 ± 60	
	12	32-34		23.8 ± 5.5	—	M-mode	5.9 ± 0.3	350 ± 80	—
	22	35-37	20	25.0 ± 1.6			6.3 ± 0.7	455 ± 80	
	15	38-40		25.0 ± 6.7			6.8 ± 0.9	535 ± 80	
Wladimiroff et al (1981)	38	27-33	20	$\bar{x} \pm$ SD 20.0 ± 3.0	range 60-80	M-mode	$\bar{x} \pm$ SD 5.0 ± 0.8	range 260-550	
		34-41		20.0 ± 3.1			6.5 ± 0.7		
Eik-Nes et al (1982)	33	32-40	10			B-mode			$\bar{x}$ 185.0
Fendel et al (1983)	35	30-41	15	$\bar{x} \pm$ SD 27.0 ± 3.0	—	B-mode	range ± SD 5.6 – 8.0 ± 0.7	range ± SD 370-830 ± 150	$\bar{x} \pm$ SD 230 ± 44
Griffin et al (1983a)	65	28-40	3					$\bar{x} \pm$ SD 276.5 ± 85	
Tonge et al (1983)	10	30-35	10	—	$\bar{x} \pm$ SD 70.1 ± 7.5	TD-method	$\bar{x} \pm$ SD 5.1 ± 0.5	$\bar{x} \pm$ SD 390.2 ± 94.0	$\bar{x}$ 236.1
	10	36-41			70.4 ± 13.0		6.5 ± 0.9	602 ± 142.0	204.8
Griffin et al (1983b)	19	28-30		$\bar{x} \pm$ SD 30.1 ± 5.0			$\bar{x} \pm$ SD 5.3 ± 0.5	x ± SD 400 ± 90	$\bar{x} \pm$ SD
	21	31-35		33.0 ± 6.0			6.0 ± 0.7	590 ± 200	
	22	34-36	3	31.0 ± 6.0	—	B-mode	6.7 ± 0.6	630 ± 160	280 ± 45
	22	37-39		30.6 ± 7.0			7.2 ± 0.6	780 ± 160	
	9	40+		25.5 ± 5.0			7.6 ± 0.4	640 ± 100	
Marsal et al (1984)	6	27-28		$\bar{x} \pm$ SD 28.9 ± 3.6			$\bar{x} \pm$ SD 4.8 ± 0.4		$\bar{x} \pm$ SD 263.5 ± 31.8
	5	29-30		34.5 ± 6.1			4.9 ± 0.4		265.4 ± 39.5
	9	31-32		31.9 ± 5.3			5.4 ± 0.6		251.4 ± 37.2
	11	33-34	15	29.5 ± 6.5		B-mode	6.1 ± 0.5	—	226.0 ± 41.1
	8	35-36		30.1 ± 7.3			6.5 ± 0.5		251.7 ± 45.2
	14	37-38		26.7 ± 5.1			6.8 ± 0.5		220.6 ± 36.2
	11	39-40		28.3 ± 4.1			7.3 ± 0.5		221.5 ± 32.7

5.1.2.2. Comments

Whereas in the qualitative assessment of arterial blood flow, angle-independent parameters such as the Pulsatility Index, Resistance Index and A/B ratio are used, estimation of volume flow in the descending aorta is subject to a number of potential errors inherent to the measurement of mean blood flow velocity and vessel size as discussed in Chapter 4. The marked discrepancy in flow velocity between early and recent reports (Table I) may be caused by the use of different filters which are necessary to remove the low frequency, high intensity Doppler signals produced by pulsatile movements of the vessel wall. In earlier studies filters with a cut-off frequency at 600 Hz were used (Eik-Nes et al, 1980a; Wladimiroff et al, 1980), resulting in considerable loss of diastolic flow velocity information and underestimation of volume flow. In all later studies filters with cut-off levels at 150 Hz or lower have been used. Calculation of volume flow per kg fetal body weight introduces a further inaccuracy when indirect weight estimates from ultrasonic head and trunk measurements are made. It seems therefore that from the quantitative data presented in Table I it can only be concluded that there is a rise in volume flow in the lower thoracic part of the descending aorta during the 3rd trimester of pregnancy which is mainly determined by the increase in cardiac ventricular and aortic vessel size. Since fetal aortic size increases in proportion to weight gain it is not surprising that volume flow values per kg fetal body weight remains constant. It also explains the normal volume flow values per kg fetal body weight found in small-for-dates and thus shows the limited value of these calculations in the assessment of fetal condition.

5.2. Venous measurements

Flow studies have been carried out in the inferior vena cava and intra-abdominal part of the umbilical vein using pulsed-wave Doppler equipment.

5.2.1. *Blood flow in the inferior vena cava*

Only qualitative examinations on IVC flow have been carried out (Griffin et al, 1983b). The IVC diverges from the descending aorta towards the right atrium. The direction of blood flow in the IVC is contrary to that in the descending aorta. Fig. 5.4. shows a Doppler sonogram of the IVC near the heart. As has been described by Griffin et al (1983b) the sonogram is characterized by the "s" wave representing rapid atrial filling during ventricular systole and the "a" trough reflecting atrial contraction. The same authors did not observe any flow reversal in normal 3rd trimester pregnancies whereas reversal of flow was detected in cases of congestive cardiac failure such as in fetal hydrops due to severe Rh isoimmunisation or supraventricular tachycardia. Griffin et al (1983b) point out that the monitoring of IVC flow may be useful in the progress and evaluation of treatment of cases of fetal hydrops.

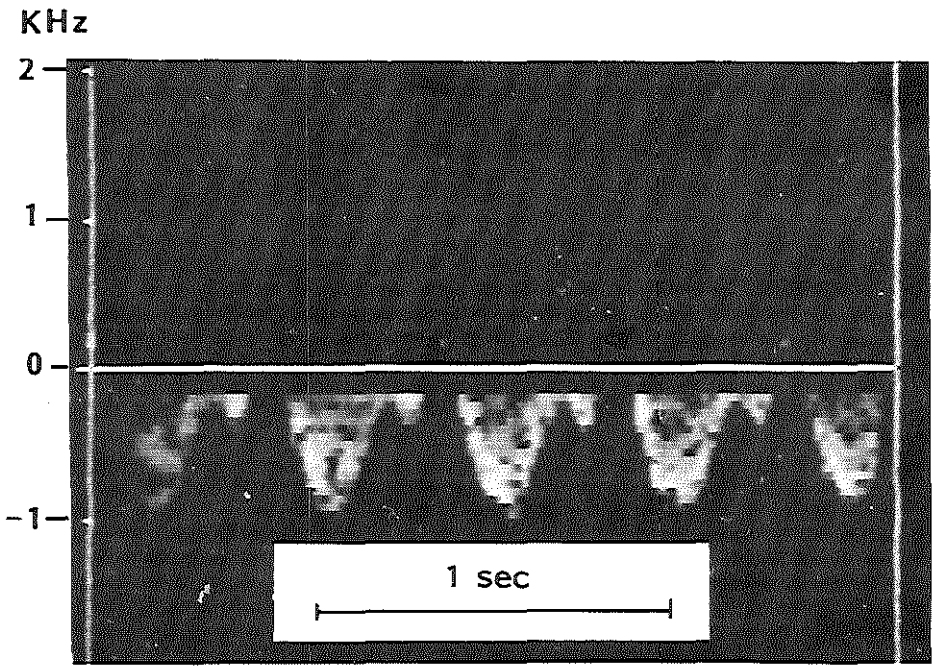


Fig. 5.4. Flow velocity wave profile in the inferior vena cava at a gestational age of 30 weeks.

5.2.2. *Blood flow in the umbilical vein*

The flow profile in the umbilical vein is probably parabolic which means that the mean blood flow velocity is equal to half the maximum blood flow velocity. Blood flow studies in the umbilical vein have been mainly of a quantitative nature, i.e. like in the descending aorta, volume flow calculations have been carried out from flow velocity and vessel size data.

5.2.2.1. Clinical findings

Since the first report by Gill in 1978 on non-invasive measurements of blood flow in the umbilical vein, several centres became actively involved in this particular kind of flow studies. Table II presents an overview of published umbilical venous flow data, which are all cross-sectional. Most studies were carried out during the 3rd trimester of pregnancy. Mean blood flow velocity mainly derived from recordings of 10 seconds duration, is fairly constant until 36 weeks with a slight fall thereafter. Like in the descending aorta, individual results show a wide distribution with flow velocities ranging between 5 and 25 cm/sec. Vessel diameter as measured by B-mode ultrasound, depicts a significant increase in vessel size, resulting in a rise in

Table II. Normal data for blood flow velocity, vessel diameter and volume flow in the intra-abdominal part of the umbilical vein during the third trimester of pregnancy in different centers.

authors	number of patients studied	gestational age (weeks)	mean blood flow velocity (cm/sec)	vessel diameter (mm)	volume flow (ml/min)	volume flow/ fetal weight (ml/min/kg)
Gill and Kossoff (1979)	12	25½-40	—	—	—	$\bar{x}$ 103
Gill (1979)	12	25½-40	range 6.1-16.0	range 5.0-9.0	range 99-349	range 80-129
Eik-Nes et al (1980a)	20	32-41	—	—	—	$\bar{x} \pm$ SEM 110 ± 5.8
Eik-Nes et al (1980c)	27	32-40	—	—	—	$\bar{x} \pm$ SEM 113 ± 5.1
Gill et al (1980a)	50	20-40	—	—	—	$\bar{x}$ 100
Gill et al (1980b)	47	20-40	—	—	—	$\bar{x} \pm$ SD 113 ± 21
Gill et al (1981)	47	20-35	range 6.3-26.1	—	—	$\bar{x}$ 120
		35-40				$\bar{x}$ 90
Jouppila et al (1981)	—	—	—	—	—	$\bar{x}$ 108
Rajhvajn et al (1981)	56	32-41				$\bar{x}$ 109
Kurjak (1982)	63	30-41				$\bar{x}$ 107
Eik-Nes (1982)	27	32-40			range 250-420	$\bar{x} \pm$ SEM 122 ± 4.2
Fendel (1983)	30	30-40	$\bar{x} \pm$ SD 14 ± 2	range ± SD 6.7-7.7 ± 0.5		$\bar{x} \pm$ SD 122 ± 2.7
Gill (1984)	118	20-35	—	—	—	$\bar{x}$ 120
		35-40	—	—	—	$\bar{x}$ 90

volume flow in the umbilical vein up to 36 weeks. A volume flow per kg fetal body weight of 120 ml/kg/min was calculated at 36 weeks with a fall to 90 ml/kg/min at 40 weeks of gestation. Reduced volume flow values in fetal growth retardation were first reported by Gill et al (1979) and later by Jouppila et al (1981) and Kurjak and Rajhvajn (1982). Umbilical vein Doppler shifts have been reported to be technically unrecordable in severe oligohydramnios with associated breech presentation and fetal hypoflexion (Griffin et al, 1983b). Gill et al (1984) noted that in cases in which flow was reduced only in proportion to fetal weight (resulting in a normal value of flow per kg/fetal body weight), there was very seldom antenatal hypoxia an no neonatal morbidity or mortality. Infants belonging to this group usually displayed the so-called "low-profile" pattern of growth (Campbell and Dewhurst, 1971). On the other hand in almost half of small-for-dates with low values of both flow and flow per kg fetal body weight, abnormal CTG traces indicating fetal hypoxia were found. The majority of these infants followed the "late flattening" pattern of fetal growth (Campbell and Dewhurst, 1971). Gill et al (1984) also noted that the length of time for which the flow is low may also determine the degree of risk. They therefore formulated the concept of "flow deficit", which takes into account both the amount by which flow falls below normal and the length of time for which low values are observed. The deficit for each individual flow reading is defined as the amount by which that reading falls below the medium value for normal pregnancies of the appropriate gestational age. A close relationship between the degree of flow deficit and the incidence of perinatal complications was oberved. In a recent paper Jouppila and Kirkinen (1984a) suggest that the reduction in umbilical blood flow in fetal hypoxia is mainly associated with constriction of the umbilical vein.

Raised volume flow values in the umbilical vein have been reported in Rh-isoimmunisation (Gill et al, 1984; Jouppila and Kirkinen, 1984b), antepartum haemorrhage and maternal anaemia (Jouppila and Kirkinen, 1984b). A close correlation between umbilical vein blood flow velocity and postpartum haemoglobin concentration has been established (Jouppila and Kirkinen, 1984b).

5.2.2.3. Comments

The non-invasive Doppler results from the human umbilical vein are in agreement with direct measurements in the human fetus during hysterotomy using electromagnetic flow meters (Assali et al, 1960) and slightly higher than data obtained postpartum by local thermodilution (Stembera et al, 1964). Umbilical blood flow in fetal lambs has been measured using different methods, such as the Fick method (Meschia et al, 1967), the radionuclide-labelled microsphere technique (Rudolph and Heymann, 1967) and electromagnetic flow meters around the common umbilical artery (Berman et al, 1975). Despite those different techniques, they demonstrate remarkable consistency in umbilical blood flow data in the fetal lamb with averaged values of 180-200 ml/min per kg fetal weight over the gestational period of 110-145 days (Rudolph, 1976). Recently, Huikeshoven et al (1985) using a

mathematical model of the fetal circulation indicated that the human fetus can maintain its oxygen delivery with a relatively high fetal haemoglobin concentration as compared with the fetal lamb. This may explain the marked discrepancy in umbilical blood flow between the human and sheep fetus. A further support for the relatively low umbilical flow values in the human fetus can be found in the distribution of cardiac output. Rudolph and Heymann (1979) calculated that 45-50% of the total cardiac output in the fetal lamb is distributed to the placenta. Based on ultrasonically calculated cardiac output data in the human fetus of 250-300 ml/min per kg fetal body weight (Vosters, 1983) and assuming a similar blood flow distribution, umbilical venous flow values of 110-125 ml/min per kg fetal body weight in the human fetus can be expected. The rise in volume flow in the umbilical vein during the 3rd trimester is mainly determined by the increase in vessel size.

Reduced volume flow per kg fetal body weight particularly over a longer period of time, seems to be associated with poor fetal outcome. However, as has already been pointed out in the descending aorta studies, it should be realized that the umbilical venous flow results should be considered in the light of the errors introduced by vessel size and fetal weight estimations. Jouppila and Kirkinen (1984a), however, believe that the vasoconstriction of the umbilical vein in hypoxic fetuses is not a methodological error but should be considered a fundamental factor in impaired umbilical venous blood flow.

The rise in volume flow in the umbilical vein in Rh-isoimmunisation appears to be determined by both an increase in blood flow velocity and vessel size (Jouppila and Kirkinen, 1984b). The rise in blood flow velocity has been attributed to insufficient tissue oxygenation or alteration of blood viscosity due to the decreased red cell mass in fetal haemolytic anaemia, whereas the significant increase in umbilical vein diameter indicates a possible active vasodilatation process (Jouppila and Kirkinen, 1984b). Dilatation of the umbilical vein in severe Rh-isoimmunisation has been described before by de Vore (1981). The raised volume flow values in maternal anaemia and uterine bleeding are more difficult to appreciate, although also here some compensatory mechanism should be considered.

5.3. **Effects of internal and external variables on fetal blood flow**

Fetal blood flow is affected by internal variables such as fetal breathing movements and fetal cardiac arrhytmia. Only a few reports are available on possible effects of external variables, such as maternal smoking, exercise and medication on fetal blood flow.

5.3.1. *Internal variables*

In 1976, Boyce et al were able to detect Doppler shifts synchronous with fetal breathing movements. A little later, it was established that during fetal inspiration a momentary increase in inferior vena cava flow velocity and decrease in umbilical

venous flow velocity occurred (Gough and Poore, 1977; Goodman and Mantell, 1978). Eik-Nes et al (1980c) carefully analysed the relationship between different patterns of fetal breathing movements (FBM) and umbilical venous blood flow. During a period of high amplitude FBM an average increase of 20-30% in venous blood flow was observed, whereas during low amplitude FBM the velocity curve was affected, but volume flow stayed unaltered. They also established that a decrease in flow velocity occurred during inspiration and an increase during expiration.

Similar findings were done in the lower thoracic part of the fetal descending aorta. During apnoea the flow is pulsatile and regular. During FBM there are rhythmic changes in the flow velocity pattern mainly during diastole. As a result a flow increase during FBM of about 15-20% was observed (Marsal et al, 1984).

Fetal cardiac arrhythmia is usely first detected by routine auscultation. They may demonstrate as ectopic beats, usely of supraventricular origin or as different degrees of bradycardia and tachycardia. An increase in fetal aortic blood flow following ectopic beats was first reported by Eik-Nes et al (1980b) and later by Marsal et al (1982). Wladimiroff et al (1983) established an increase in flow acceleration and peak mean blood flow velocity in the lower thoracic part of the descending aorta during marked bradycardia reflecting a rise in cardiac contraction force, whereas during severe tachycardia, a very low flow acceleration and peak mean blood flow velocity as a result of markedly reduced cardiac concentration force was noted. From further studies by Tonge et al (1984) it appeared that at heart rates less than 50 and more than 250 beats per minute a fall off in blood flow in the lower thoracic part of the descending aorta occurs.

5.3.1.1. Comments

The described modulations of umbilical venous and aorta blood flow velocity during breathing periods in the human fetus resemble the modulation in electromagnetically measured flow in the descending aorta (Dawes et al, 1972) and inferior vena cava in fetal lamb (Rudolph and Heymann, 1979). Of interest is that during inspiration a distinct elongation of the umbilical vein occurs. This seems less likely in the descending aorta because of its stiffer vessel wall structure. It seems reasonable to assume that the velocity changes observed in the umbilical vein and the descending aorta are directly related to pressure changes during contractions of the diaphragm. Since it has been demonstrated that in particular high amplitude FBM exert a profound influence on fetal blood flow, it seems correct to carry out flow measurements only during periods of fetal apnea.

The increased peak mean blood flow velocity following an ectopic beat and during severe bradycardia indicates that the fetal heart is capable of increasing its stroke volume in compensation of ineffective beats. Although this was previously denied by several workers in the animal experimental field (Arcilla et al, 1966; Rudolph and Heymann, 1974) it is supported by the finding of a significant

correlation between the beat-to-beat interval and peak mean blood flow velocity in the aorta of fetal lamb (Kirkpatrick et al, 1976).

The fall off in aortic stroke volume and blood flow below 50 and above 250 b.p.m. in the human fetus suggests that heart rates around these levels are the functional limits of the fetal myocardium to the Frank-Starling mechanism (Tonge et al, 1984).

5.3.2. *External variables*

Only a very limited number of reports have appeared on external variables and fetal blood flow. Short term intravenous infusion of ritodine hydrochloride (maximum dose of 200 μg/minute) to pregnant women with premature labour did not result in any significant change in volume blood flow in the umbilical vein and fetal descending aorta (Jouppila et al, 1981). This is in agreement with results obtained in chronic sheep preparations (Ehrenkranz et al, 1976; Siimes et al, 1978).

Intravenous maternal dihydralazine infusion (maximum dose 10 μg/minute) during sixty minutes did not result in any appreciable change in volume blood flow in the umbilical vein and fetal descending aorta, although in some cases an increased diastolic flow profile in the fetal descending aorta indicating diminished peripheral resistance, was demonstrated (Jouppila et al, 1983c).

Recently, the influence of maternal oxygen inhalation on human placental and umbilical venous blood flow was studied (Jouppila et al, 1983b). The direct reason for this study was based on the longstanding assumption that inhalation of oxygen by the mother may improve fetal condition during threatening or manifest hypoxia. Whereas the intervillous blood flow as measured by the 133 Xe isotope clearance method showed a significant reduction, following maternal short term inhalation of oxygen ($5LO_2$/min), umbilical venous blood flow maintained its original level. Similar results were reported by Longo and Lower (1976), who suggested that umbilical blood flow in the sheep does not primarily alter the direction of the change in oxygen transfer to the fetus. Also Battaglia et al (1968) in anaesthetized sheep did not observe any significant elevations in oxygen pressure in uterine and umbilical blood.

Only one report has so far appeared on the effect of maternal smoking and on the effect of maternal exercise on the human fetal cardiovascular system. The latter two external variables are the subjects of our own studies which are presented in Chapter 7 and Chapter 8.

References

Arcilla, R.A., J. Lind, P. Zetterqvist, W. Oh, I.H. Gessner. Hemodynamic features of extrasystoles in newborn and older infants. Am. J. Cardiol.: 18, 191-199, 1966.

Assali, N.S., L. Rauramo, T. Peltonen. Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy. Am. J. Obstet. Gynecol.: 79, 86-98, 1960.

Battaglia F.C., G. Meschia, E.L. Makowski, W. Bowes. The effect of maternal oxygen inhalation upon fetal oxygenation. J. Clin. Invest.: 47, 548-555, 1968.

Berman, W., R.C. Goodlin, M.D. Heymann, A.M. Rudolph. Measurement of umbilical blood flow in fetal lambs in utero. J. Appl. Physiol.: 39, 1056-1059, 1975.

Boyce, E.S., G.S. Dawes, J.D. Gough, E.R. Poore. Doppler ultrasound method for detecting human fetal breathing in utero. Br. Med. J.: 2, 17-18, 1976.

Campbell, S., C.J. Dewhurst. Diagnosis of the small-for-dates fetus by serial ultrasonic cephalometry. Lancet, ii, 1002-1006, 1971.

Campbell, S., D. Wilkin. Ultrasonic measurement of fetal abdomen circumference in the estimation of fetal weight. Br. J. Obst. & Gyn.: 82, 689-697, 1975.

Clapp, J.F., H.H. Szeto, R. Larrow, J. Hewitt, L.I. Mann. Umbilical blood flow response to embolisation of the uterine circulation. Am. J. Obstet. Gynecol.: 138, 60-67, 1980.

Dawes, G.S. The umbilical circulation. In: Fetal and neonatal physiology yearbook. Chicago: Medical Publishers, pp. 66-78, 1968.

Dawes, G.S., H.E. Fox, B.M. Leduc, G.C. Liggins, R.T. Richards. Respiratory movements and rapid eye movement sleep in the fetal lamb. J. Physiol.: 220, 119-143, 1972.

DeVore, E., K. Mayden, M. Tortora, R. Berkowitz, J. Hobbins. Dilatation of the fetal umbilical vein in rhesus hemolytic anaemia: a predictor of severe disease. Am. J. Obstet. Gynecol.: 141, 464-466, 1981.

Ehrenkranz, R.A., A.M. Walker, E.K. Oates, M.K. McLaughlin, R.A. Chez. Effect of ritodrine infusion on uterine and umbilical blood flow in pregnant sheep. Am. J. Obstet. Gynecol.: 126, 343-349, 1976.

Eik-Nes, S.H., A.O. Brubakk, M.K. Ulstein. Measurement of human fetal blood flow. Br. Med. J.: 1, 283-284, 1980a.

Eik-Nes, S.H. Ultrasonic assessment of human fetal weight, growth and blood flow. Thesis. Malmo, 1980b.

Eik-Nes, S.H., K. Marsal, A.O. Brubakk, M.K. Ulstein. Ultrasonic measurements of human fetal blood flow in aorta and umbilical vein. Influence of fetal breathing movements. In: Recent advances in Ultrasound Diagnosis II. Ed: Kurjak, A. Amsterdam Excerpta Medica.: pp. 233-240, 1980c.

Eik-Nes, S.H., K. Marsal, A.O. Brubakk, K. Kristofferson, M.K. Ulstein. Ultrasonic measuremen of human fetal blood flow. J. Biomed. Engng.: 4, 28-36, 1982a.

Eik-Nes, S.H., P. Grottum, N.J. Andersson. Estimation of fetal weight by ultrasound measurement. 2. Clinical application of a new formula. Acta Obstet. Gynecol. Scand.: 61, 307-312, 1982b.

Fendel, H., M. Fendel, R. Warnking. Fehlermöglichkeiten der gepulsten Dopplermethode zur Blutflussmessung am Feten. Z. Geburtsh. u. Perinat.: 187, 83-87, 1983.

FitzGerald, D.E., J.E. Drumm. Non-invasive measurement of the fetal circulation using ultrasound. Br. Med. J.: 2, 1450-1451, 1977.

FitzGerald, D.E., B. Stuart, J.E. Drumm, N.M. Duignan. The assessment of the feto-placental circulation with continuous wave Doppler ultrasound. Ultrasound in Med. & Biol.: 10, 371-376, 1984.

Giles, W.B., B.J. Trudinger, P.J. Baird. Antenatal assessment of placental flow resistance and placental microvascular anatomy. In: 10th Conference on fetal breathing movements and other fetal measurements. Malmö. pp. 81., 1983.

Gill, R.W. Quantitavie blood flow measurement in deep lying vessels using pulsed Doppler with the Octoson. In: Ultrasound in Medicine, Vol. 4, Ed: White, D.N. and E.A. Lyons, New York, Plenum Press, pp. 341-348, 1978.

Gill, R.W., Pulsed Doppler with B-mode imaging for quantitative blood flow measurement. Ultrasound in Med. Biol.: 5, 223-235, 1979.

Gill, R.W., G. Kossoff. Pulsed Doppler combined with B-mode imaging for blood flow measurement. Contr. Gynec. Obstet.: 6, 139-141, 1979.

Gill, R.W., B.J. Trudinger, W.J. Garrett, G. Kossoff, P.S. Warren. Fetal umbilical venous flow measured in utero by pulsed Doppler and B-mode ultrasound. 1. Normal pregnancies. Am. J. Obstet. Gynecol.: 139, 720-725, 1981.

Gill, R.W., P.S. Warren, G. Kossoff, W.J. Garrett. Umbilical venous flow in normal and complicated pregnancy. Ultrasound in Med. Biol.: 10, 349-363, 1984.

Goodman, J., C.D. Mantell. Two means of measuring fetal breathing movements by the Doppler method. In: Proceedings of the 5th Conference on fetal breathing. Ed: T.K.A.B. Eskes Nijmegen, pp. 106, 1978.

Gosling, R.G., D.H. King. Ultrasound Angiology In Arteries and Veins. Ed: Maran, A.W., L. Adamson, Edinburgh, Churchill Livingstone, pp. 61-98, 1975.

Gough, J.D., E.R. Poore. A continuous wave Doppler ultrasound method for recording fetal breathing in utero. Ultrasound in Med. Biol.: 5, 249-256, 1977.

Griffin, D., K. Bilardo, J. Diaz, M. Teague, S. Campbell. The measurement of human fetal blood flow with linear array pulsed Doppler duplex. In: Proceedings VIIIth European Congress of Perinatal Medicine, Brussels. Eur. J. Obstet. Gynec. Reprod. Biol.: 15, 426-430, 1983a.

Griffin, D., T. Cohen-Overbeek, S. Campbell. Fetal and uteroplacental blood flow. In Clinics in Obstetrics and Gynecology. Ed: Campbell, S. London Saunders Company, pp. 565-602, 1983b.

Hamilton, W.J., J.D. Boyd. Development of the human placenta. In: Scientific Foundations of Obstetrics and Gynecology. Ed: Philpp, E.E., J. Barnes, M. Newton. London. William Heineman Medical books limited, 1970.

Huikeshoven, F.J., I.D. Hope, G.G. Power, R.D. Gilbert, L.D. Longo. A comparison of sheep and fetal oxygen delivery systems with use of a mathematical model. Am. J. Obstet. Gynecol. 151, 449-455, 1985.

Jouppila, P., P. Kirkinen, S.H. Eik-Nes, A. Koivula. Fetal and intervillous blood flow measurements in late pregnancy. In: Recent advances in Ultrasound Diagnosis. III. Ed.: Kurjak, A., A. Kratochwil Amsterdam Excerpta Medica, pp. 226-233, 1981.

Jouppila, P., P. Kirkinen, S.H. Eik-Nes. Acute effect of maternal smoking on the human fetal blood flow. Br. J. Obst. Gyn.: 90, 7-10, 1983a.

Jouppila, P., P. Kirkinen, A. Koivula, R. Jouppila. The influence of maternal oxygen inhalation on human placental and umbilical venous blood flow. Europ. J. Obstet. Gynaec. reprod. Biol.: 16, 151-156, 1983b.

Jouppila, P., P. Kirkinen, A. Koivula. Effect of maternal dihydralazine infusion of the human placental and fetal blood flow. In: 10th Conference on fetal breathing movements and other fetal measurements Malmö, pp. 85, 1983c.

Jouppila, P., P. Kirkinen. Umbilical vein blood flow as an indicator of fetal hypoxia. Br. J. Obstet. Gyn.: 91, 107-110, 1984a.

Jouppila, P., P. Kirkinen. Umbilical vein blood flow in the human fetus in cases of maternal and fetal anemia and uterine bleeding. Ultrasound in Med. Biol.: 10, 365-370, 1984b.

Kirkpatrick S.E., P.T. Pitlick, J. Nabiloff, W.F. Friedman. The importance of the Frank-Starling relationship as a determinant of fetal cardiac output. Am. J. Physiol.: 231, 495-500, 1976.

Kurjak A., B. Rajhvajn. Ultrasonic measurement of umbilical blood flow in normal and complicated pregnancies. J. Perinat. Med.: 10, 3-16, 1982.

Lingman, G., J. Laurin, K. Marsal. Aortic blood flow in normal and growth retarded fetuses. In: 10th Conference on fetal breathing movements and other fetal measurements, Malmö, pp. 79, 1983.

Longo, L.D., G.G. Lower. Placental oxygen transfer: a system approach. In: Reviews in Perinatal Medicine. Ed. Scarpelli, E.M., E.V. Cosmi. Baltimore University Park Press, pp. 1-34, 1976.

McCallum, W.D., C.S. Williams, S. Napel, R.E. Daigle. Fetal blood velocity waveforms. Am. J. Obstet. Gynecol.: 132, 425-429, 1978.

McDonald, D.A. Blood flow in arteries. 2nd Edition, London, Edward Arnold Publish. Limited 1974.

Marsal, K., S.H. Eik-Nes, P.H. Persson, M.K. Ulstein. Blood flow in the human fetal aorta in normal pregnancy and in fetal cardiac arrhythmia. Acta Obstet. & Gynec. Scandinavica (supplement): 93, 39, 1982.

Marsal K., S.H. Eik-Nes, A. Lindblad, G. Lingman. Blood flow in the fetal descending aorta. Intrinsic factors affecting fetal blood flow. Ultrasound in Med. Biol.: 10, 339-348, 1984.

Maulik, D., V.D. Saini, N.C. Nauda, M.S. Rosenzweig. Doppler evaluation of fetal hemodynamics. Ultrasound in Med. Biol.: 6, 705-710, 1982.

Meschia, G., J.R. Cotter, E.L. Makowski, D.H. Barron. Simultaneous measurement of uterine and umbilical blood flows and oxygen uptakes. Q. J. Exp. Physiol.: 52, 1-18, 1967.

Planiol, T., L. Pourcelot. Doppler effect study of the carotid circulation. In: Proceedings of the 2nd World Congres of Ultrasound in Medicine. Ed: de Vlieger, M., D.N. White, P. Creedy. New York American Elsevier Publications Company Incorporated, 1975.

Rajhvajn, B., A. Kurjak. Ultrasound measurements of umbilical blood flow in normal and complicated pregnancies. In: Recent advances in ultrasound diagnosis III. Ed.: Kurjak, A., A.A. Kratochwil, Amsterdam, Excerpta Medica, pp. 240-242, 1981.

Reuwer, P.J.H.M., W.C. Nuyen, H.J.M. Beijer, R.M. Heethaar, H.W. Bruinse, Ph. Stoutenbeek, A.A. Haspels. Characteristics of flow velocities in the umbilical arteries, assessed by Doppler ultrasound. Europ. J. Obstet. Gynec. Reprod. Biol.: 17, 397-408, 1984.

Reuwer, P.J.H.M., H.W. Bruinse, Ph. Stoutenbeek, A.A. Haspels. Doppler assessment of the feto-placental circulation in normal and growth-retarded fetuses. Europ. J. Obstet. Gynec. reprod. Biol.: 18, 199-205, 1984b.

Rudolph, A.M., M.A. Heymann. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ. Research.: 21, 163-184, 1967.

Rudolph, A.M., M.A. Heymann. Fetal and neonatal circulation and respiration. Ann. Review Physiol.: 36, 187-207, 1974.

Rudolph, A.M., Factors affecting umbilical blood flow in the lamb in utero. In: Proceedings 5th European Congress of Perinatal Medicine, Uppsala, pp. 159-172, 1976.

Schulman, H., A. Fleischer, W. Stern, G. Farmakides, N. Jagani, P. Blattner. Umbilical velocity wave ratios in human pregnancy. Am. J. Obstet. Gynecol.: 148, 985-990, 1984.

Siimes, A.S.I., R.K. Creasy, M.A. Heymann, A.M. Rudolph. Cardiac output and its distribution and organ blood flow in the fetal lamb during ritodrine administration. Am. J. Obstet. Gynecol.: 132, 42-48, 1978.

Stembera, Z.K., J. Hodr, V. Ganz, A. Fronek. Measurement of umbilical cord blood flow by local thermodilution. Am. J. Obstet. Gynecol.: 90, 532-536, 1964.

Stuart, B., J. Drumm, D.E. FitzGerald, N.M. Duignan. Fetal blood flow velocity waveform in normal pregnancy. Br. J. Obstet. Gyn.: 85, 780-785, 1980.

Stuart, B., J. Drumm, D.E. FitzGerald, N.M. Duignan. Fetal blood velocity waveforms in uncomplicated labour. Br. J. Obstet. Gyn.: 88, 865-869, 1981.

Tonge, H.M., P.C. Struijk, P. Custers, J.W. Wladimiroff. Vascular dynamics in the descending aorta of the human fetus in normal late pregnancy. Early Human Development: 9, 21-26, 1983.

Tonge, H.M., P.A. Stewart, J.W. Wladimiroff. Fetal blood flow measurements during fetal cardiac dysrhythmia. Early Human Development: 10, 23-24, 1984.

Trudinger, B.J., C.M. Cook. Fetal umbilical artery waveforms. Ultrasound in Med. Biol.: 8, 197, 1982.

Trudinger, B.J., W.B. Giles, C.M. Cook. Fetal umbilical artery flow velocity waveforms and placental resistance. The relationship to clinical outcome. In: 10th Conference on fetal breathing movements and other fetal measurements. Malmö, pp. 87, 1983.

Vosters, R.P.L. Fetal and early neonatal cardiac ventricular geometry and function. An echografic study. Thesis. Rotterdam, 1983.

Wladimiroff, J.W. Preliminary report on fetal cardiovascular dynamics in normal and hypertensive pregnancy. In: Current status of EPH Gestosis. Ed.: Kurjak, A., E.T. Rippmann, V. Sulovic. Amsterdam Excerpta Medica, pp. 317-325, 1980.

Wladimiroff, J.W., R.P.L. Vosters, J.S. McGhie, P.C. Struijk. Human fetal cardiovascular dynamics during the last trimester of pregnancy and first 48 hours following delivery. In: Recent advances in Ultrasound diagnosis III. Ed: Kurjak, A., A.A. Kratochwil. Amsterdam Excerpta Medica. pp. 203-208, 1981.

Wladimiroff, J.W., P.C. Struijk, P.A. Stewart, P. Custers, V.H. de Villeneuve. Fetal cardiovascular dynamics during cardiac dysrhythmia. Case report. Br. J. Obstet. Gyn.: 90, 573-577, 1983.

Chapter 6

MEAN BLOOD FLOW VELOCITY AND VESSEL DIAMETER AT THE LOWER THORACIC LEVEL OF THE HUMAN FETAL DESCENDING AORTA DURING THE LAST TRIMESTER OF PREGNANCY

In this chapter the reproducibility of flow velocity and vessel diameter measurements as well as normal values for these measurements and calculated volume flow in the lower thoracic part of the fetal descending aorta during the third trimester of pregnancy will be presented. All measurements were carried out during fetal apnoea.

6.1. **Reproducibility of flow velocity and vessel diameter measurements**

The reprodubicility of mean blood flow velocity and vessel diameter was assessed in six normal pregnancies between 34 and 38 weeks of gestation.

In each subject, mean blood flow velocity and vessel diameter recordings were analysed during six consecutive periods of 7.5 minutes each. This recording period of 7.5 minutes was determined by our criterion that only high quality blood flow recordings of at least one minute duration were acceptable for evaluation. All subjects wer studied at 3 different occasions of forty-five minutes each: on day 1 at 14.00 and 16.00 hours by one observer for the assessment of the intra-observer variation and on day 2 at 14.00 hours by another observer for the assessment of the inter-observer variation.

The results for the mean blood flow velocity are represented in Tables 6.1 and 6.2 and for the vessel diameter in Tables 6.3 and 6.4.

From Tables 6.1 and 6.2 the variance between the intra- and inter-observer study for all six periods can be calculated. The variance for the intra-observer study ranges between 0.25 and 0.60 and for the inter-observer study between 0.30 and 0.63. From these results it can be concluded that there is no difference in mean blood flow velocity variance between the intra- and inter-observer study.

The variance in vessel diameter measurements in the intra-observer study (Table 6.3) ranges between 0.02 and 0.04 and in the inter-observer study (Table 6.4) between 0.03 and 0.05. From these results it can be concluded that there is no difference between vessel diameter variance in the intra- and inter-observer study.

Table 6.1. Intra-observer variation for the mean blood flow velocity (cm/sec).

Patient no.	Time of measurement	STUDY PERIODS I	II	III	IV	V	VI
1.	14.00 h	26.1	26.6	27.7	26.5	28.1	27.4
	16.00 h	27.4	26.5	27.2	28.1	27.4	26.4
2.	14.00 h	28.1	27.5	28.8	29.3	28.4	28.9
	16.00 h	29.2	27.1	28.6	27.9	28.2	26.4
3.	14.00 h	28.8	28.6	29.6	30.3	27.9	28.9
	16.00 h	27.3	29.4	29.3	30.1	28.4	29.3
4.	14.00 h	27.7	27.6	28.5	27.4	27.8	29.3
	16.00 h	28.5	29.4	27.6	28.4	26.3	28.1
5.	14.00 h	30.1	29.6	29.1	30.4	30.2	28.8
	16.00 h	29.9	30.5	28.6	31.0	30.3	27.5
6.	14.00 h	26.8	27.4	27.2	28.1	27.6	27.7
	16.00 h	28.1	28.4	29.0	27.1	27.6	28.6

Mean blood flow velocity values during six study periods at 14.00 and 16.00 h as studied by one observer.

Table 6.2. Inter-observer variation for the mean blood flow velocity (cm/sec).

Patient no.	Day and Time of measurement	STUDY PERIODS I	II	III	IV	V	VI
1.	1 14.00 h	26.1	26.6	27.7	26.5	28.1	27.4
	2 14.00 h	25.7	28.0	26.8	26.5	26.6	27.4
2.	1 14.00 h	28.1	27.5	28.8	29.3	28.4	28.9
	2 14.00 h	27.3	27.7	29.6	28.6	29.2	27.8
3.	1 14.00 h	28.8	28.6	29.6	30.3	27.9	28.9
	2 14.00 h	29.3	29.4	30.1	30.4	28.7	29.1
4.	1 14.00 h	27.7	27.6	28.5	27.4	27.8	29.3
	2 14.00 h	29.0	28.6	27.4	28.8	28.7	27.7
5.	1 14.00 h	30.1	29.6	29.1	30.4	30.2	28.8
	2 14.00 h	29.0	29.5	30.3	28.9	29.2	29.5
6.	1 14.00 h	26.8	27.4	27.2	28.1	27.6	27.7
	2 14.00 h	27.4	27.4	27.0	26.4	29.0	27.3

Mean blood flow velocity values during six study periods at 14.00 h on two consecutive days as studied by two different observers.

Table 6.3. Intra-observer variation for the vessel diameter (mm).

Patient no.	Time of measurement	STUDY PERIODS I	II	III	IV	V	VI
1.	14.00 h	6.6	6.9	6.7	6.5	6.4	6.6
	16.00 h	6.5	6.6	6.5	6.8	6.7	6.3
2.	14.00 h	5.8	5.5	5.4	5.6	5.3	5.9
	16.00 h	5.5	5.6	5.6	5.4	5.4	5.7
3.	14.00 h	4.9	5.2	4.8	5.1	5.4	5.3
	16.00 h	5.1	5.2	5.0	4.9	5.0	5.1
4.	14.00 h	7.1	7.4	7.3	7.5	7.0	7.2
	16.00 h	7.0	6.9	7.1	7.2	7.2	7.3
5.	14.00 h	6.6	6.9	7.0	6.5	6.4	6.8
	16.00 h	6.8	6.7	7.1	6.6	6.7	6.9
6.	14.00 h	6.0	6.4	6.2	5.9	6.1	6.3
	16.00 h	6.3	6.1	6.0	6.3	6.2	6.4

Averaged vessel diameter values during six study periods at 14.00 and 16.00 h as studied by one observer.

Table 6.4. Inter-observer variation for the vessel diameter (mm)

Patient no.	Day and Time of measurement	STUDY PERIODS I	II	III	IV	V	VI
1.	1 14.00 h	6.6	6.9	6.7	6.5	6.4	6.6
	2 14.00 h	6.3	6.5	6.4	6.8	6.3	6.7
2.	1 14.00 h	5.8	5.5	5.4	5.6	5.3	5.9
	2 14.00 h	5.8	5.7	5.6	5.7	5.7	5.5
3.	1 14.00 h	4.9	5.2	4.8	5.1	5.4	5.3
	2 14.00 h	5.3	5.1	5.2	4.9	5.0	5.1
4.	1 14.00 h	7.1	7.4	7.3	7.5	7.0	7.2
	2 14.00 h	7.3	7.1	7.2	7.1	7.5	7.1
5.	1 14.00 h	6.6	6.9	7.0	6.5	6.4	6.8
	2 14.00 h	6.9	7.0	6.6	6.8	6.7	6.5
6.	1 14.00 h	6.0	6.4	6.2	5.9	6.1	6.3
	2 14.00 h	6.3	6.2	6.0	6.2	5.9	6.0

Averaged vessel diameter values during six study periods at 14.00 h on two consecutive days by two different observers.

6.2. Mean blood flow velocity, vessel diameter and calculated volume flow

6.2.1. *Data selection*

Data were derived from 126 randomly selected subjects with an uncomplicated pregnancy between 28 and 39 weeks of gestation. In six patients we were not able to obtain a high quality blood flow velocity recording, mostly due to an unfavourable position of the fetus. All women were of caucasian origin. Pregnancy was considered normal when the following conditions were fulfilled:

- known date of last menstrual period and confirmation of calculated gestational age from a single measurement of the fetal biparietal diameter (B.P.D.) between 16 and 22 weeks of gestation;
- spontaneous delivery after a pregnancy duration of at least 38 weeks;
- normal fetal growth resulting in a birth weight between 10th and 90th percentile for weight of gestation according to the Tables of Kloosterman (Kloosterman, 1970), corrections being made for maternal parity and fetal sex;
- Apgarscore at one minute 8 or more;
- no congenital abnormalities.

6.2.2. *Recording procedure*

Mean blood flow velocity (cm/sec) was established from 20 consecutive cardiac cycles representing high quality flow velocity waveforms as defined in chapter 3.

The aortic diameter (mm) was measured from an M-mode recording at the same level of the lower thoracic part of the descending aorta during 20 consecutive cardiac cycles. For each cardiac cycle the mean vessel diameter was determined from the following equation:

$$\frac{\text{systolic diameter} + \text{diastolic diameter}}{2}$$

The averaged value over 20 cardiac cycles was subsequently calculated.

6.2.3. *Calculation of volume flow*

Volume blood flow (Q) in the lower thoracic level of the fetal descending aorta is calculated using the formula:

$$Q(\text{ml/min}) = \frac{V \times A}{\cos \alpha}$$

where V = mean blood flow velocity, A = vessel luminal area and α = angle between the Doppler and real-time transducer. Vessel lumina area (A) is established from the (averaged vessel diameter)$^2 \times \frac{1}{4} \pi$.

6.2.4. *Results*

6.2.4.1. Mean blood flow velocity

Figure 6.1 demonstrates the mean ± SD for the mean blood flow velocity data (cm/sec) between 28 and 39 weeks of gestation. Numerical data are presented in Table 6.5. There is a gradual decrease from 30.3 ± 2.0 cm/sec at 28 weeks to 26.5 ± 1.5 cm/sec at 39 weeks. This decrease is statistically significant as is shown in figure 6.2 (line of regression: $y = 0.33x + 39.68$; correlation coefficient: –0.59).

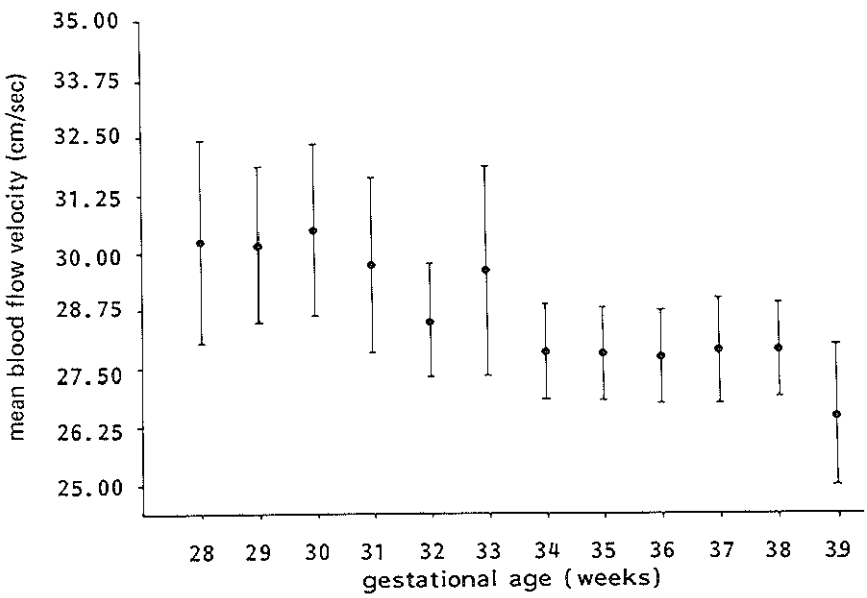


Fig. 6.1. Mean ± SD for the mean blood flow velocity during the third trimester of pregnancy.

Table 6.5. Mean ± 1 SD values at different gestational ages for mean blood flow velocity (cm/sec), averaged vessel diameter (mm) and volume flow (ml/min).

	GETATIONAL AGE (weeks)											
	28	29	30	31	32	33	34	35	36	37	38	39
Mean blood flow velocity	30.3 ± 2.1	30.2 ± 1.7	30.5 ± 1.9	29.8 ± 1.9	28.5 ± 1.2	29.6 ± 2.3	27.9 ± 0.9	27.8 ± 1.0	27.6 ± 1.0	27.9 ± 1.2	27.9 ± 1.0	26.5 ± 1.5
Averaged vessel diameter	4.8 ± 0.2	5.0 ± 0.2	5.2 ± 0.2	5.4 ± 0.3	5.6 ± 0.3	5.8 ± 0.1	6.0 ± 0.2	6.4 ± 0.2	6.8 ± 0.1	7.1 ± 0.2	7.3 ± 0.4	7.5 ± 0.3
Volume flow	327 ± 46	352 ± 26	388 ± 36	411 ± 45	423 ± 54	473 ± 40	479 ± 36	543 ± 43	605 ± 28	667 ± 57	705 ± 61	696 ± 57

Normal values for mean blood flow velocity, averaged vessel diameter and volume flow during the third trimester of pregnancy.

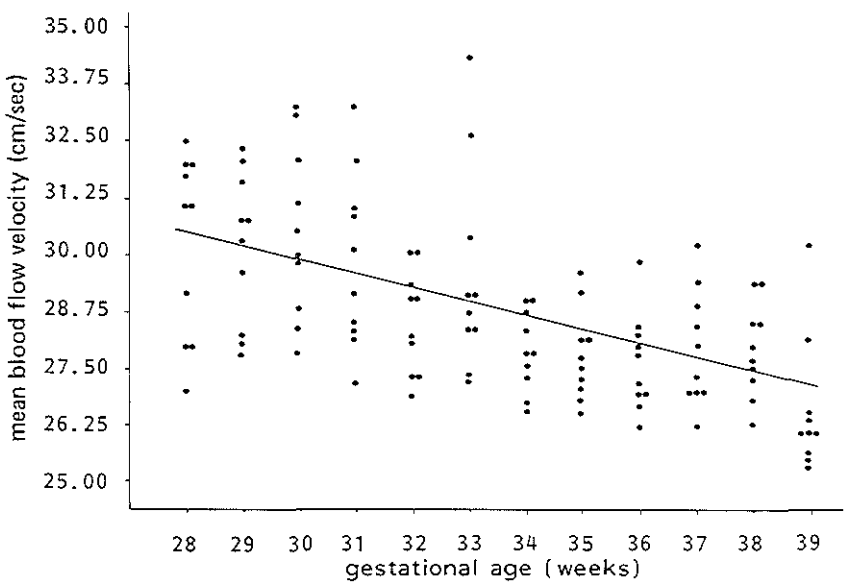


Fig. 6.2. Normal values for the mean blood flow velocity and the linear regression line during the third trimester of pregnancy.

6.2.4.2. Vessel diameter

Figure 6.3 depicts the mean ± 1 SD for the averaged values (mm) between 28 and 39 weeks of gestation. Numerical data are given in Table 6.5. There is a marked increase from 4.8 ± 0.2 mm at 28 weeks to 7.5 ± 0.3 mm at 39 weeks. This increase is statistically highly significant as is demonstrated in figure 6.4 (line of regression: $y = 0.26x - 2.55$; correlation coefficient: 0.96).

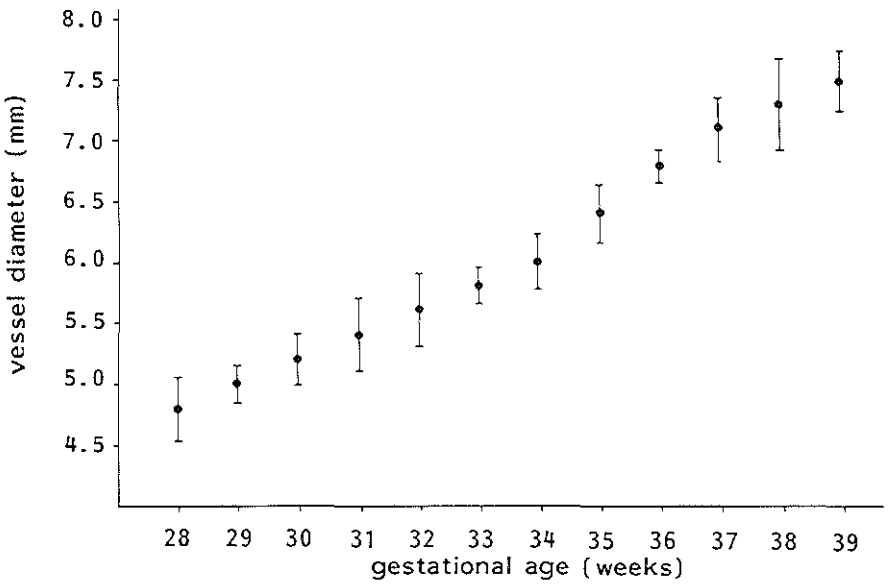


Fig. 6.3. Mean ± SD for the averaged vessel diameter during the third trimester of pregnancy.

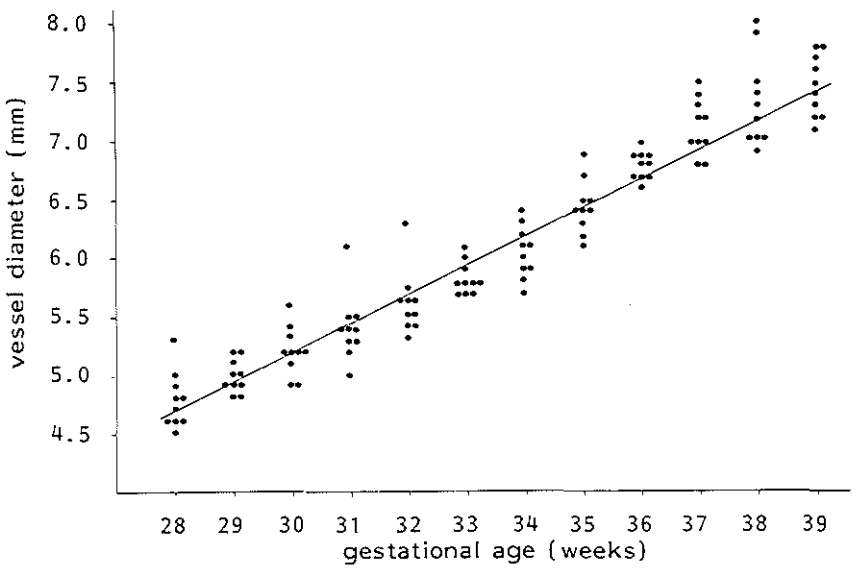


Fig. 6.4. Normal values for the averaged vessel diameter and the linear regression line during the third trimester of pregnancy.

6.2.4.3. Volume flow

Figure 6.5 shows the mean ± 1 SD between 28 and 39 weeks of gestation. Numerical data are presented in Table 6.5. There is a pronounced rise in volume flow from 327 ± 46 ml/min at 28 weeks to 705 ± 61 ml/min at 38 weeks. This rise is statistically highly significant as is demonstrated in figure 6.6 (line regression: $y = 36.8x - 727.4$; correlation coefficient: 0.93).

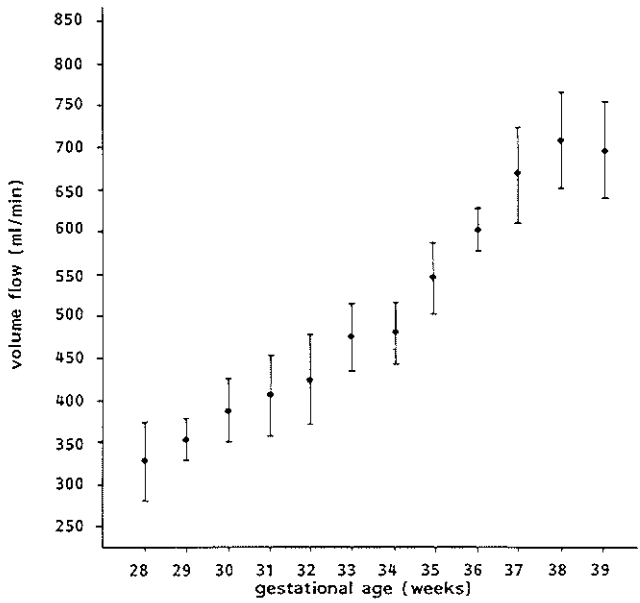


Fig. 6.5. Mean ± SD for the volume flow during the third trimester of pregnancy.

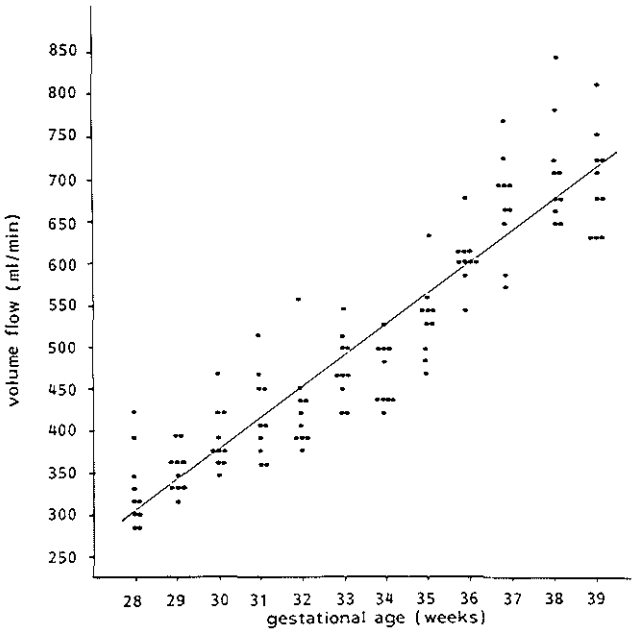


Fig. 6.6. Normal values for the volume flow and the linear regression line during the third trimester of pregnancy.

6.2.5. *Discussion*

The presented data on mean blood flow velocity are in the same range as reported by Griffin et al (1983), Fendel et al (1983) and Marsal et al (1984). The gradual reduction in mean blood flow velocity during the third trimester of pregnancy, as observed in our study, has not been established in others, although there is a general agreement on lower mean blood flow velocity values around term. The present results on mean blood flow velocity are higher than those published at an earlier stage by Eik-Nes et al (1980) and Wladimiroff et al (1980). The difference is determined by the lowering of the cut-off level of the high-pass filters from 600 to 150 Hertz, thus providing more realistic information on Doppler shifts during diastole.

The demonstrated increase in vessel diameter of about 50% during the third trimester of pregnancy is in close agreement with the findings reported by Fendel et al (1983), and Marsal et al (1984). The marked rise in volume flow is mainly determined by the increase in vessel size, i.e. aortic volume flow is proportional to the growing fetal body.

From studies in the fetal lamb (Shinebourne, 1974) it is known that about 70% of the total cardiac output is directed to the descending aorta. In the human fetus a total cardiac output in late pregnancy between 800 and 900 ml was calculated by Vosters (1983). Based on our aortic volume flow values of about 700 ml, this means

that also in the human term fetus 70-80% of the total cardiac output is directed to the descending aorta. The wide distribution in presented volume flow data is mainly determined by the errors introduced by vessel diameter measurements from M-mode recordings, the limitations and pitfalls of which have been discussed in Chapter 9.

It seems therefore, as pointed out earlier in Chapter 5.1.1.2., that the clinical value of volume flow measurements based on present recording techniques is limited. It was therefore decided that in studies dealing with possible effects of external stimuli (maternal smoking and exercise) blood flow velocity and vessel diameter as determined from M-mode recordings should be considered separately.

References

Eik-Nes, S.H., A.O. Brubakk, M.K. Ulstein. Measurement of human fetal blood flow. Br. Med. J. 1, 283-284, 1980.

Fendel, H., M. Fendel, R. Warnking. Fehlermöglichkeiten der gepulsten Doppler Methode zur Blutflussmessung am Feten. Z. Geburtsh. u. Perinat. 187, 83-87, 1983.

Griffin, D., T. Cohen-Overbeek, S. Campbell. Fetal and uteroplacental blood flow. In: Clinics in Obstetrics and Gynecology. Ed: Campbell, S. London Saunders Company, pp. 565-602, 1983.

Kloosterman, G. On intra-uterine growth. The significance of prenatal care. Int. J. Gynaecol. Obstet. 8, 895-904, 1970.

Marsal, K., S.H. Eik-Nes, A. Lindblad, G. Lingman. Blood flow in the fetal descending aorta. Intrinsic factors affecting fetal blood flow. Ultrasound in Med. Biol., 10, 339-348, 1984.

Shinebourne, E.A. Growth and development of the cardiovascular system. In: Scientific Foundations of Pediatrics. Ed: DaviesJ.A., J. Dobbing, London, William Heineman. Medical Books Ltd, 13b, 198-212, 1974.

Vosters, R.P.L. Fetal and early neonatal cardiac ventricular geometry and function. An echographic study. Thesis, Rotterdam, 1983.

Wladimiroff, J.W. Preliminary report on fetal cardiovascular dynamics in normal and hypertensive pregnancy. In: Current status of E.P.H. Gestosis. Ed: Kurjak, A., E.T. Rippmann and V. Sulovic, Amsterdam, Excerpta Medica 317-325, 1980.

Wladimiroff, J.W., R.P.L. Vosters, J.S. McGhie, P.C. Struijk. Human fetal cardiovascular dynamics during the last trimester of pregnancy and first 48 hours following delivery. In: Recent advances in Ultrasound diagnosis III. Ed: Kurjak A., A.A. Kratochwil, Amsterdam, Excerpta Medica, 203-208, 1981.

Chapter 7

ACUTE EFFECT OF MATERNAL SMOKING ON THE MATERNAL AND FETAL CARDIOVASCULAR SYSTEM

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Introduction

Many reports have appeared on the effect of maternal smoking on the human fetus (4,5,16). Smoking is not beneficial to the mother and her fetus. In the mother nicotine acts on the sympathetic ganglia and adrenal medulla resulting in an increase in heart rate, cardiac output and peripheral vasoconstriction causing a rise in blood pressure and reduction in intervillous blood flow (9). In the fetus intrauterine growth retardation (7,15), prematurity (13) and therefore increased perinatal mortality has been observed (1,14). The main factors responsible are the afore-mentioned reduction in intervillous blood flow caused by nicotine and the production of carboxyhaemoglobin in the fetus resulting in hypoxia (11,19). Recently, the introduction of low frequency pulsed Doppler systems combined with 2-D real-time scanning equipment has allowed non-invasive investigations of blood flow in the human fetus (2,3).

The present study was undertaken to examine the possible acute hypoxic effects of smoking on human fetal cardiovascular function. Simultaneous monitoring of maternal cardiovascular function was carried out in order to establish changes reflecting proper inhaling of cigarette smoke by the mother.

Material and methods

Eighteen nulliparous subjects with a singleton pregnancy between 34 and 38 weeks of gestation were asked to participate in the study. All had been smokers for several years and during the present pregnancy smoked between 5 and 15 cigarettes daily.

The use of drugs was not permitted. Subsequent delivery and fetal outcome were uneventful. Fetal birth weights were situated between the 10th and 90th percentile according to the tables of Kloosterman corrected for fetal sex (8). The subjects were divided at random into a smoking group (A; n = 9; mean 36.3 weeks) and a control group (B; n = 9; mean 36.1 weeks).

All women had abstained from smoking during the last 24 h before the examination. Measurements were performed between 2 p.m. and 4 p.m. with the subject in the semi-Fowler position. The duration of the examination was 50 min, which for analysis of the maternal data was divided into ten periods of 5 min, i.e. pre-stimulus periods, I, II and III (15 min), stimulus period IV (5 min) and post-stimulus periods V-X (30 min). For the fetal measurements, a subdivision into slightly longer periods of 7.5 min each was necessary. This was due to our criterion that only high quality blood flow velocity recordings of at least 1 min duration were accepted for evaluation. Fetal data analysis took place in the following 6 periods: pre-stimulus periods I and II (15 min), post-stimulus periods IV-VII (30 min) and stimulus period III which represented the remaining 5 min during which fetal blood flow velocity signals could not be obtained for technical reasons. Subjects in group A were invited to smoke one cigarette (nicotine concentration 1.0 mg/cigarette), inhaling the smoke over a period of approximately 5 min.

The following variables were recorded and analyzed: (a) Maternal heart rate (MHR in bpm) derived from the maternal ECG. (b) Maternal systolic and diastolic blood pressure (mmHg) measured at 1 min intervals by means of an automatic blood pressure apparatus (DYNAMAP). (c) Fetal mean blood flow velocity (cm/s) at the lower thoracic level of the descending aorta by means of a combined real-time linear array system (Organon Teknika) and a pulsed Doppler system (Pedof) according to the method described by Eik-Nes et al (2). Fetal aortic diameter (mm) was measured from a time motion recording at the same level of the descending aorta. In each period, 10 consecutive cardiac cycles were analyzed. Following determination of the mean of the diastolic and systolic vessel diameter in each of the 10 cardiac cycles, the average value for a particular period was calculated. The reproducibility of the mean blood flow velocity and vessel diameter was tested in six normal pregnant subjects between 34 and 38 weeks of gestation. In each subject mean blood flow velocity and vessel diameter recordings were analyzed during 6 consecutive periods of 7.5 min each. (d) Fetal heart rate (FHR in bpm) was derived from the peak-to-peak intervals of the blood flow velocity signals.

For each period the mean (SD) was calculated. The differences between the mean values of the variables in the different periods were tested by means of the non-parametric paired Wilcoxon-Rank test. The computer program we used was the Statistical Package for the Social Sciences (SPSS).

Results

In the reproducibility study, no significant change in mean blood flow velocity and vessel diameter was observed. The coefficient of variation varied between 0.083 and 0.132 for the mean blood flow velocity and between 0.048 and 0.066 for the vessel diameter in these subjects. In four subjects recording of fetal blood flow velocity was unsuccessful, leaving 7 women in group A and 7 women in group B for further data analysis. Frequent fetal gross body movements were the main reason for not being able to obtain an acceptable fetal blood flow velocity signal. Mean values (SD) for the maternal variables are given in Table I and for the fetal variables in Table II.

It can be seen that the smoking group is characterized by a significant increase in MHR during smoking ($P < 0.05$, period IV), and the first 5 min following smoking ($P < 0.05$, period V); in the control group no change occurred. A similar pattern is followed by the systolic blood pressure depicting a significant increase during smoking ($P < 0.05$) which is sustained during the first 15 min thereafter ($P < 0.05$); in the control group maternal systolic blood pressure remained unaltered. Maternal diastolic blood pressure showed an increase in the smoking group, which, however, was not significant ($0.05 < P < 0.1$); in group B no change occurred. There were no statistical differences (Mann-Whitney Test) in maternal blood pressure and heart rate between group A and B.

Fetal heart rate demonstrates an increase following smoking which becomes significant during period V ($P < 0.05$; fig. 1); no changes were observed in Group B (fig. 2). Fetal mean blood flow velocity (figs. 3 and 4) and fetal aortic diameter (figs. 5 and 6) remained fairly constant during the entire study period both in Group A and B.

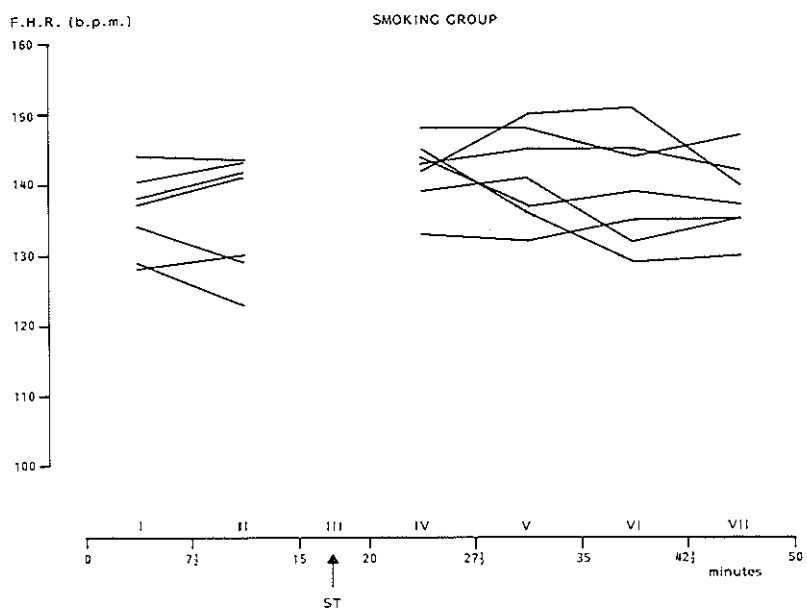

Fig. 1. Mean of the fetal heart rate (bpm) for each period in the smoking group.

Table I. Mean (±SD) during each period of the entire study for each of the maternal variables in groups A and B (ST = stimulus period).

Periods		I	II	III	IV ST	V	VI	VII	VIII	IX	X
Systolic blood pressure (mmHg)	A	112.1 (±7.1)	113.6 (±7.4)	113.4 (±6.3)	117.8 (±7.3)	118.2 (±6.9)	116.9 (±7.7)	116.9 (±6.6)	115.0 (±7.4)	113.8 (±7.0)	114.6 (±6.0)
	B	117.7 (±4.7)	116.7 (±6.3)	116.9 (±5.0)	117.3 (±6.1)	116.7 (±6.1)	117.6 (±6.6)	116.7 (±7.5)	115.7 (±5.5)	116.3 (±5.3)	115.7 (±5.5)
Diastolic blood pressure (mmHg)	A	64.0 (±4.5)	63.7 (±4.1)	66.1 (±2.6)	70.6 (±6.9)	70.5 (±6.2)	69.0 (±6.5)	67.6 (±6.5)	66.9 (±5.9)	66.9 (±6.3)	64.9 (±6.1)
	B	73.0 (±7.2)	72.6 (±6.4)	72.0 (±7.6)	71.6 (±7.0)	72.4 (±7.0)	72.9 (±7.4)	72.7 (±6.9)	71.9 (±7.3)	72.3 (±8.2)	72.0 (±6.8)
Maternal heart rate (bpm)	A	90.2 (±17.2)	90.3 (±18.3)	90.7 (±16.0)	98.6 (±18.0)	99.4 (±19.8)	100.2 (±22.5)	98.5 (±21.6)	98.8 (±20.4)	95.6 (±20.0)	94.4 (±17.5)
	B	81.7 (±8.9)	81.3 (±10.3)	81.8 (±9.9)	82.7 (±10.8)	82.9 (±9.4)	82.3 (±8.5)	82.6 (±8.1)	81.3 (±9.4)	81.9 (±8.3)	81.7 (±8.4)

Table II. Mean (± SD) during each period of the entire study for each of the fetal variables in groups A and B (ST = stimulus period).

Periods		I	II	III ST	IV	V	VI	VII
Fetal heart rate (bpm)	A	135.9 (±5.9)	136.6 (±8.0)		142.0 (±4.8)	141.3 (±6.7)	139.3 (±7.9)	138.0 (±5.0)
	B	137.0 (±7.7)	136.7 (±9.5)		136.9 (±8.7)	136.7 (±7.3)	138.3 (±10.0)	138.1 (±11.2)
Mean blood flow velocity (cm/s)	A	28.6 (±0.8)	29.1 (±1.6)		28.8 (±1.5)	29.0 (±1.6)	28.8 (±1.1)	28.5 (±0.9)
	B	27.9 (±1.0)	27.8 (±1.1)		28.3 (±0.9)	28.1 (±1.6)	27.9 (±1.3)	28.2 (±1.4)
Aortic diameter (mm)	A	6.9 (±0.8)	6.9 (±0.6)		6.9 (±0.8)	6.9 (±0.8)	6.9 (±0.7)	6.9 (±0.6)
	B	7.3 (±0.7)	7.3 (±0.7)		7.2 (±0.7)	7.2 (±0.7)	7.2 (±0.7)	7.2 (±0.6)

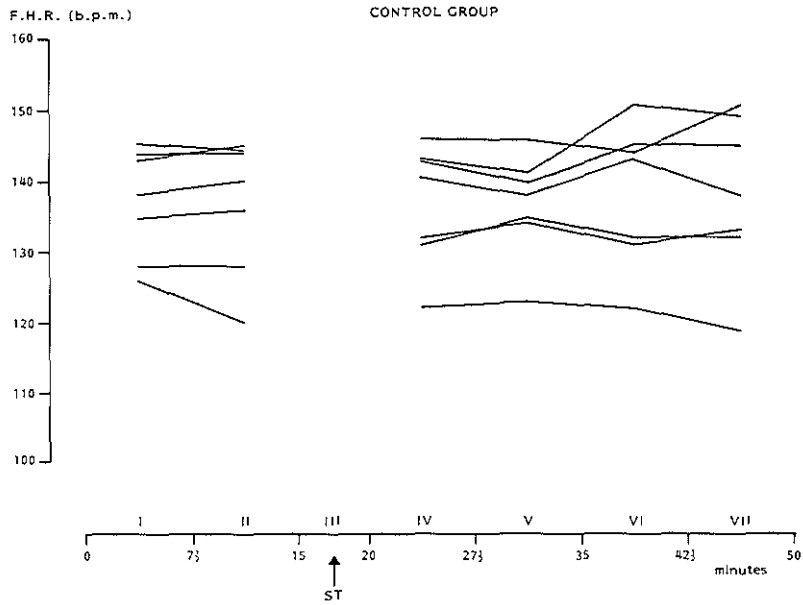

Fig. 2. Mean of the fetal heart rate (bpm) for each period in the control group.

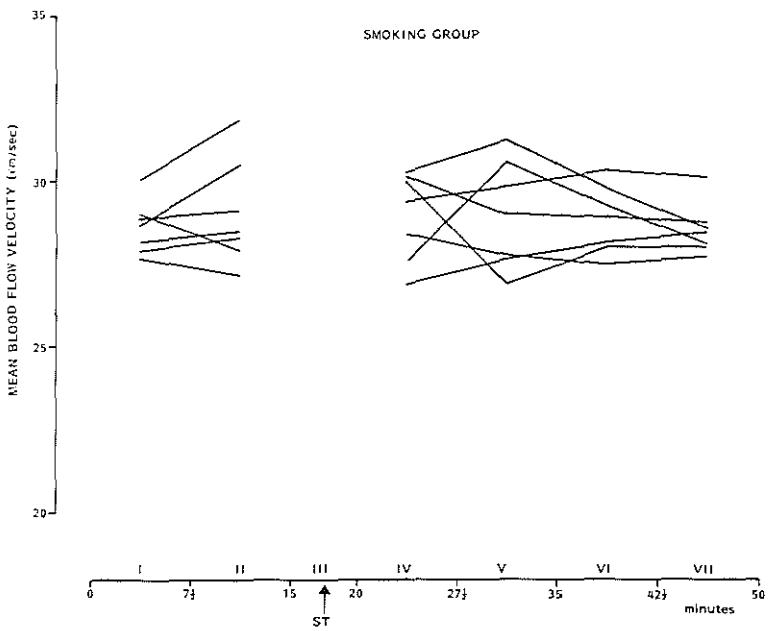

Fig. 3. Mean blood flow velocity (cm/s) for each period in the smoking group.

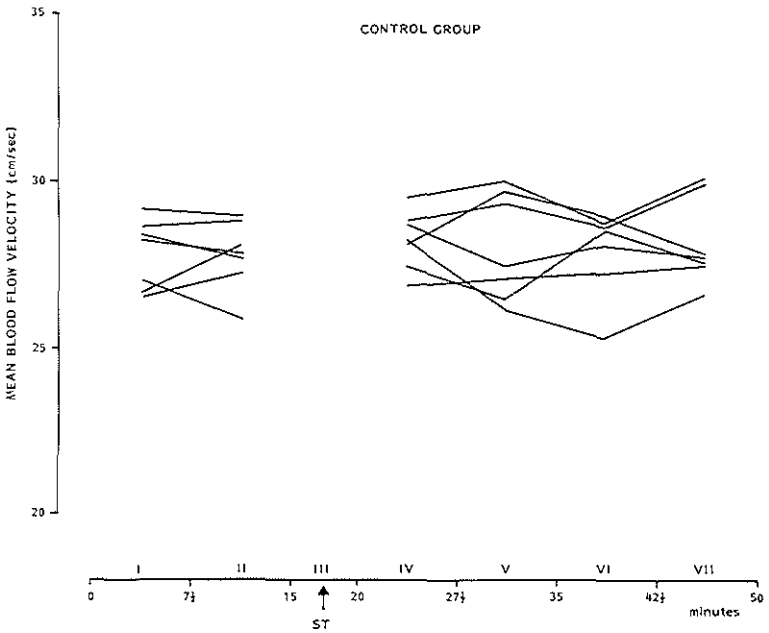

Fig. 4. Mean blood flow velocity (cm/s) for each period in the control group.

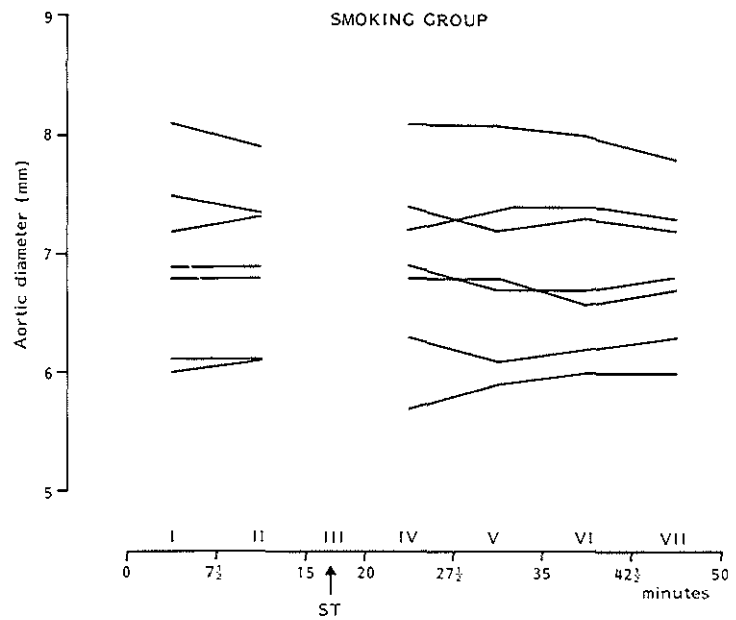

Fig. 5. Mean of the vessel diameter (mm) for each period in the smoking group.

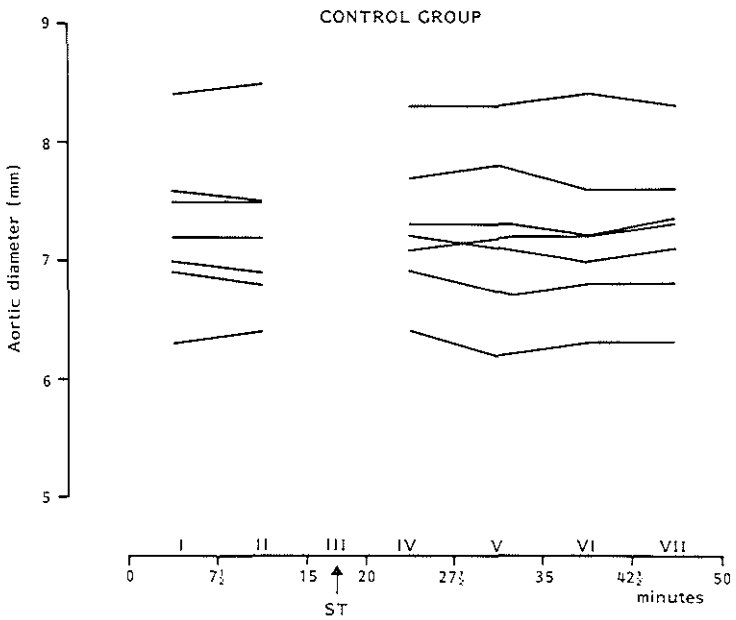

Fig. 6. Mean of the vessel diameter (mm) for each period in the control group.

Discussion

In the present study there is a marked increase in maternal heart rate and systolic blood pressure during maternal smoking with an insignificant increase in diastolic blood pressure. The effect of smoking on heart rate and systolic blood pressure lasted from 5 up to 15 min following the smoking periods.

When taking gestational age, smoking habits and the amount of nicotine in the cigarette into account, only a few studies are available for comparison with our own data. Lehtovirta and co-workers (9,10) not only observed a significant increase in maternal heart rate and systolic blood pressure, but also a marked increase in diastolic blood pressure during and following smoking. On the other hand, in a study by Jouppila et al. (6) in which only maternal heart rate was recorded following smoking, no significant change could be established. The maternal cardiovascular changes just described seem to be determined by the deleterious effect of nicotine through the release of catecholamines by the adrenal medulla and chromaffin cells (17,18).

In our study, fetal heart rate was derived from the peak-to-peak intervals of the flow velocity signals before and after maternal smoking. In four other reports, in which fetal heart rate was derived from the fetal ECG, in two a marked rise in fetal heart rate during and following smoking was observed (5,17), in one a non-significant rise occurred (6) and in one report no changes in fetal heart rate could be

established (10). The observed increase in fetal heart rate may be multifactorial.

Firstly, the diminished uteroplacental perfusion will result in fetal hypoxia. Secondly, nicotine which readily passes the placenta (20) may directly activate the fetal adrenergic system. Lastly, cigarette smoking is a potent source of carbon monoxide, which binds haemoglobin and forms carboxyhaemoglobin. This substance decreases the oxygen-carrying capacity of blood and the maternal and fetal oxyhaemoglobin saturation curves shift to the left (12).

In our study mean blood flow velocity and vessel diameter stayed fairly constant during the entire study period. In the only other report on acute effects of smoking on human fetal blood flow (6), no changes in umbilical venous and aortic blood flow could be established. Observations in fetal lamb have demonstrated that a rise in carboxyhaemoglobin in the aorta up to levels equivalent to those measured in cord blood of smoking women results in a drop of oxygen partial pressure. Longo (11) suggests that this drop of oxygen partial pressure should be followed by a marked increase in blood flow to maintain tissue oxygenation. This mechanism could not be substantiated in fetal lamb studies (9).

Since also the human fetal heart at physiological rates seems to operate near the plateau of its Starling function curve (21), stroke volume should remain fairly constant. The observed rise in fetal heart rate following maternal smoking should, therefore, result in some increase in fetal cardiac output and therefore blood flow. However, this increase in blood flow apparently is so small that this is not reflected in changes in mean blood flow velocity and vessel diameter values measured in the fetal descending aorta by present Doppler techniques. It can be concluded from both the study by Jouppila (6) and ourselves that maternal smoking of a cigarette with a nicotine concentration of about 1.0 mg during the last trimester of pregnancy does not result in measurable fetal blood flow velocity and diameter changes.

Acknowledgements

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References

1. Butler, N.R., Goldstein, H. and Ross, E.M. (1972): Cigarette smoking in pregnancy: its influence on birth weight and perinatal mortality. Br. Med. J., 2, 127-130.
2. Eik-Nes, S.H., Brubakk, A.O. and Ulstein, M.K. (1980): Measurement of human fetal blood flow. Br. Med. J., 1, 283-284.
3. Gill, R.W. (1979): Pulsed Doppler combined with B-mode imaging for quantitative blood flow measurement. Ultrasound Med. Biol., 5, 223-235.
4. Haas, J.H. de (1975): Parental smoking. Its effect on the fetus and the child health. Eur. J. Obstet. Gynecol. Reprod. Biol., 5, 283-296.
5. Hellman, .M., Johnson, H.L., Tolles, W.E. and Jones, E.H. (1961): Some factors affecting the fetal heart rate. Am. J. Obstet. Gynecol., 82, 1055-1062.

6. Jouppila, P., Kirkinen, P. and Eik-Nes, S.H. (1983): Acute effect of maternal smoking on the human fetal blood flow. Br. J. Obstet. Gynaecol., 90, 7-10.
7. Kirkinen, P. (1979): Intrauterine growth followed ultrasonically in normal and some complicated pregnancies. Ann. Chir. Gynaecol. (Suppl.), 194, 5-65.
8. Kloosterman, G. (1970): On intrauterine growth. The significance of prenatal care. Int. J. Gynaecol. Obstet., 8, 895-904.
9. Lehtovirta, P. and Forss, M. (1978): The acute effect of smoking on intervillous blood flow of the placenta. Br. J. Obstet. Gynaecol., 85, 729-731.
10. Lehtovirta, P., Forss, M., Kariniemi, V. and Rauramo, I. (1983): Acute effects of smoking on fetal heart rate variability. Br. J. Obstet. Gynaecol., 90, 3-6.
11. Longo, L.D. (1977): The biological effects of carbon monoxide on the pregnant women, fetus and the newborn infant. Am. J. Obstet. Gynecol., 129, 69-103.
12. Longo, L.D. and Hill, E.P. (1977): Carbon monoxide uptake and elimination in fetal and maternal sheep. Am. J. Physiol., 232, H 324-330.
13. Lowe, C.R. (1959): Effects of mothers' smoking habits on birth weight of their children. Br. Med. J. 2, 673-676.
14. Ontario Department of Health (1967): Supplement of the Second Report of Perinatal Mortality Study in Ten University Teaching Hospitals, Vol. II.
15. Persson, P.H., Grennert, L., Gennser, G. and Kullander, S. (1978): A study of smoking and pregnancy with special reference to fetal growth. Acta Obstet. Gynecol. Scand. (Suppl.), 78, 33-39.
16. Pirani, B.B.K. (1978): Smoking during pregnancy. Obstet. Gynecol. Surv., 33, 1-13.
17. Quigley, M.E., Sheenan, K.L., Wilkes, M.M. and Yen, S.S.C. (1979): Effects of maternal smoking on circulatory catecholamic levels and fetal heart rates. Am. J. Obstet. Gynecol., 133, 685-690.
18. Resnik, R., Bruk, G.W. and Wilkes, M.M. (1979): Catecholamine mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. J. Clin. Invest., 63, 1133-1136.
19. Socol, M.L., Manning, F.A., Murata, Y. and Druzin, M.L. (1982). Maternal smoking causes fetal hypoxia. Experimental evidence. Am. J. Obstet. Gynecol., 142, 214-218.
20. Suzuki, K., Horiguchi, T., Comas, P., Urrutia, A.C., Muller-Hembach, E., Morishima, H.O. and Adamsons, K. (1971): Pharmacologic effects of nicotine upon the fetus and the mother in the rhesus monkey. Am. J. Obstet. Gynecol., 11, 1092-1101.
21. Tonge, H.M., Stewart, P.A. and Wladimiroff, J.W. (1984). Fetal blood flow measurements during fetal cardiac arrhythmia. Early Hum. Dev., 10 (1984) 23-34.

Chapter 8

EFFECT OF SHORT-TERM MATERNAL EXERCISE ON MATERNAL AND FETAL CARDIOVASCULAR DYNAMICS

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Introduction

Since the introduction of combined real-time and pulsed Doppler ultrasound techniques for non-invasive blood flow measurements in the umbilical vein (Gill 1979; Gill et al. 1981) and fetal descending aorta (Eik-Nes et al. 1980a; Griffin et al. 1983) a number of reports have appeared on the effect of internal and external stimuli, such as fetal breathing movements, uterine contractions and maternal smoking on fetal blood flow (Eik-Nes et al. 1980b; Jouppila et al. 1983; Marsál et al. 1984). In the present study we investigated the effects of short-term moderate maternal exercise on the human maternal and fetal cardiovascular system.

Subjects and methods

A total of 28 healthy nulliparous women with normal pregnancies between 34 and 38 weeks gestation (mean 35.6 weeks) were recruited to the study. Maternal age ranged between 22 and 29 years (mean 26.1), maternal weight between 61 and 73 kg (mean 66.1). Informed consent was obtained from all patients. Subsequent delivery and fetal outcome were uneventful. The patients were allocated at random to an exercise group (A) and a control group (B); there were 14 patients in each group.

Each study was performed between 14.00 and 16.00 hours with the patient in a semi-recumbent position with thighs flexed to allow pedalling on a bed-type cycle ergometer. Cigarette smoking or intake of drugs was not permitted during this period. The room temperature was 20°C. The total recording time for all women was 50 min, which was divided up into 10 periods of 5 min each.

Periods I and II were recorded before exercise, i.e. pre-stimulus.

Period III was the first stimulus period during which the women in group A were asked to cycle on a bed-type ergometer with a work load of 25 W. This type of ergometer was chosen to ensure minimal disruption of the recording of maternal and fetal measurements. All women were used to cycling. A small pilot study on five women had shown that 5 min of this type of exercise generally did not result in any feeling of discomfort. The women in group B remained in the resting position throughout period III.

Periods IV and V were considered as post-stimulus.

Periods VI and VII were considered as pre-stimulus for the second exercise period. This was based on the assumption that at that time any effect from the first exercise on the fetal and maternal cardiovascular system had worn off.

Period VIII was the second exercise period, during which the women in group A exercised in the same manner as described for the first exercise and the women in group B remained in the resting position.

Periods IX and X were considered as post-stimulus periods.

During the entire study the following variables were recorded and analysed: (i) maternal ECG for calculation of maternal heart rate (MHR in beats/min); (ii) maternal systolic and diastolic blood pressure (mmHg) measured by an automatic blood pressure monitor (DYNAMAP) at 1-min intervals; (iii) mean blood flow velocity (cm/s) at the lower thoracic level of the fetal descending aorta by means of a combined real-time linear array (Organon Teknika) and pulsed Doppler (Pedof) system according to Eik-Nes et al. (1980a). Only blood flow velocity recordings with a successful recording time of $\geqslant$30 s for each period were accepted; (iv) fetal heart rate (FHR in beats/min) which was calculated from the peak-to-peak intervals of the blood flow velocity signals.

For each period the mean (SD) was calculated. The differences between the mean values of the variables in the different periods were tested by means of the non-parametric paired Wilcoxon Rank test. The computer program we used was the Statistical Package for the Social Sciences (SPSS).

Results

Recording of fetal blood flow velocity was unsuccessful in five women, leaving 11 women in the exercise group (A) and 12 women in the control group (B) for further analysis. Fetal gross body movements were the main reason for not obtaining an acceptable fetal blood flow velocity signal. The same signal was totally unobtainable during the periods of maternal exercise, so that the effect of maternal exercise on fetal heart rate and aortic blood flow velocity could only be assessed after the exercise. Table I gives the detailed results for both groups. Maternal diastolic and systolic blood pressure are depicted in Fig. 1 for the exercise group. There was a significant increase ($P < 0.001$) in maternal diastolic and systolic blood pressure during both exercise periods with a return to pre-stimulus levels within the first 5

Table 1. Maternal and fetal cardiovascular changes during 10 5-min periods before and after exercise in group A and in a control group B.

Cardiovascular variable	Group	Time period									
		I	II	III (1st ex)	IV	V	VI	VII	VIII (2nd ex)	IX	X
Maternal blood pressure (mmHg)											
Systolic	A	114.0 (6.8)	113.3 (6.7)	129.5 (8.8)	135.5 (7.0)	112.1 (8.0)	112.0 (7.9)	112.9 (7.7)	125.1 (7.4)	115.6 (8.1)	113.6 (7.7)
	B	119.2 (8.9)	119.4 (8.8)	119.3 (7.7)	118.7 (7.9)	118.8 (9.3)	118.7 (9.5)	119.0 (8.5)	118.5 (8.3)	119.9 (8.5)	118.8 (8.6)
Diastolic	A	65.7 (4.0)	65.7 (4.9)	75.0 (6.4)	64.3 (4.8)	62.5 (4.8)	62.3 (4.6)	63.4 (4.3)	72.1 (5.0)	62.2 (5.2)	62.4 (4.6)
	B	72.4 (6.9)	73.4 (7.1)	72.9 (6.9)	72.5 (7.7)	72.3 (7.0)	72.4 (7.1)	72.7 (7.3)	72.1 (8.3)	72.5 (8.4)	72.0 (7.7)
Maternal heart rate (beats/min)	A	85.2 (8.8)	85.7 (9.7)	111.8(10.1)	90.6(10.2)	87.2 (9.7)	86.4 (8.8)	85.9(10.8)	114.2(11.3)	92.1(10.3)	87.9(10.0)
	B	93.3 (7.7)	93.9 (8.5)	94.5 (8.1)	94.3 (7.8)	94.5 (7.7)	94.4 (8.1)	95.2 (8.7)	94.5 (8.2)	93.7 (8.4)	93.1 (7.9)
Fetal heart rate (beats/min)	A	138.1(12.8)	136.5(12.7)		135.0(12.9)	136.3(13.0)	141.3(11.2)	140.3(11.2)		137.1 (9.4)	136.5 (8.6)
	B	137.8 (8.0)	138.2 (7.8)		137.8 (7.5)	136.8 (7.0)	137.5 (8.7)	136.9 (8.6)		136.8 (9.6)	137.0 (8.4)
Fetal mean blood flow velocity (cm/s)	A	27.5 (1.3)	27.3 (1.3)		27.9 (1.8)	27.7 (1.3)	27.6 (1.3)	27.8 (1.5)		28.2 (1.4)	28.3 (1.4)
	B	27.5 (1.3)	27.0 (1.1)		27.1 (1.5)	27.3 (1.5)	27.4 (1.9)	27.6 (1.1)		27.4 (1.5)	27.4 (1.3)

Results are mean (SD).
Ex, Exercise.

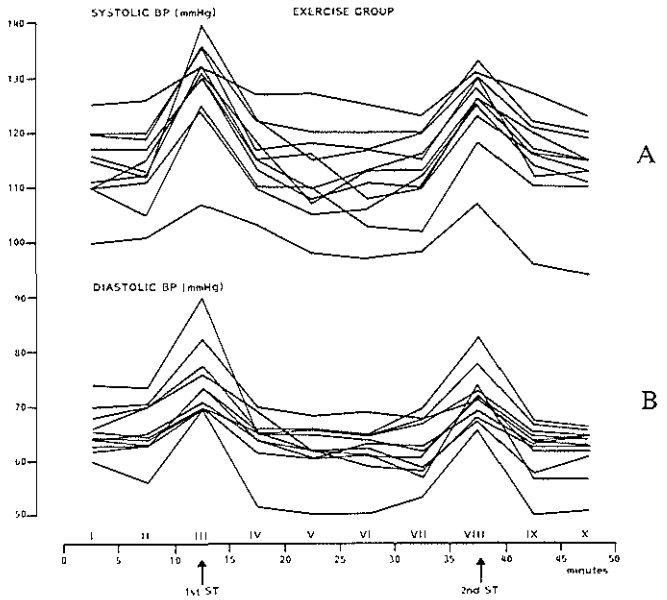

Fig. 1. Mean maternal systolic (a) and diastolic (b) blood pressure over 50 min. before and after two 5-min periods of exercise (Ex).

min after each exercise period. Maternal heart rate (Fig. 2) also exhibited a significant increase ($P < 0.001$) during both exercise periods. In the control group no significant changes in maternal blood pressure and maternal heart rate were

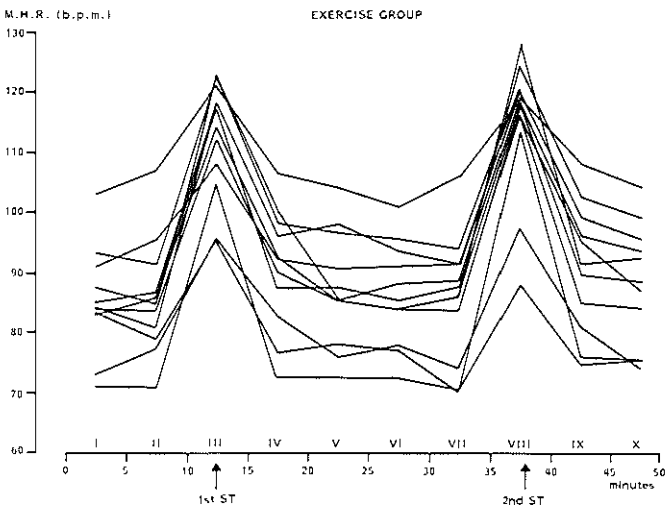

Fig. 2. Mean maternal heart rate over 50 min, before and after two 5-min periods of exercise (Ex).

observed. Figs. 3 and 4 show the mean fetal blood flow velocity at the lower thoracic level of the fetal descending aorta and fetal heart rate in the exercise group. Both in the exercise and control group no significant changes in mean blood flow velocity and fetal heart rate were observed.

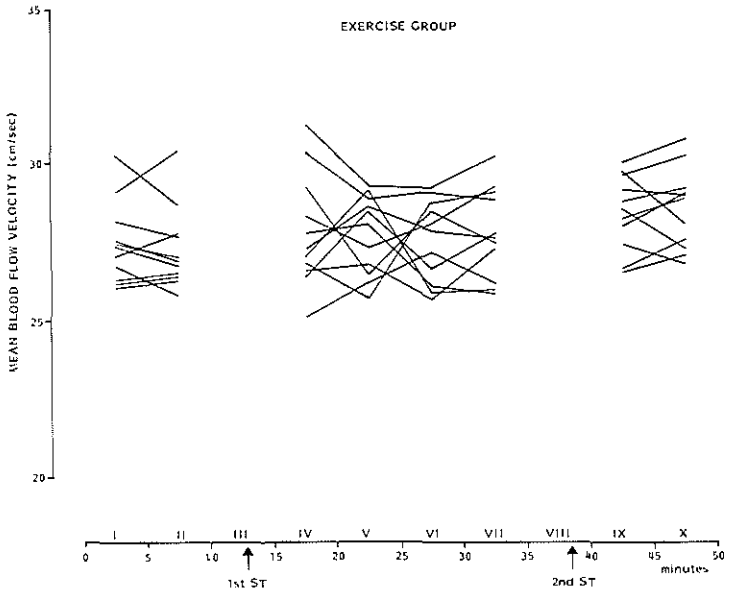

Fig. 3. Mean fetal blood flow velocity in 11 women over 50 min, before and after two 5-min periods of exercise (Ex). Recordings were unsuccessful during the exercise periods.

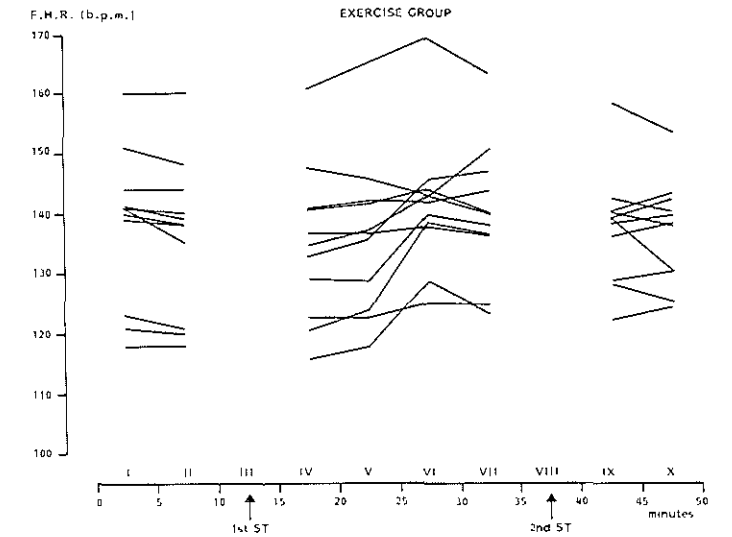

Fig. 4. Mean fetal heart rate in 11 women over 50 min, before and after two periods of exercise (Ex). Recordings were unsuccessful during the exercise periods.

Discussion

Response to exercise is affected by the type, level and duration of the exercise; age; body weight; physical condition and motivation; and body position. In the present study, subjects in the exercise and control group were comparable in terms of maternal age, weight and gestational age. But the wide range in percentage increase in maternal heart rate during maternal exercise shows that there was some variability in work level probably due to differences in physical fitness. The level and duration of the exercise regimen was determined by the subjective judgements of acceptability by the respective subjects participating in the pilot study. In order to quantify the exercise stress in physiological terms, we estimated % VO_2 max indirectly from the increase in maternal heart rate during exercise (Åstrand & Rhyming 1954). The percentage increase in maternal heart rate of 20–40% corresponds with a % VO_2 max of about 30 to 40% and suggests only moderate exercise. The observed rise in maternal arterial blood pressure during maternal exercise is in agreement with other reported findings in man (Marsál et al. 1979a; Artal et al. 1981) and sheep (Clapp 1980; Lotgering 1983). However, whereas these studies found a predominantly systolic rise, we observed an increase in both diastolic and systolic blood pressure of 10-12.5% during the exercise periods.

In the present study fetal blood flow measurements could only be obtained before and after maternal exercise. We assumed that the first 10 min after exercise would still reflect fetal cardiovascular changes, if present, for two reasons. First, recent exercise studies in pregnant sheep (Lotgering et al. 1983a) have shown that uterine blood flow has returned to normal at about 10 min after the exercise. Second, since fetal cardiovascular changes as a result of maternal exercise would reflect fetal hypoxia, these changes would probably display a certain delay time. The mean blood flow velocity did not show any significant changes, suggesting unaffected fetal cardiac ventricular function and vascular resistance.

Human fetal heart rate has in most studies been recorded before and after moderate exercise of short duration (Soiva et al. 1963; Marsál et al. 1979b). The small changes we observed in fetal heart rate were unrelated to the exercise periods and should therefore be considered physiological. Variable data are presented in literature. Soiva et al. (1963) found the fetal heart rate changed in the range of −7 to +21 beats/min after 18 min of progressive exercise. Collings et al. (1983) observed a significant increase in fetal heart rate during and following maternal exercise. In sheep, fetal heart rate is unaffected by short-term exercise even at VO_2 max (Lotgering et al. 1983b). These data support our conclusion that immediately following moderate short-term maternal exercise, there are no cardiovascular signs of fetal stress.

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We like to thank Pie Data for their support in this study, Mr. C. van Kooten for the statistical analysis of the data and Dr. F.K. Lotgering for his critical assessment of the manuscript.

References

Artal, R., Platt; L.D., Sperling, M., Kammula, R.K., Jilek, J. & Nakamura, R. (1981) Exercise in pregnancy. 1. Maternal cardiovascular and metabolic response in normal pregnancy. Am. J. Obstet. Gynecol. 140: 123-127.

Åstrand, P.O. & Rhyming, I. (1954) A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. J. Appl. Physiol. 7: 218-221.

Clapp, J.F. III (1980) Acute exercise stress in the pregnant ewe. Am. J. Obstet. Gynecol. 136, 419-423.

Collings, C.A., Curet, L.B. & Mullen, J.P. (1983) Maternal and fetal response to a maternal exercise program. Am. J. Obstet. Gynecol. 145, 702-707.

Eik-Nes, S.H., Brubakk, A.O. & Ulstein, M.K. (1980a) Measurement of human fetal blood flow. Br. Med. J. 1, 283-284.

Eik-Nes, S.H., Marsál, K., Brubakk, A.O. & Ulstein, M. (1980b). Ultrasonic measurements of human fetal blood flow in aorta and umbilical vein: influence of fetal breathing movements. In Recent Advances in Ultrasonic Diagnosis 2 (Kurjak, A., Ed.), Excerpta Medica, Amsterdam, pp. 233-240.

Gill, R.W. (1979) Pulsed Doppler with B-mode imaging for quantitative blood flow measurement. Ultrasound Med. Biol. 5, 223-235.

Gill, R.W., Trudinger, B.J., Garrett, W.J., Kossoff, G. & Warren, P.S. (1981) Fetal umbilical venous flow measured *in utero* by pulsed Doppler and B-mode ultrasound. 1. Normal pregnancies. Am. J. Obstet. Gynecol. 139, 720-725.

Griffin, D., Bilardo, K., Diaz, J., Teague, M. & Campbell, S. (1983) The measurement of human fetal blood flow with linear array pulsed Doppler duplex. Proceedings VIIIth European Congress of Perinatal Medicine. Eur. J. Obstet. Gynecol. Reprod. Biol. 15, 426-430.

Jouppila, P., Kirkinen, P. & Eik-Nes, S.H. (1983). Acute effect of maternal smoking on the human fetal blood flow. Br. J. Obstet. Gynaecol. 90, 7-10.

Lotgering, F.K. (1983) Exercise in pregnancy. An experimental study of maternal and fetal responses to exercises in sheep. Thesis, Rotterdam.

Lotgering, F.K., Gilbert, R.D. & Longo, L.D. (1983a) Exercise responses in pregnant sheep: oxygen consumption, uterine blood flow and blood volume. J. Appl. Physiol. 55, 834-841.

Lotgering, F.K., Gilbert, R.D. & Longo, L.D. (1983b) Exercise responses in pregnant sheep: blood gases, temperatures and fetal cardiovascular system. J. Appl. Physiol. 55, 842-850.

Marsál, K., Gennser, G. & Löffgren, O. (1979a) Effect on fetal breathing movements of maternal challenges. Cross-over study on dynamic work, static work, passive movements, hyperventilation and hyperoxygenation. Acta Obstet. Gynecol. Scand. 58, 335-342.

Marsál, K., Löffgren, O. & Gennser, G. (1979b) Fetal breathing movements and maternal exercise. Acta Obstet. Gynecol. Scand. 58, 197-201.

Marsál, K., Lindblad, A., Lingman, G. & Eik-Nes, S.H. (1984) Blood flow in the fetal descending aorta: intrinsic factors affecting fetal blood flow, i.e. fetal breathing movements and cardiac arrhythmia. Ultrasound Med. Biol. 10, 339-349.

Soiva, K., Slami, A., Grönroos, M. & Peltonen, T. (1963) Physical working capacity during pregnancy and effect of physical work test on fetal heart rate. Ann. Chir. Gynaecol. Fenn. 53, 187-196.

Chapter 9

THE TIME-DISTANCE RECORDER AS A MEANS OF IMPROVING THE ACCURACY OF FETAL BLOOD FLOW MEASUREMENTS

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Introduction

Since the introduction of a combined 2-D real-time and pulsed Doppler technique for measuring blood flow in the abdominal part of the umbilical vein (Gill, 1979a) and in the fetal descending aorta (Eik-Nes et al. 1980), a number of reports has appeared on fetal blood flow under physiological and pathophysiological circumstances. For a comprehensive review of the current status in this area of fetal research, the reader is referred to the third issue of this Journal.

Aortic diameter measurements have been carried out from 2-D real-time images (Eik-Nes et al. 1980; Wladimiroff and McGhie, 1981; Griffin et al. 1983; Jouppila et al. 1983) and M-mode recordings (Eik-Nes et al. 1982). The pulsatility in aortic diameter is a major source of error in volume flow measurement. Eik-Nes et al. (1981, 1982, 1984) have repeatedly pointed out the significance of a time-distance (TD) recorder in registering the changes in the diameter of the pulsating fetal aorta. For correct calculation of flow, knowledge of instantaneous average velocity over the vessel area and the instantaneous vessel area must be known. For the area estimation, in practice an approximation is used based on the time averaged diameter or a parameter derived from values for the maximum diameter during systole and the minimum diameter during diastole. The area is then calculated assuming rotational symmetry.

The purpose of the present paper was to assess:

(a) The calculated volume flow as obtained with a combined 2-D real-time and Doppler technique together with a TD recording method against the volume flow

obtained with an electromagnetic measurement. This was carried out under in vitro and in vivo animal experimental circumstances.

(b) The error in flow estimation when a comparison was made between various diameter approximations and the diameter as derived from an instrument which did yield diameter as a function of time (TD-method).

Material and methods

A combined dynamically focused linear array 2-D real-time (Organon Teknika) and a 2 MHz pulsed Doppler system (PEDOF) as first described by Eik-Nes et al. (1980) were used. The Doppler instrument is capable of estimating the mean frequency shift from the Doppler power spectrum. The mean velocity over the cross-section of the tube (or the vessel) is derived from the mean frequency if the tube area is completely within the sample volume. A pulsed Doppler transducer with a diameter of 12 mm was used. The sample volume has a length along the ultrasonic beam of 8 mm and a width which is determined by the width of the beam. After the dispersion point, the beam width diverges from 12 to 21 mm at a depth of 10.5 cm. Uniform scattering is feasible in vessels with a maximum diameter of 5.4 mm at a depth of 7 cm up to a maximum diameter of 9.2 mm at a depth of 10.5 cm. From the 2-D real-time image a line was selected for diameter measurement. The basic principle of the time-distance method was described by Hokanson et al. (1972). We developed an instrument (Blom, Research Department, Rotterdam) which was capable of following two preselected echoes by a tracking method. From these data an analog output is derived which is proportional to the distance between them. The markers of the TD recorder were positioned on the onset of the deflections of an *A*-mode representation of both vessel walls (Fig. 1). Thus the changes of the vessel diameter were directly and continuously recorded. Diameter and flow velocity measurements were done at the same level of the aorta.

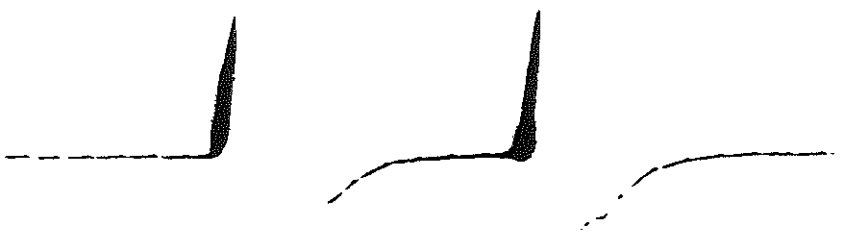

Fig. 1. *A*-mode presentation of the outer and inner wall of an elastic latex tube. The two black spots represent the selected zero-crossing tracking points.

In vitro *experiments*

A pump system (Fig. 2) pulsating at a rate of 140 bpm was used, allowing volume flows to vary between 100 and 700 ml/min. The circulating fluid consisted of a 0.9% saline solution, in which minute starch particles were dissolved, acting as reflectors for the emitted Doppler ultrasound waves. Mean volume flow (ml/min) was subsequently calculated in a stiff polyvinyl chloride (PVC) tube and in an elastic latex tube. Magnetic mean volume flow measurements were carried out

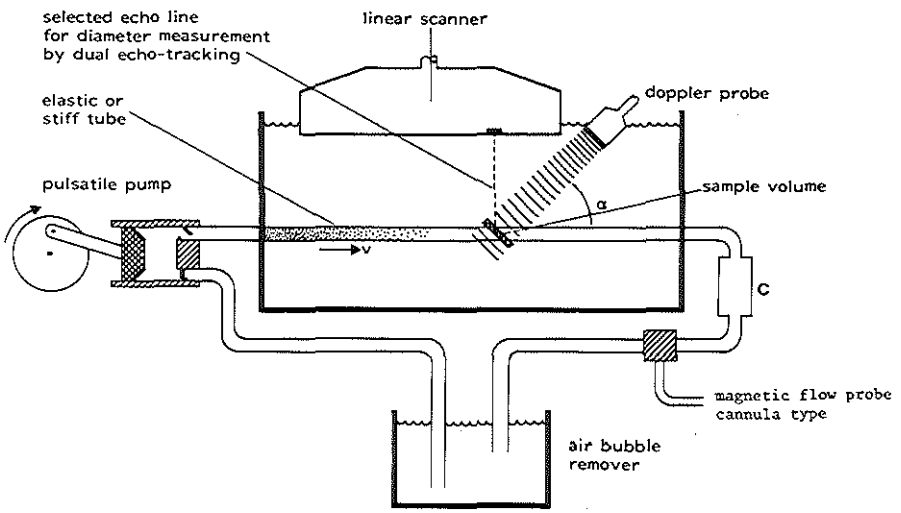

Fig. 2. Set-up for in vitro flow tests: V, flow velocity; α, angle of 45° between Doppler beam and flow direction; C, compliance.

employing a cannula type magnetic flow probe (type FF series; NIHON/KOHDEN) of 10 mm internal diameter. The error of the magnetic flow probe, which was established before the experiment was less than 5%, which was within the factory specified range. Doppler volume flow in the PVC tube was calculated from the mean flow velocity and internal diameter of the tube. Seven recordings were made from stepwise increased volume flows between 100 and 700 ml/min. From each recording five consecutive stroke periods were analyzed. Similar recordings were made from the pulsatile flow through the elastic latex tube. This resulted in pulsatile diameter changes as shown in Fig. 3. It may be noticed from Fig. 3 that the peak magnetic flow occurs later than the peak Doppler velocity. This is explained by the fact that the magnetic flow is measured after the volume compliance in our experimental set-up. For a pulsatile flow in an elastic pulsating tube, the flow is determined by

$$\bar{F} = \frac{\pi}{4T} \int_0^T v(t)d^2(t)\,dt$$

where
$\bar{F}$ is the mean volume flow over T, T the integration time, $v(t)$ the flow velocity as a function of time and $d(t)$ the diameter as a function of time.

We sampled both the Doppler flow velocity and the pulsatile diameter signal at a frequency of 33 Hz, corresponding with 15 sampling points during each stroke period (Fig. 4). From the volume flow values calculated at each of the 15 sampling points in each stroke period, the mean volume flow for that particular stroke period was established. The interference between the ultrasound signals from the real-time and Doppler transducer did not allow simultaneous recording of blood flow velocity and pulsatile diameter. Instead, both profiles were recorded immediately after each other. The correct time relationship between the two profiles was obtained by using the magnetic flow profile which was recorded simultaneously with both diameter and velocity profiles.

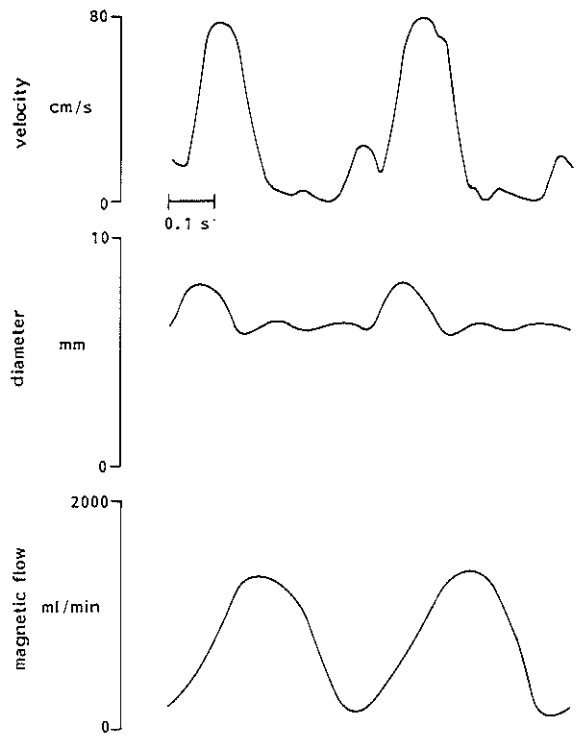

Fig. 3. Flow velocity, tube diameter and magnetic flow in an elastic latex tube.

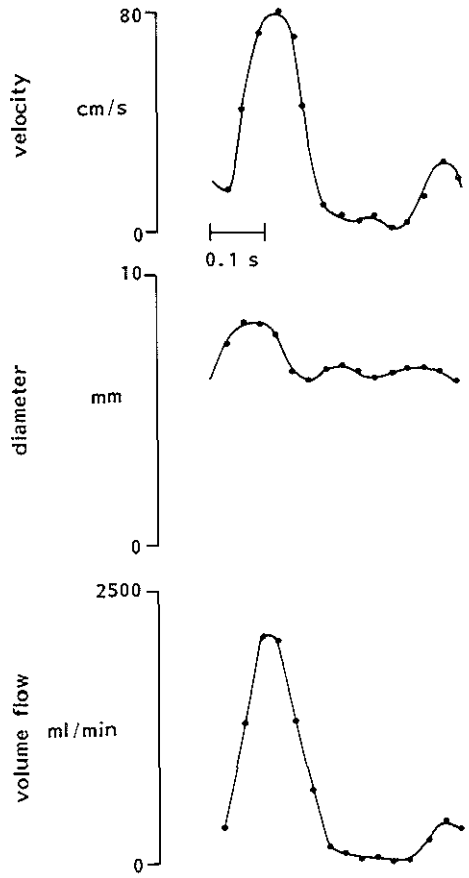

Fig. 4. Volume flow profile in an elastic tube as calculated from the sampled flow velocity and diameter profile.

Sheep experiment

An acute experiment was performed in a pregnant ewe of 139 days gestation, using standard anaesthesia techniques. With the ewe placed in the supine position, the uterus was exposed through a low midline incision. The uterine wall, membranes and fetal abdomen were opened, and the fetal aorta was dissected from its surroundings. A magnetic perivascular flow probe (Transflow 601 system; Scalar) of 5.5 mm in diameter was placed around the descending part of the fetal aorta, about 1 cm above the origin of the renal artery, and the incisions were closed. The accuracy of the electromagnetic flowmeter used in the sheep experiment was measured in a laboratory set-up. The error was less than 5%.

Blood flow velocity and pulsatile diameter of the descending aorta were documented about 1 cm above the level of the magnetic flow probe employing the same 2-D real-time and pulsed Doppler set-up as was used during the in vitro experiment. A maximum time interval of 30 s was allowed between the blood flow velocity and pulsatile diameter recording. Assessment of the correct time relationship between the two profiles was similar to that described in the in vitro experiment. Volume flow was calculated from ten equidistant sampling points in each cardiac cycle. Fetal heart rate was derived from the flow velocity recordings.

Clinical study

Blood flow velocity and pulsative vessel diameter changes were recorded at the lower thoracic level of the fetal descending aorta in 16 normal pregnancies between 30 and 38 weeks of gestation (median 35 weeks). Blood flow was studied in those cardiac cycles during which flow velocity and vessel diameter characteristics were comparable on the basis of equal period times of two consecutive cardiac cycles. A volume flow profile was subsequently constructed from ten equidistant point in the flow velocity and pulsatile vessel diameter profile per cardiac cycle (Tonge et al. 1983). In order to establish the influence of the pulsatile aortic diameter on the calculation of volume flow, the following vessel diameter approximations were considered:

(a) the maximum vessel diameter within one cardiac cycle;
(b) the minimum vessel diameter within one cardiac cycle;
(c) the mean of the maximum and minimum vessel diameter within one cardiac cycle;
(d) the time-averaged vessel diameter, which is derived from ten sampling points of the pulsatile vessel diameter profile within one cardiac cycle.

These results were compared with a reference or 'effective diameter'. This diameter is derived from the effective vessel area which is calculated by dividing the time-averaged volume flow by the time-averaged flow velocity. This diameter takes into account the pulsatile nature of the vessel wall as recorded with the TD system.

Results

In vitro experiments

In the stiff PVC tube mean flow velocity was varied between 7 and 44 cm/s. When comparing Doppler and magnetic volume flow in the stiff PVC tube, a regression line ($y = 0.98x + 29$) close to the line of identity was found ($r = 0.99$; Fig. 5). In the elastic tube mean flow velocity was varied between 7 and 36 cm/s, the diameter change ranged between 17 and 43% from the diastolic value. When comparing Doppler and magnetic volume flow, whereby the Doppler flow was calculated as

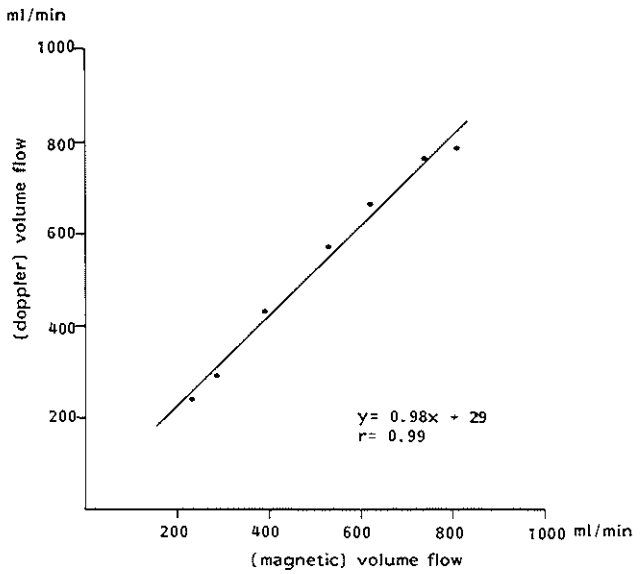

Fig. 5. Relation between Doppler and magnetic volume flow in stiff PVC tube.

described in Section 2 in the in vitro experiment, we observed a regression line of $y = 1.16x - 28$ (Fig. 6, regresion line I). Apart from an intercept of -28 ml/min, this results in a 16% overestimate. However, corrected for known wall thickness, apart from an intercept of -28 ml, no overestimation of flow could be demonstrated (Fig. 6, regression line II).

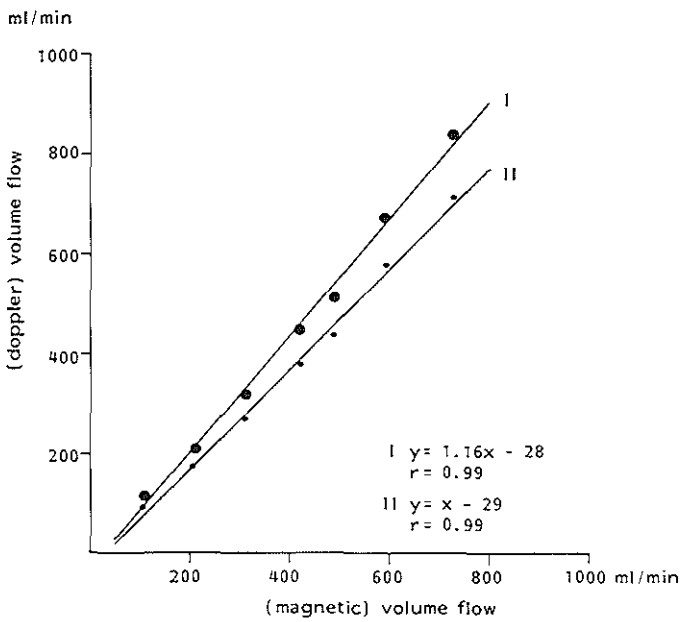

Fig. 6. Relation between Doppler and magnetic volume flow in elastic tube. Line I, Doppler volume flow calculated from the outer-to-inner tube diameter. Line II, Doppler volume flow calculated from the inner-to-inner tube diameter.

Sheep experiment

In the sheep experiment fetal heart rate varied between 225 and 235 bpm, while magnetic volume flow ranged between 448 and 520 ml/min. Doppler flow velocity and pulsatile diameter recordings were carried out at three different periods each lasting 30-60 s. The mean flow velocity varied between 31 and 35 cm/s and the diameter change ranged between 5.4 and 7.4% from the diastolic value. From each period, ten consecutive cardiac cycles were selected, depicting technically acceptable Doppler flow velocity, pulsatile diameter and magnetic volume flow recordings. In Fig. 7 the calculated Doppler volume flow values are superimposed on the magnetic flow profiles, indicating a good agreement between the two flow profiles. Nonetheless, the differences in volume flow as averaged over ten cardiac cycles between Doppler and magnetic volume flow values were –7.5% (at 520 ml/min), 17% (at 464 ml/min) and 5% (at 448 ml/min).

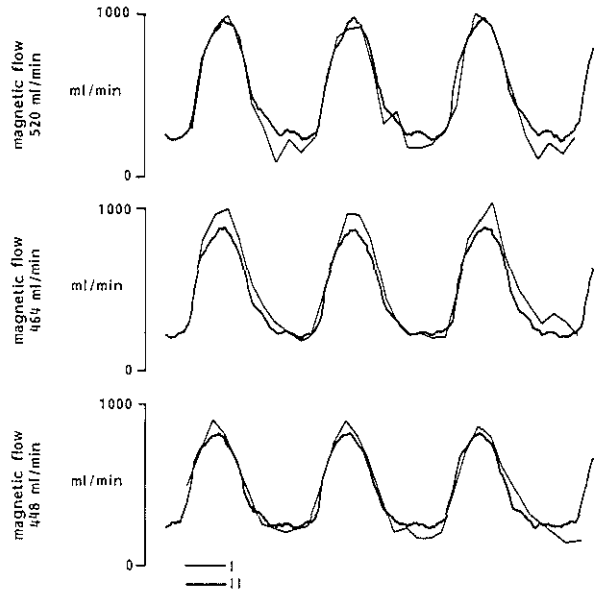

Fig. 7. Doppler volume flow values (dots) superimposed on magnetic volume flow profiles in the fetal aorta at different magnetic flow values.

Clinical study

The results of the clinical study are given in Table 1. This table demonstrates the differences in volume flow calculated from the maximum diameter, minimum diameter, mean of maximum and minimum diameter and time-averaged diameter when related to the effective diameter.

Discussion

The high degree of accuracy of the Doppler flow measurement technique in the stiff tube is in agreement with earlier reports by Angelsen and Brubakk (1976) and Gill (1979b) who used stiff tubing and a time constant flow to compare Doppler volume flow with true volume flow as measured by the amount of fluid collected in a reservoir. In our study, the cut-off level of the high pass filter was 150 Hz, so that the 29 ml/min Doppler flow overestimate in the stiff tube can be explained by the effect of filtering the low flow velocity components as described by Gill (1979b). The experiment in the elastic tube shows a high degree of accuracy between Doppler flow based on Doppler flow velocity measurements and pulsatile tube diameter as established by TD recorder, and electromagnetically measured flow (Fig. 6). The 28 ml/min Doppler flow underestimate in the elastic tube may be explained by the strong low frequency components originating from the pulsatile tubal wall which could not be completely eliminated by the high pass filters.

Table 1. Percentage flow under and overestimation for the maximum (D_{max}) and minimum vessel diameter (D_{min}), the mean of the maximum and minimum diameter ($D_{max} + D_{min}$)/2) and the time-averaged vessel diameter (D_{TA}), relative to the effective diameter (D_{eff}).

Patient	D_{eff}(mm)	D_{max}(mm)	Flow overest	D_{min}(mm)	Flow underest	$\frac{D_{max} + D_{min}}{2}$	Flow underest	D_{TA}	Flow underest
1	7.2	7.5	9%	6.5	18%	7.0	5%	7.0	5%
2	5.9	6.2	10%	5.3	19%	5.8	3%	5.7	7%
3	7.7	8.2	13%	7.1	15%	7.6	3%	7.5	5%
4	6.4	6.6	6%	5.7	21%	6.2	6%	6.2	6%
5	6.7	7.0	9%	6.0	20%	6.5	6%	6.5	6%
6	6.5	6.8	9%	5.8	20%	6.3	6%	6.3	6%
7	5.7	6.0	11%	5.1	20%	5.6	3%	5.6	3%
8	6.9	7.2	9%	6.2	19%	6.7	6%	6.7	6%
9	5.7	5.9	7%	5.2	17%	5.6	3%	5.6	3%
10	6.4	6.7	10%	5.7	21%	6.2	6%	6.2	6%
11	7.5	7.8	8%	6.7	20%	7.3	5%	7.2	8%
12	6.0	6.2	7%	5.4	19%	5.8	7%	5.8	7%
13	7.7	8.1	11%	7.0	17%	7.5	5%	7.5	5%
14	6.8	7.2	12%	6.0	22%	6.6	6%	6.6	6%
15	5.2	5.4	8%	4.8	15%	5.12	4%	5.1	4%
16	6.6	6.8	6%	6.1	15%	6.5	3%	6.5	3%
Mean	6.6	6.9	9.1%	5.9	18.6%	6.4	4.8%	6.4	5.4%
SD	0.7	0.8	2.1	0.7	2.3	0.7	1.4	0.7	1.5

The axial resolution of present ultrasound equipment is until now insufficient to measure distances less than 1 mm. As a result, measurements of the tube diameter always include the outer wall thickness. This explains the Doppler overestimate of 16% when the diameter was calculated from the outer-to-inner wall distance, for which we could correct in our in vitro study. However, this observation is not applicable to the in vitro situation because with present equipment the vessel wall thickness cannot be measured and because it is not known whether the echo reflecting boundary of the fetal aortic wall is determined by the muscular layer or by the surrounding connective tissue. We were unable to find any literature on the wall thickness of the fetal aorta. Therefore, in a pilot study we measured the wall thickness of the fetal aorta of a normal weight 38 week old stillborn fixed at a filling pressure of 50 mmHg. In six samples we measured a mean vessel inner diameter of 6.3 (±0.7 S.D.) mm and a mean ratio between wall thickness and inner diameter of 4% (±0.5 S.D.) when only considering the muscular layer (0.25 mm ± 0.03 S.D.) and of 5.6% (±1.9 S.D.) when the surrounding connective tissue (0.36 mm ± 0.11 S.D.) was taken into account. Using these data we calculated an overestimate of 8.0 and 11.5%, respectively, in absolute blood flow in the fetal descending aorta. Comparison between Doppler flow and magnetic flow in the acute sheep experiment shows an overestimation in two recordings (5 and 17%) and an underestimation (–7.5%) in one recording. These results are comparable to those obtained by Eik-Nes et al. (1981) at flow levels between 400 and 500 ml/min in the pig aorta. It seems likely that at lower flow rates the accuracy will be even lower.

Although we studied only a comparatively narrow flow range in one fetal lamb, these data indicate that even with continuous monitoring of the pulsatile aortic wall movements by means of a TD recorder, the accuracy of Doppler flow measurements is low so that in vivo measurements should be interpreted with utmost care.

In the clinical part of the study (Table 1), the influence of the pulsatile aortic diameter on volume flow calculations was evaluated. We considered the effective diameter as the correct diameter, since it completely compensates for the influence of vessel pulsations on volume flow. From this it follows that, if one calculates volume flow from the maximum vessel diameter, this will lead to a volume flow overestimation of 9.1% (±2.1 S.D.) and from the minimum vessel diameter to an underestimation of –18.6% (±2.3 S.D.). This implies that if a diameter measurement is carried out from one frozen *B*-mode image, arbitrarily chosen within the cardiac cycle, the error in the volume flow calculation will vary between 9 and –19%. If ten randomly selected *B*-mode images are taken, the calculated mean diameter will approximate the time-averaged diameter, which in our study shows a volume flow underestimation of –5.4% (±1.5 S.D.). From *M*-mode recordings, usually the mean of the minimum and maximum diameter is taken for volume flow calculations. For this situation, a volume flow underestimation of –4.8% (±1.4 S.D.) similar to that of the time-averaged diameter, can be expected.

It can be concluded that continuous recording of the pulsatile vessel diameter by a TD recorder provides a more correct approach for volume flow calculations than can be expected from *B*- and *M*-mode images. With the use of the latter methods,

calculated flow values are anywhere from 19% lower to 9% higher than values obtained with the use of a TD recorder.

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References

Angelsen, B.A.J. and Brubakk, A.O. (1976) Transcutaneous measurement of blood flow velocity in the human aorta. Cardiovasc. Res. 10, 368-379.

Eik-Nes, S.H., Brubakk, A.O. and Ulstein, M. (1980) Measurement of human fetal blood flow. Br. Med. J. 1, 283-284.

Eik-Nes, S.H., Marsal, K., Kristoffersen, K. and Vernersson, E. (1981) Transcutaneous measurement of human fetal blood flow. Methodological studies. In Recent Advances in Ultrasound Diagnosis (111) (Edited by A. Kurjak and A. Kratochwil), pp. 209-219. Excerpta Medica, Amsterdam.

Eik-Nes, S.H., Marsal, K., Brubakk, A.O., Kristofferson, K. and Ulstein, M. (1982) Ultrasonic measurement of human fetal blood flow. J. Biol. Engng. 4, 28-36.

Eik-Nes, S.H., Marsal, K. and Kristoffersson, K. (1984). Methodology and basic problems related to blood flow studies in the human fetus. Ultrasound Med. Biol. 10, 320-332.

Gill, R.W. (1979a) Pulsed Doppler with *B*-mode imaging for quantitative blood flow measurement. Ultrasound Med. Biol. 5, 223-235.

Gill, R.W. (1979b) Performance of the mean frequency Doppler modulator. Ultrasound Med. Biol. 5, 237-247.

Griffin, D., Bilardo, K., Diaz, M., Teague, M. and Campbell, S. (1983) The measurement of human fetal blood flow with linear array pulsed Doppler duplex. In Proc. 8th European Congress of Perinatal Medicine, Brussels, pp. 426-430.

Hokanson, D.E., Mozersky, D.E., Summer, D.S. and Strandness D.E., Jr. (1972) A phase-locked echo tracking for recording arterial diameter changes in vivo. J. Appl. Physiol. 32, 728-733.

Jouppila, P., Kirkinen, P. and Eik-Nes, S.H. (1983) Acute effect of maternal smoking on the human fetal blood flow. Br. J. Obstet. Gynaecol. 90, 7-10.

Tonge, H.M., Struijk, P.C., Custers, P. and Wladimiroff, J.W. (1983) Vascular dynamics in the descending aorta of the human fetus in normal late pregnancy. Early Human Development 9, 21-26.

Wladimiroff, J.W. and McGhie, J. (1981) Ultrasonic assessment of cardiovascular geometry and function in the human fetus. Br. J. Obstet. Gynaecol. 88, 870-875.

CONCLUSIONS

The following conclusions can be drawn:

1. Using the combined 2-D real-time and pulsed Doppler system as described in this thesis the error in the measurement of blood flow velocity in the lower thoracic part of the fetal descending aorta due to the angle of insonation is less than 4.5%.

2. Doppler transducer uniform scattering occurs if the diameter of the fetal descending aorta is 9.2 mm or less. In our study the vessel diameter was always below this critical level.

3. No difference in mean blood flow velocity and vessel diameter variance for the lower thoracic part of the fetal descending aorta was demonstrated between the intra- and inter-observer study.

4. During the third trimester of pregnancy a gradual decrease in mean blood flow velocity and a highly significant rise both in vessel diameter and volume flow was established at the lower thoracic part of the fetal descending aorta. The wide distribution in individual volume flow data renders this flow parameter of little clinical value.

5. During the third trimester of pregnancy both maternal smoking of one cigarette (nicotine concentration about 1.0 mg) and moderate short-term exercise (work-load of 25 Watt) did not result in any measurable change in blood flow velocity and vessel diameter at the lower thoracic level of the fetal descending aorta.

6. Continuous recording of the pulsatile vessel diameter by a TD recorder provides a more correct approach for volume flow calculations than can be expected from B- and M-mode images.

SUMMARY

Chapter 1
For many years considerable interest has been demonstrated in the fetal circulation. Most of the current knowledge has been obtained from animal experimental research. Diagnostic ultrasound has opened the possibility of performing non-invasive studies of the fetal circulation under physiological circumstances. The main purpose of the study described in this thesis was to establish the reproducibility and normal values for blood flow velocity, vessel diameter and volume flow in the lower thoracic part of the fetal descending aorta. Furthermore the influence of external stimuli i.e. smoking and short-term moderate exercise on these parameters was studied and a more precise method of recording the vessel diameter changes of the lower thoracic part of the fetal descending aorta was developed.

Chapter 2
In this chapter a review of the history of Doppler, of the basic principles of Doppler velocity measurement, of continuous-wave and pulsed-Doppler systems and of the Doppler frequency spectrum is given.

Chapter 3
The equipment used for non-invasive measurement of blood flow velocity is described. The lower thoracic part of the fetal descending aorta was visualised using a 2D dynamically focused linear array system (Organon Teknika), whereas the blood flow velocity measurement at this particular level was carried out by means of a pulsed Doppler system (Pedof). Simultaneous use of both systems is not feasible due to unacceptable interference from simultaneous emissions of sound pulses from the 2D real-time transducer and the pulsed Doppler probe. This problem was overcome by the introduction of a self-constructed interface. For calculation of blood flow measurement of the fetal vessel diameter is necessary. The various techniques, i.e. M-mode and Time Distance recording used for the measurement of the vessel diameter are discussed. Computer analysis of the results was carried out.

Chapter 4
The scanning technique as employed in the present study is described. A mathematical model was used to establish the effects of incorrect transducer positioning on the angle of insonation and therefore on blood flow velocity measurement. An error in blood flow velocity of less than 4.5% was calculated. The effect of the sample volume on uniform scattering is discussed. Uniform scattering occurs if the vessel diameter of the lower thoracic part of the fetal descending aorta is less than 9.2 mm.

Chapter 5
An overview of the literature of non-invasive blood flow velocity measurement in the fetal circulation is presented. Measurements have been performed in the umbilical arteries, the intra-abdominal part of the umbilical vein, the lower thoracic part of the descending aorta and the inferior vena cava. The results obtained in these vessels were compared with those obtained under animal experimental conditions. Furthermore the effects of both external and internal stimuli on these measurements are described.

Chapter 6
The results for mean blood flow velocity, vessel diameter and volume flow of our own study in the uncomplicated pregnancy are described. The criteria for selection of the pregnant women are defined.

The variance between the inter- and intra-observer study demonstrated no difference either for mean blood flow velocity or the vessel diameter. The mean blood flow velocity showed a significant decrease from 28 weeks till 39 weeks of gestation, while the vessel diameter and the volume flow both significantly increase. Distribution of the volume flow values was so great that the clinical value of these parameters is of little importance. The results of our study were compared with those of other centres.

Chapter 7
Maternal and fetal cardiovascular dynamics were studied in relation to maternal smoking in 18 healthy nulliparous subjects between 34 and 38 weeks of gestation randomly divided into a smoking (n=9) and a control group (n=9). At the end of the study, data from 7 smokers and 7 controls were available for analysis. A significant rise in maternal heart rate and systolic blood pressure was observed during and following smoking one cigarette. A significant increase in fetal heart rate occurred following smoking, whereas mean blood flow velocity and vessel ldiameter in the fetal descending aorta as measured by pulsed Doppler and time motion techniques did not demonstrate any significant changes.

Chapter 8

Maternal and fetal cardiovascular dynamics were studied immediately after moderate short-term maternal exercise in 28 healthy nulliparous subjects between 34 and 38 weeks gestation who were randomly assigned to an exercise group (n=14) or a control group (n=14). At the end of the study, data from 11 exercise and 12 control subjects were available for analysis. A significant rise in maternal heart rate and systolic and diastolic blood pressure during exercise was observed.

Mean blood flow velocity in the fetal descending aorta as measured by pulsed Doppler ultrasound and fetal heart rate did not show any significant changes. These data indicate that there are no cardiovascular signs of fetal stress immediately after moderate short-term maternal exercise.

Chapter 9

The influence of pulsatile diameter changes on calculation of volume flow has been studied. In vitro studies and an animal study were carried out with a real-time imaging and pulsed Doppler velocity measurement system. For precise pulsatile diameter information a wall motion tracking device was incorporated. Whereas in vitro a high degree of accuracy was found for the measurements of volume flow, this could not be substantiated in the descending aorta of the fetal lamb, in which Doppler volume flow differed between -7.5 and 17% from magnetic volume flow. In a clinical study the relative influence of various diameter approximations on calculated fetal aortic volume flow was assessed in 16 normal third trimester pregnancies. Depending on the selected diameter approximation method it appeared that differences from 19% underestimation to 9% overestimation in calculated volume flow could be obtained when reference was made to volume flow derived from diameter and velocity information.

SAMENVATTING

Hoofdstuk 1
De foetale circulatie staat reeds vele jaren in de belangstelling van veel onderzoekers. Het merendeel van de tot nu toe verworven kennis betreffende de foetale circulatie is vergaard uit dierexperimenteel onderzoek. Ultrageluidsonderzoek heeft het mogelijk gemaakt om de foetale circulatie non-invasief onder fysiologische omstandigheden te bestuderen.

In het onderzoek, beschreven in dit proefschrift, werd een antwoord gezocht op de vraag of met behulp van Doppler technieken reproduceerbare metingen van de bloedstroom in het laag thoracale deel van de foetale aorta descendens kunnen worden verricht. Bovendien werd het effect van uitwendige stimuli zoals roken en matige kortdurende inspanning op deze parameters onderzocht. Een nauwkeuriger methode voor het meten van de vaatdiameter werd ontwikkeld.

Hoofdstuk 2.
In dit hoofdstuk worden de geschiedenis, de basisprincipes van de Doppler bloedstroomsnelheidsmetingen, het continue en het gepulsde Dopplersysteem en het Dopplerfrequentiespectrum uiteengezet.

Hoofdstuk 3
Hier wordt de apparatuur die gebruikt werd voor het op non-invasieve wijze meten van de bloedstroomsnelheid beschreven. De lokalisatie van het laag thoracale deel van de foetale aorta descendens vond plaats met behulp van een dynamisch gefocuseerd 2D linear array systeem (Organon Teknika) terwijl de bloedstroomsnelheidsmetingen in het laag thoracale deel van de foetale aorta descendens werden uitgevoerd met een gepulsde Doppler systeem (Pedof). Het gelijktijdig gebruik van beide apparaten is tengevolge van interferentie niet mogelijk. Een interface die gelijktijdig gebruik van beide systemen mogelijk maakte wordt besproken. Om de bloedstroom te berekenen is meting van de vaatdiameter noodzakelijk. De verschillende technieken, M-mode en Time Distance recording, waarmee de diameter gemeten werd wordt uiteengezet. De analyse van de resultaten werd met behulp van een computersysteem uitgevoerd.

Hoofdstuk 4
Op de scantechniek zoals toegepast in dit onderzoek wordt ingegaan. De gevolgen die een onjuiste scantechniek heeft op de hoek van insonatie en dientengevolge op de bloedstroomsnelheidsmetingen worden met behulp van een mathematisch model berekend. De fout in de bloedstroomsnelheidsmeting zal in een dergelijke situatie altijd minder dan 4.5% zijn. De rol van het sample volume met betrekking tot uniforme scattering wordt uiteengezet. Uniforme scattering treedt op indien de diameter van het laag thoracale deel van de foetale aorta descendens kleiner is dan 9.2 mm.

Hoofdstuk 5
Een overzicht van de literatuur betreffende non-invasieve bloedstroomsnelheidsmetingen aan de foetale circulatie wordt gegeven. Metingen worden verricht in de navelstrengarterieën, het intra-abdominale deel van de navelstrengvene, het laag thoracale deel van de aorta descendens en de vena cava inferior. De resultaten van de metingen in bovengenoemde vaten worden vergeleken met de resultaten verkregen bij dierexperimenteel onderzoek. Ook de effecten van zowel uitwendige als inwendige stimuli op deze metingen worden beschreven.

Hoofdstuk 6
In dit hoofdstuk worden de resultaten van het eigen onderzoek in de ongestoorde zwangerschap met betrekking tot de bloedstroomsnelheid, de vaatdiameter en de bloedstroom beschreven. De criteria voor selectie van de normale zwangeren wordt gedefinieerd.

De variantie tussen de inter- en intra-observer studie toonde geen verschillen zowel voor de bloedstroomsnelheid als voor de vaatdiameter. De bloedstroomsnelheid gaf een significante afname te zien vanaf 28 weken tot 39 weken zwangerschapsduur terwijl de vaatdiameter en de bloedstroom beiden significant toenamen. De spreiding van de bloedstroomwaarden was zodanig groot dat de klinische betekenis van deze parameter van zeer weinig waarde moet worden geacht. De resultaten uit ons onderzoek werden vergeleken met die van andere centra.

Hoofdstuk 7
Het effect van moederlijk roken op het maternale en foetale cardiovasculaire systeem werd in een gerandomiseerd onderzoek bij 18 gezonde nullipara zwangeren (9 rooksters, 9 niet-rooksters) tussen 34 en 38 weken zwangerschap onderzocht. Uiteindelijk waren er gegevens van 7 rooksters en 7 niet-rooksters beschikbaar voor verdere analyse. Een significante toename in moederlijke hartfrequentie en systolische bloeddruk werd gedurende en direct in aansluiting op het roken van 1 sigaret waargenomen. In de foetus werd direct na roken een significante stijging in de hartfrequentie gezien, terwijl de gemiddelde bloedstroomsnelheid en de vaatdiameter met betrekking tot het laag thoracale deel van de aorta descendens zoals vastgesteld door middel van een gepulsde Doppler en M-mode technieken geen essentiële veranderingen vertoonde.

Hoofdstuk 8
Het effect van matige kortdurende moederlijke inspanning op de maternale en foetale cardiovasculaire dynamiek werd in een gerandomiseerd onderzoek bestudeerd bij 28 gezonde nullipara zwangeren (14 zwangeren verrichten inspanning, de overige 14 dienden als controle) tussen 34 en 38 weken zwangerschap. Uiteindelijk waren gegevens van 11 zwangeren in de inspannings- en 12 in de controle groep beschikbaar voor verdere analyse. Tijdens inspanning werd een significante toename in moederlijke hartfrequentie, systolische en diastolische bloeddruk waargenomen. De gemiddelde bloedstroomsnelheid in het laag thoracale deel van de foetale aorta descendens zoals gemeten met een gepulsed Doppler systeem alsmede de foetale hartfrequentie toonden geen essentiële veranderingen. Deze gegevens suggereren dat er onmiddellijk na matige kortdurende moederlijke inspanning geen meetbare veranderingen in het foetale cardiovasculaire systeem optreden.

Hoofdstuk 9
De invloed van pulsatiele vaatdiameterveranderingen op de berekening van volume bloeddoorstroming werd onderzocht. In vitro en dierexperimenteel onderzoek werd uitgevoerd met een 2D-real-time scanner en een gepulsed Doppler systeem. Voor nauwkeurige meting van de pulsatiele diameterveranderingen werd gebruik gemaakt van een Time Distance recorder. Terwijl in vitro een hoge graad van nauwkeurigheid voor de berekening van de volume bloeddoorstroming werd vastgesteld kon dit niet worden waargemaakt voor bloeddoorstromingsmetingen in het laag thoracale deel van de aorta descendens van het foetale lam. Bij vergelijking van de bloeddoorstromingsmetingen met het gepulsde Doppler systeem en een elektromagnetische flow transducer werd een verschil gevonden dat varieerde tussen -7.5 en +17%. In een klinisch onderzoek werd de invloed van verschillende vaatdiametertechnieken op de uiteindelijke foetale bloeddoorstroming in het laag thoracale deel van de aorta descendens vastgesteld. Afhankelijk van de gekozen meetmethodiek ter bepaling van de vaatdiameter werden er verschillen van 19% onderwaardering en 9% overwaardering van de berekende bloeddoorstroming gevonden.

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CURRICULUM VITAE

The author was born on January 21th 1951 in Vlaardingen, The Netherlands. In 1971 he obtained the diploma Gymnasium β at "Het Groen van Prinsterer Lyceum" te Vlaardingen. In the same year he commenced his medical study at the Erasmus University of Rotterdam.
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