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Fetal pulmonary venous flow into the left atrium relative to diastolic and systolic cardiac time intervals

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ABSTRACT

Objective *To establish the nature and gestational age dependency of the pulmonary venous flow velocity pattern into the left atrium relative to systolic and diastolic phases of the cardiac cycle.*

Design *This was a cross-sectional study of Doppler measurements of fetal pulmonary venous inflow velocities, which were correlated with simultaneous recordings of transmitral and aortic flow velocity waveforms based on an equal cardiac cycle length (± 5%).*

Results *Successful recordings were obtained in 28 out of 60 (47%) normal singleton pregnancies at 20–36 weeks of gestation. Reproducibility of waveform analysis of the various phases of the cardiac cycle was satisfactory, within-patient variance ranging between 1.7% and 6.5%. A statistically significant increase ($p < 0.05$) in pulmonary venous time average velocity and velocity integral with advancing gestational age was established. A statistically significant increase ($p < 0.05$) of the pulmonary flow velocity integral was also found when related to each of the systolic and diastolic segments of the cardiac cycle, with the exception of isovolemic relaxation time. The duration of each of the diastolic and systolic segments of the cardiac cycle, as well as the pulmonary venous velocity integral expressed as a percentage of the cardiac cycle, remained constant with advancing gestational age.*

Conclusions *The second half of pregnancy is characterized by pulmonary venous inflow into the left atrium throughout the cardiac cycle. Pulmonary venous inflow into the left atrium occurs predominantly during the filling and ejection phases of the cardiac cycle. Absolute cardiac diastolic and systolic time intervals as well as the percentage distribution of pulmonary venous flow velocity integrals between these cardiac time intervals remain unchanged with advancing gestational age.*

INTRODUCTION

Recently, a number of reports have appeared on pulmonary venous flow velocity patterns during fetal life[1–5]. These patterns, which show great similarity with flow velocity waveforms originating from the ductus venosus, are characterized by a systolic and early diastolic forward flow component followed by a late diastolic forward flow[3–5], absent or reverse flow[4,5] component coincident with atrial contraction.

Simultaneous recordings of transmitral and aortic flow velocities have provided detailed information on diastolic and systolic time intervals in the developing heart[6]. A study of pulmonary venous inflow into the left atrium corresponding with these different cardiac time intervals may further deepen our understanding of normal cardiac function and may serve as a reference for fetal developmental pathology. The objective of the study was to establish the nature and gestational age dependency of the pulmonary venous flow velocity pattern into the left atrium relative to the systolic and diastolic phases of the cardiac cycle.

PATIENTS AND METHODS

Study subjects

A total of 60 healthy, non-smoking women with a normal singleton pregnancy recruited from our routine antenatal clinic consented to participate in the study. Gestational age varied between 20 and 36 weeks (mean 27 weeks) and was calculated from a reliable menstrual history or from early ultrasonic measurement of crown–rump length or biparietal diameter. Maternal age ranged between 16 and 36 years (median 24 years); parity varied between 1 and 5 (median 2). Women were selected to obtain a homogeneous distribution over the gestational age period studied. Each woman participated in the study only once. All pregnancies were uncomplicated. All women gave birth to a healthy

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infant with a birth weight between the 10th and 90th centiles of weight for gestation[7].

Recording technique

Ultrasound Doppler studies were performed on a Toshiba SSH 140A machine (Toshiba Corporation, Medical Systems Division, Tokyo, Japan) with a combined transabdominal real-time and pulsed Doppler system (carrier frequency 3.75 MHz in Doppler mode and 5 MHz in B-mode). Spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes, according to the manufacturer's specifications. Recordings were performed with the woman in a semi-recumbent position. After a clear sonographic transverse cross-section of the fetal chest was obtained at the level of the five-chamber view, the sample volume was set at 3–4 mm to cover the area immediately distal to the mitral and the aortic valves. Pulsed wave Doppler was switched on and transmitral wave flow patterns were recorded simultaneously with ventricular ejection patterns into the ascending aorta. Only transmitral waveforms consisting of a clear E- and A-wave and a distinctive aortic flow pattern were accepted. The smallest detectable time interval of the Doppler equipment used was 1 ms. The angle of insonation was kept below 30°. Subsequently, color Doppler was used to visualize one of the pulmonary veins. Depending on the fetal position, the sample volume was placed over the best visualized vein of the right or left lung, just proximal to the entrance into the left atrium. Maximum flow velocity envelopes were collected during fetal apnea, since fetal breathing movements modulate venous Doppler waveforms[8]. For the sake of depicting single waveforms with maximum accuracy, the fastest possible scrolling speed option of 12.5 cm/s was selected. All Doppler recordings were performed by one examiner (C.B.). Pulmonary venous flow velocity recordings and simultaneous recordings of transmitral and ascending aortic flow velocity waveforms were selected on the basis of equal cardiac cycle length (± 5%). Comparison of pulmonary venous inflow velocity and simultaneously registered transmitral and transaortic flow velocities was feasible through synchronization of the transmitral peak A-wave velocity and the pulmonary venous end-diastolic trough, both of which coincide with atrial contraction (Figure 1)[1,6]. The mean value was calculated from measurements during two consecutive cardiac cycles.

Waveform analysis

Technically acceptable flow velocity waveforms were documented on hard copies during each of the recordings. The largest possible format of hard copies was chosen (12.5 × 10 cm graph size). Off-line waveform analysis was performed on a microcomputer (Commodore 386 CX) linked to a graphics tablet as described previously[9].

First, the time average velocity (cm/s) and flow velocity integral (cm) for the entire pulmonary venous waveform were determined. This was followed by the calculation of filling time (ms) and ejection time (ms) on the simultaneous recording of transmitral and ascending aortic flow velocities. Filling time is defined as the time interval between the beginning and the end of the transmitral flow curve; ejection time is defined as the time interval between the beginning and the end of the aortic flow curve. Isovolemic relaxation time (ms) represents the time interval between the end of the aortic flow velocity waveform and the onset of the transmitral flow velocity waveform, whereas isovolemic contraction time (ms) lasts from the end of the transmitral flow velocity waveform to the onset of the aortic flow velocity waveform.

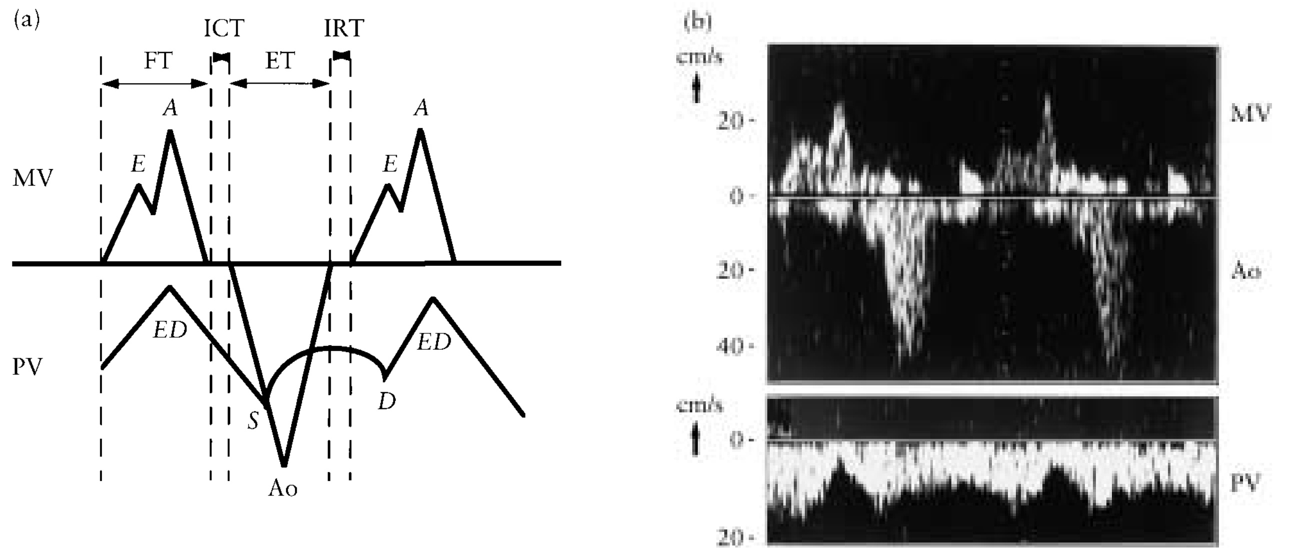

Figure 1 (a) Schematic presentation of pulmonary venous flow velocity waveforms relative to simultaneous recordings of mitral and aortic flow velocity waveforms. MV, transmitral flow velocity waveform with E- and A-waves; Ao, aortic flow velocity waveform; PV, pulmonary venous flow velocity waveform with S (peak systolic; cm/s), D (peak diastolic; cm/s) and ED (end-diastolic; cm/s) velocities. FT, filling time (s); ICT, isovolemic contraction time (s); ET, ejection time (s); IRT, isovolemic relaxation time (s). (b) Example of Doppler recordings of pulmonary venous flow velocity waveforms relative to simultaneous recordings of mitral and aortic flow velocity waveforms

This was followed by dividing the pulmonary venous waveform into four segments corresponding to the systolic (ejection time and isovolemic contraction time) and diastolic (filling time and isovolemic relaxation time) phases of the cardiac cycle. Flow velocity integral measurements of these four segments were subsequently performed on the pulmonary vein tracing.

Reproducibility study

In order to assess the reproducibility of the measurements of pulmonary vein flow corresponding to the different phases of the cardiac cycle, a reproducibility study was performed. A total of 15 women, with acceptable Doppler recordings, were selected: five at 21–25 weeks, five at 26–30 weeks and five at 31–35 weeks of gestation. Five copies were made of each hard copy, resulting in a total of 75, which were numbered, shuffled into random order and analyzed on the graphics tablet in the manner described.

Statistical analysis

All data obtained during the measurements were analyzed using the SPSS for Windows package (Torrance, CA, USA). The relationships between the various parameters and gestational age were analyzed by least squares linear regression. Pearson's correlation coefficients (r) are given.

To assess the reproducibility, analysis of variance was used in which the total variation was divided into the variation between fetuses and the variation between hard-copy analyses within fetuses. Data are represented as mean ± SD. Statistical significance was set at $p < 0.05$.

RESULTS

Technically acceptable flow velocity waveforms were collected in 28 out of 60 women, resulting in a success rate of 47%. Recording failures were caused by fetal movements, fetal breathing, maternal obesity and unfavorable fetal position. In 12 patients (38% of all failures), recordings were omitted from further analysis, since there was a cardiac cycle difference of more than 5% between the measurement of the aortic/mitral waveform and pulmonary vein waveforms. Data on reproducibility are shown in Table 1. Within-patient variance as a percentage of total variance was always below 7%.

Cardiac cycle length remained constant at 428 ± 21.1 ms throughout the observation period. A statistically significant increase ($p < 0.05$) in pulmonary venous time average velocity (Figure 2) and velocity integral (Figure 3) with advancing gestational age was established. A statistically significant increase ($p < 0.05$) of the pulmonary flow velocity integral was also found when related to each of the systolic and diastolic segments of the cardiac cycle, with the exception of isovolemic relaxation time (Figures 4–7).

The duration of each of the diastolic and systolic segments of the cardiac cycle (Table 2) as well as the

Table 1 Reproducibility of the pulmonary venous flow velocity integral measurement corresponding to each of the diastolic and systolic phases of the cardiac cycle

	Within-patient variance (cm)	*Between-patient variance* (cm)	*Within-patient variance as a percentage of total variance*
Filling time	0.0132	0.6552	1.7
Isovolemic contraction time	0.004	0.0749	5.4
Ejection time	0.0079	0.6816	1.1
Isovolemic relaxation time	0.0027	0.0386	6.5

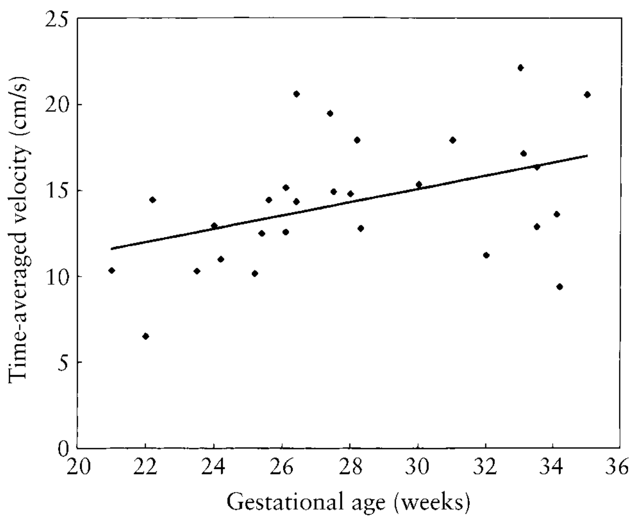

Figure 2 Fetal pulmonary venous time average velocity relative to gestational age. Regression line, with slope = 0.37 cm/s per week; $r = 0.41$; $p = 0.03$

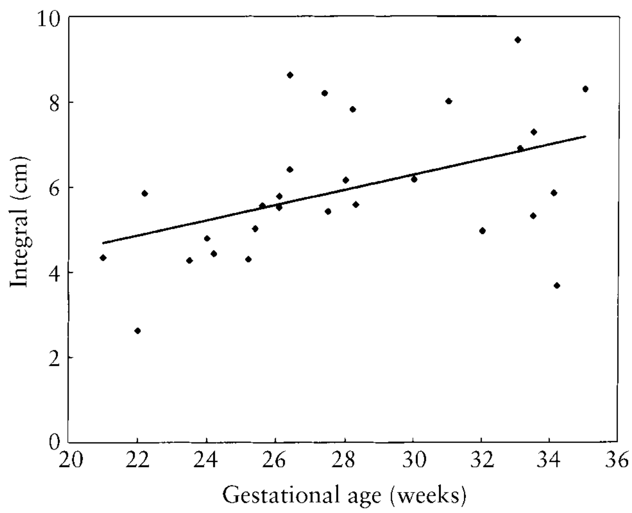

Figure 3 Fetal pulmonary venous flow velocity integral relative to gestational age. Regression line, with slope = 0.16 cm/week; $r = 0.40$; $p = 0.03$

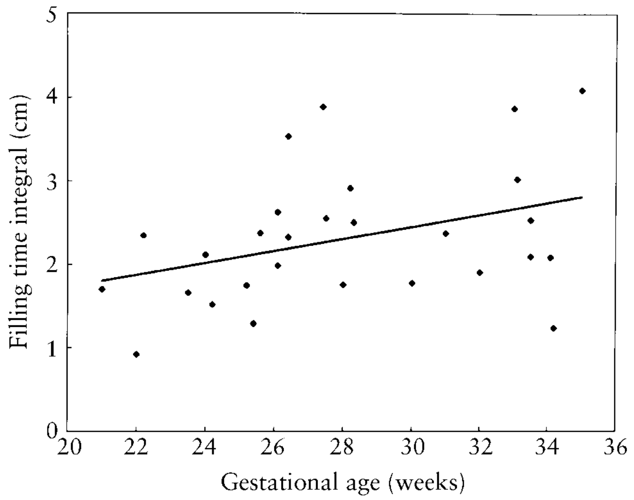

Figure 4 Fetal pulmonary venous flow velocity integral during filling time relative to gestational age. Regression line, with slope = 0.07 cm/week; $r = 0.38$; $p = 0.047$

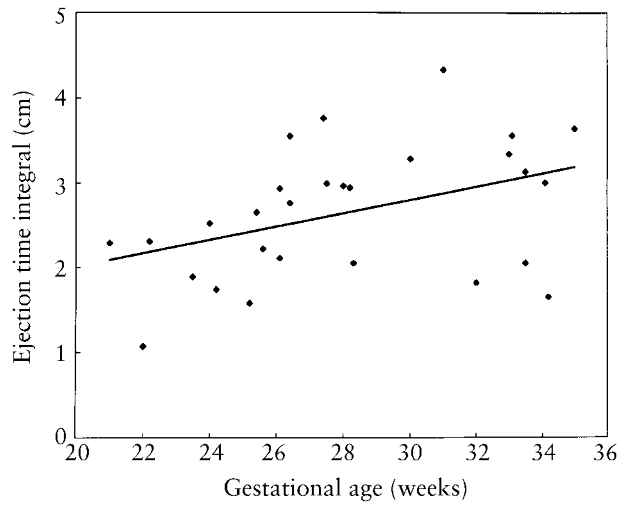

Figure 6 Fetal pulmonary venous flow velocity integral during ejection time relative to gestational age. Regression line, with slope = 0.08 cm/week; $r = 0.41$; $p = 0.03$

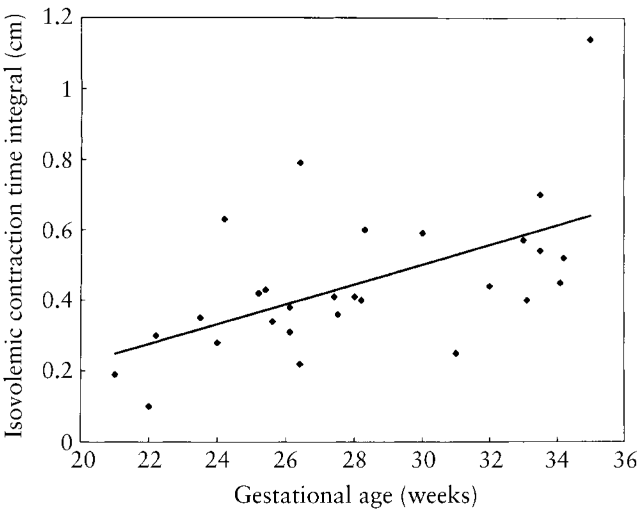

Figure 5 Fetal pulmonary venous flow velocity integral during isovolemic contraction time relative to gestational age. Regression line, with slope = 0.02 cm/week; $r = 0.50$; $p = 0.007$

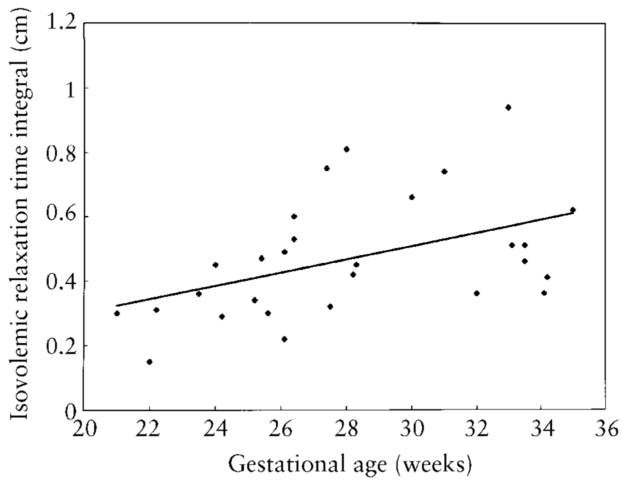

Figure 7 Fetal pulmonary venous flow velocity integral during isovolemic relaxation time relative to gestational age. Regression line, with slope = 0.02 cm/week; $r = 0.35$; NS

Table 2 Mean ± SD for each of the diastolic and systolic phases of the cardiac cycle (ms)

	Mean	*SD*
Filling time	184.5	23.9
Ejection time	179.8	16.6
Isovolemic contraction time	26.1	8.1
Isovolemic relaxation time	37.6	9.3
Heart cycle length	428.0	21.1

Table 3 Mean ± SD and percentage of pulmonary venous integral corresponding to each of the diastolic and systolic phases of the cardiac cycle (cm)

	Mean	*SD*	%
Filling time	2.32	0.80	39
Ejection time	2.65	0.78	45
Isovolemic contraction time	0.45	0.20	7.5
Isovolemic relaxation time	0.47	0.18	8.5

pulmonary venous velocity integral expressed as a percentage of the cardiac cycle (Table 3) remained constant with advancing gestational age.

DISCUSSION

The present study presents the first data on pulmonary venous inflow into the left atrium relative to the different systolic and diastolic time components of the fetal cardiac cycle. The fetal pulmonary venous waveform consists of a systolic and early diastolic forward flow component followed by a late diastolic forward flow component coincident with atrial contraction[3]. There is pulmonary venous inflow into the left atrium throughout the cardiac cycle. The trough caused by atrial contraction is followed by an increase in velocity towards atrial diastole. As atrial capacitance decreases, flow velocity stabilizes but increases again as the mitral valve opens. The lowest velocity of the fetal pulmonary venous flow velocity waveform pattern is reached at the peak of the mitral A-wave when there is rapid emptying of the left atrium into the left ventricle. In the adult, there is virtually no measurable flow from the pulmonary vein into the left atrium at this point of late diastole[10], whereas in the fetus forward[3–5], absent or even reverse flow[4,5] may be observed during atrial contraction. In the adult, the pulmonary venous inflow pattern mirrors the left atrial pressure waveform[11]. If a similar relationship is assumed in the fetus, then the systolic component of the pulmonary venous flow velocity waveform would coincide with a reduction in atrial pressure.

The increase in both pulmonary venous time average flow velocity and flow velocity integral with advancing gestational age may reflect a rise in volume flow as a result of an increase in pulmonary vasculature in the growing fetus[12,13]. Van Splunder and Wladimiroff[6] have demonstrated that it is possible to determine diastolic and systolic time relationships from simultaneous left ventricular inflow and outflow tract flow velocity waveforms. Our data demonstrate that a gestational age-related increase in pulmonary venous flow velocity integral was also observed for each of the diastolic and systolic cardiac time intervals, except for the isovolemic relaxation time. These data further support the view that the previously mentioned increase in flow velocity is volume flow determined. Alternatively, the increase in pulmonary venous flow velocity could be explained by a rise in the pulmonary venous pressure gradient with advancing gestational age, as a result of increasing relaxation in both the ventricles for the systolic increase, and in the atria for the diastolic increase[14,15].

Our reproducibility study of the pulmonary venous flow velocity integral relative to the different diastolic and systolic cardiac time intervals demonstrates that between-patient variance is considerably larger than within-patient variance. The latter, expressed as a percentage of total variance, is excellent for filling time (1.7%) and ejection time (1.1%), and acceptable for isovolemic contraction time (5.4%) and isovolemic relaxation time (6.5%). For both the isovolemic contraction time and the relaxation time, the time intervals are relatively short, corresponding to 2–6 mm of paper length on the hard-copy x-axis. The increase in total variance can be explained by lack of precision in the manual measurements of very short tracings for the latter two components of the cardiac cycle. This may also explain the lack of change in isovolemic relaxation time with advancing gestational age.

When looking at the absolute values for diastolic and systolic cardiac time intervals, no significant change could be established with advancing gestational age. This suggests that intrinsic myocardial properties do not alter during the normal second half of pregnancy. Also, the pulmonary venous flow velocity integral expressed as a percentage of the cardiac cycle does not change when related to the different cardiac time intervals. Approximately 84% of pulmonary venous inflow into the left atrium occurs during the filling and ejection phases of the cardiac cycle.

It can be concluded that the second half of pregnancy is characterized by pulmonary venous inflow into the left atrium throughout the cardiac cycle. Pulmonary venous inflow into the left atrium occurs predominantly during the filling and ejection phases of the cardiac cycle. Absolute cardiac diastolic and systolic time intervals as well as the percentage distribution of the pulmonary venous flow velocity integral between these cardiac time intervals remain unchanged with advancing gestational age.

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REFERENCES

1. DeVore GR, Horenstein J. Simultaneous Doppler recording of the pulmonary artery and vein: a new technique for the evaluation of a fetal arrhythmia. *J Ultrasound Med* 1993;12: 669–71
2. Emerson DS, Cartier MS. The fetal pulmonary circulation. In Copel JA, Reed KL, eds. *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Raven Press, 1995:307–23
3. Laudy JAM, Huisman TWA, de Ridder MAJ, Wladimiroff JW. Normal fetal pulmonary venous blood flow velocity. *Ultrasound Obstet Gynecol* 1995;6:277–81
4. Better DJ, Kaufman S, Allan L. The normal pattern of pulmonary venous flow on pulsed Doppler examination of the human fetus. *J Am Soc Echocardiogr* 1996;9:281–5
5. Paladini D, Palmieri S, Celentano E, Guida F, Salviati M, Morra T, Martinelli P. Pulmonary venous blood flow in the human fetus. *Ultrasound Obstet Gynecol* 1997;10:27–31
6. Van Splunder IP, Wladimirof JW. Cardiac functional changes in the human fetus in the late first and early second trimesters. *Ultrasound Obstet Gynecol* 1996;7:411–15
7. Kloosterman G. On intrauterine growth. *Int J Gynecol Obstet* 1970;8:895–912
8. Huisman TWA, van den Eijnde SM, Stewart PA, Wladimiroff JW. Changes in inferior vena cava blood flow and diameter during fetal breathing movements in the human fetus. *Ultrasound Obstet Gynecol* 1993;3:26–31
9. Groenenberg IA, Hop WCJ, Wladimiroff JW. Doppler flow velocity waveforms in the fetal cardiac outflow tract: reproducibility of waveform recording and analysis. *Ultrasound Med Biol* 1991;17:583–7
10. Keren G, Sherez J, Megidish R, Levitt B, Laniado S. Pulmonary venous flow pattern – its relationship to cardiac dynamics. A pulsed Doppler echocardiography study. *Circulation* 1985;71:1105–12
11. Ramjagopalan B, Friend JA, Stallard T, Lee G de J. Blood flow in pulmonary veins. I. Studies in dog and man. *Cardiovasc Res* 1979;13:667–76
12. Levin D, Rudolph AJ, Heymann MA, Phibbs R. Morphological development of the pulmonary vascular bed in fetal lambs. *Circulation* 1976;53:144–51
13. Morin FC III, Egan EA. Pulmonary hemodynamics in fetal lambs during development at normal and increased oxygen tension. *J Appl Physiol* 1992;73:213–18
14. Tulzer G, Khowsathit P, Gudmundsson S, Wood DC, Tian Z-Y, Schmitt K, Huhta JC. Diastolic function of the fetal heart during second and third trimester: a prospective longitudinal Doppler-echocardiographic study. *Eur J Pediatr* 1994;153: 151–4
15. Carceller-Blanchard A-M, Fouron J-C. Determinants of the Doppler flow velocity profile through the mitral valve of the human fetus. *Br Heart J* 1993;70:457–60