Heart rate and flow velocity variability as determined from umbilical Doppler velocimetry at 10–20 weeks of gestation

Nicolette T. C. URSEM*, Piet C. STRUIJK*, Wim C. J. HOP†, Edward B. CLARK‡, Bradley B. KELLER§ and Jurij W. WLADIMIROFF*

*Department of Obstetrics and Gynaecology, Academic Hospital Rotterdam—Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; †Department of Epidemiology and Biostatistics, Erasmus University Rotterdam, Dr Molewaterplein 40, 3015 GE Rotterdam, The Netherlands; ‡Medical Director’s Office, University of Utah, School of Medicine, Primary Children’s Medical Center, 100 North Medical Drive, Salt Lake City, UT 84113, U.S.A.; and §Department of Pediatrics, University of Rochester, 601 Elmwood Avenue, Rochester, NY 14642, U.S.A.

ABSTRACT

1. The aim of this study was to define from umbilical artery flow velocity waveforms absolute peak systolic and time-averaged velocity, fetal heart rate, fetal heart rate variability and flow velocity variability, and the relation between fetal heart rate and velocity variables in early pregnancy.

2. A total of 108 women presenting with a normal pregnancy from 10 to 20 weeks of gestation consented to participate in a cross-sectional study design. Doppler ultrasound recordings were made from the free-floating loop of the umbilical cord.

3. Umbilical artery peak systolic and time-averaged velocity increased at 10–20 weeks, whereas fetal heart rate decreased at 10–15 weeks of gestation and plateaued thereafter. Umbilical artery peak systolic velocity variability and fetal heart rate variability increased at 10–20 and 15–20 weeks respectively.

4. The inverse relationship between umbilical artery flow velocity and fetal heart rate at 10–15 weeks of gestation suggests that the Frank–Starling mechanism regulates cardiovascular control as early as the late first and early second trimesters of pregnancy. A different underlying mechanism is suggested for the observed variability profiles in heart rate and umbilical artery peak systolic velocity. It is speculated that heart rate variability is mediated by maturation of the parasympathetic nervous system, whereas peak systolic velocity variability reflects the activation of a haemodynamic feedback mechanism.

INTRODUCTION

Fetal heart rate variability in the late second and third trimester of pregnancy is widely used to study the condition of the fetus in utero. Reduced heart rate variability occurs in pathophysiological states like intra-uterine growth retardation and may be related to fetal stress and diminished cardiovascular functional reserve [1]. In the late first and early second trimester of human pregnancy, there is a decrease in fetal heart rate and

Key words: Doppler ultrasound, flow velocity variability, heart rate variability, umbilical artery.
Abbreviations: CV, coefficient of variation; FHR, fetal heart rate; PSV, peak systolic velocity; TAV, time-averaged velocity.
Correspondence: Dr J. W. Wladimiroff.
appearance of beat-to-beat variation in fetal heart rate. These changes probably reflect maturation of vagal parasympathetic functional control [2,3]. In normal pregnancy there is a positive correlation between fetal heart rate variability and gestational age throughout the second trimester [4]. Therefore, fetal heart rate variability is a marker of normal physiological and pathophysiological processes.

Combined transvaginal and transabdominal Doppler ultrasonography provides measures of human fetal arterial flow velocities during the late first and early second trimester of pregnancy [5,6]. Moreover, using Doppler ultrasonography it has also become possible to obtain information on beat-to-beat variability in arterial blood flow velocity during this early period of pregnancy [7].

Spectral analysis of blood flow velocity in the dorsal aorta of the chick embryo showed a change in velocity modulation with development, which probably reflects shifts in haemodynamic control associated with cardiovascular morphogenesis [8].

The aims of the present study were to determine from umbilical artery flow velocity waveforms: (i) absolute peak systolic and time-averaged velocities; (ii) fetal heart rate, fetal heart rate variability and flow velocity variability; and (iii) the interrelationship between fetal heart rate and flow velocity variables in normal pregnancies at 10–20 weeks of gestation.

METHODS

Subjects

A total of 108 women with a normal singleton pregnancy between 10 and 20 weeks of gestation (median 15 weeks) consented to participate in the cross-sectional study. The study was approved by the Hospital Ethics Committee at the Erasmus University, Rotterdam and the University of Rochester, Rochester, NY. Forty-seven women were nulliparous. Maternal age ranged between 14 and 46 years (median 29 years). Pregnancy duration was estimated from the last menstrual period and confirmed by ultrasonic measurement of the fetal crown–rump length (10–12 weeks) or biparietal diameter (12–20 weeks). All pregnancies were uncomplicated and resulted in the term delivery of a normal infant with a birth weight between the 10th and 90th centile corrected for maternal parity and fetal sex [9].

Doppler recordings

Ultrasound Doppler studies were performed with a Toshiba SSH 140A (Toshiba Corp., Medical Systems Division, Tokyo, Japan). A combined transvaginal real-time and colour Doppler system (carrier frequency 6 MHz and 5 MHz respectively) was used at 10–13 weeks of gestation, and a combined transabdominal real-time and colour Doppler system (carrier frequency 5.0 MHz and 3.75 MHz respectively) was used at 14–20 weeks of gestation. For a more detailed visualization of fetal vessels, transvaginal ultrasonography was used at 10–13 weeks, whereas due to increasing fetal size the transabdominal approach was used from 13–14 weeks of gestation. The system operates at power outputs of < 100 mW/cm² spatial peak-temporal average in both imaging and Doppler modes by manufacturer’s specification. These output levels are clearly situated in the lower regions for acoustic output of Japanese and American diagnostic equipment [10]. The total examination time was limited to 15 min in each instance. Colour Doppler was used to obtain the highest velocity signal in the umbilical artery so that the angle of insonation was kept as small as possible. The high-pass filter was set at 100 Hz and the sample volume length was 0.2–0.3 cm. Depending on the scanning depth, the pulse repetition frequency ranged between 3 and 6 kHz. All Doppler studies were performed with the women in the semi-recumbent position and during fetal apnoea. Doppler recordings were performed by one examiner. Flow velocity waveforms from the umbilical artery were obtained from the free-floating loop.

The change in methodology was validated by comparison of transvaginally and transabdominally collected umbilical artery waveforms in 10 normal singleton pregnancies at 12–13 weeks of gestation. This period of gestational age was selected because at that time a transition from transvaginal to transabdominal scanning takes place.

Data processing

Umbilical artery Doppler recordings were stored on sVHS videotape in PAL format using a Panasonic model AG7350 machine (Matsushita Electric Ind. Co., Japan). Umbilical artery audio waveforms were digitized at 12 kHz using an A/D data acquisition board (LabPC+ and BNC-2081 boards, National Instruments, Austin, TX, U.S.A.). In a previous study [7], several methods were described to reconstruct (estimate) the velocity waveform from the Doppler audio signal of the umbilical artery blood flow. The maximum velocity reconstruction method is preferred because it is relatively insensitive to noise, non-uniform insonation and wall filter settings.

The maximum velocity waveform was estimated from the Doppler data using computer algorithms developed in our centre using LabVIEW® software (National Instruments). The power spectra were calculated using a 512-point Fast Fourier transform with a Hanning window and an overlap of 75%. The maximum velocity envelope was estimated using a threshold level adaptive to the level of background noise [11]. The algorithm starts from the high-frequency end of a spectral line (power spectrum) and the highest frequency that exceeds
the threshold value is called the maximum frequency. The threshold is interactively changeable so that as the background level increases, a higher threshold value can be used.

The first derivative of the velocity waveform was used to determine the instantaneous heart rate, which is the reciprocal of the time between successive peaks. For the entire maximum velocity waveform, the peak systolic velocity (PSV, mm/s), time-averaged velocity (TAV, mm/s) and fetal heart rate (FHR, beats/min) per cardiac cycle were calculated. The duration of the Doppler recording of the umbilical artery ranged between 18 and 45 s.

Reproducibility of the umbilical artery flow velocity waveform recordings was established in a separate study of 11 singleton pregnancies at 10–20 weeks of gestation. In each of the 11 fetuses three independent measures were made at 5-min time intervals. For each of the waveform parameters (FHR, PSV and TAV) the mean coefficient of variation (CV) was determined.

**Statistical analysis**

For each fetus, the mean and S.D. were calculated for FHR, PSV and TAV. A logarithmic transformation was performed for the S.D. to stabilize the variability with gestational age. For the expression of variability in the velocity parameters we used the CV, because the S.D.s of peak systolic and time-averaged velocity were not independent of the mean. For all six variables, i.e. mean and S.D. of heart rate, mean and CV of peak systolic and time-averaged velocities, piece-wise linear regression [12], also called the ‘broken stick’ method, was used to evaluate the relation between these variables and gestational age. If the difference between the slope before and after the breaking point was statistically significant, further analysis was performed with the resulting broken stick line. Slopes are given as result ± standard error. The p50, p10 and p90 were established using the mean and the mean ± 1.64 S.D. of the residuals. Multiple regression analysis was carried out to evaluate gestational age, FHR, parity and maternal age simultaneously regarding their predictive value. A paired *t*-test was used to establish the difference between the umbilical artery flow velocity waveforms measured by the transvaginal and transabdominal approach. *P* ≤ 0.05 was taken as the level of significance. All calculations were performed with SPSS 6.1 software (SPSS Inc., Chicago, IL, U.S.A.).

**RESULTS**

The reproducibility study revealed a mean CV of 1.1 (range: 0.2–3.5) % for FHR, 1.9 (1.1–3.3) % for PSV, and 2.4 (1.2–3.9) % for TAV. Comparison of transvaginal and transabdominal flow velocity waveform recordings at 12–13 weeks revealed no statistically significant difference for umbilical artery flow velocity parameters. The intra-class correlation coefficient for the two recording methods was 0.99 for FHR, 0.92 for PSV and 0.91 for TAV.

During the gestational age period of 10–15 weeks, mean umbilical artery PSV increased (Figure 1) and mean FHR decreased (Figure 2). Both variables plateaued for the remainder of the study period. Mean umbilical artery TAV increased between 10 and 20 weeks of gestation (Figure 3), but the slope of velocity differed between 10...
and 15 and 16 and 20 weeks of gestation. Umbilical artery PSV was inversely correlated with FHR at 10–15 weeks of gestation. As both PSV and FHR were related to gestational age up to about 16 weeks, multiple regression analysis was used in this gestational age range to evaluate whether FHR and gestational age displayed an independent predictive value with regard to PSV. Both variables demonstrated a significant relation with PSV. This relationship becomes non-existent at 16–20 weeks of gestation. The resulting multiple regression analyses are given in Table 1, while the corresponding visual display of the relationships is shown in Figure 4. A similar analysis was carried out for the TAV, FHR and gestational age. Table 1 shows the resulting equations; the relationship between umbilical artery TAV and FHR is different before and after 16 weeks of gestation. A statistically significant increase is demonstrated for FHR variability, expressed as S.D., at 15–20 weeks (Figure 5), and for umbilical artery PSV variability, expressed as CV, at 10–20 weeks of gestation (Figure 6). TAV variability, expressed as CV, remained constant during the entire study period. Multiple regression analysis demonstrated that parity and maternal age were not predictive variables. The results of the multiple regression analysis of the variability parameters of heart rate and velocity are displayed in Table 1.

The CV for FHR variability was 0.97 (quartile range: 0.81–1.13)%, whereas for umbilical artery PSV and TAV variability, the median percentages were 3.63 (2.75–4.74)% and 3.75 (2.76–4.57)% respectively.

### DISCUSSION

Doppler recordings of absolute velocities in the umbilical artery over a longer period of time (18–45 s) document variability in both FHR and flow velocity amplitude. FHR decreased between 10 and 15 weeks of gestation but remained constant during the remainder of the study period. The present data agree with previous studies in which FHR decreases from approximately 175–180 beats/min at 9–10 weeks to 145–150 beats/min at 15 weeks of gestation and remains more or less constant during the remainder of intrauterine life [2,13,14]. Colour-coded Doppler ultrasound allows recordings of peak umbilical artery velocity signals at an interrogation angle of less than 15°. A good reproducibility was established for umbilical artery PSV, TAV and FHR. Both peak systolic and time-averaged umbilical artery flow velocity demonstrated a marked increase up to 15 weeks of gestation followed by plateauing or a less pronounced rise at 15–20 weeks of gestation, thus mirroring the aforementioned changes in FHR. Of interest is that a marked reduction in pulsatility index has

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**Table 1 Multiple regression analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GA (years)</th>
<th>Mathematical operation</th>
<th>GA coefficient</th>
<th>HR coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV (mm/s)</td>
<td>&lt; 16</td>
<td>$14.6 \times \text{GA} - 2.9 \times \text{HR} + 547.5$</td>
<td>$P = 0.005$</td>
<td>$P = 0.001$</td>
</tr>
<tr>
<td>PSV (mm/s)</td>
<td>$\geq 16$</td>
<td>354.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TAV (mm/s)</td>
<td>&lt; 16</td>
<td>$16.6 \times \text{GA} - 0.8 \times \text{HR} + 50.1$</td>
<td>$P &lt; 0.001$</td>
<td>$P = 0.050$</td>
</tr>
<tr>
<td>TAV (mm/s)</td>
<td>$\geq 16$</td>
<td>$6.2 \times \text{GA} + 2.2 \times \text{HR} - 233.0$</td>
<td>$P = 0.050$</td>
<td>$P = 0.025$</td>
</tr>
<tr>
<td>varHR (beats/min)</td>
<td>&lt; 16</td>
<td>$0.005 \times \text{HR} - 0.6$</td>
<td>NS</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>varHR (beats/min)</td>
<td>$\geq 16$</td>
<td>$0.03 \times \text{GA} - 0.007 \times \text{HR} + 0.7$</td>
<td>$P = 0.012$</td>
<td>$P = 0.031$</td>
</tr>
<tr>
<td>varPSV (%)</td>
<td>10–20</td>
<td>$-0.004 \times \text{HR} + 1.2$</td>
<td>NS</td>
<td>$P = 0.011$</td>
</tr>
<tr>
<td>varTAV (%)</td>
<td>10–20</td>
<td>0.56</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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Early haemodynamics in the normal fetus

Figure 4 Umbilical artery PSV relative to FHR
Drawn lines represent mean PSV versus FHR at different gestational ages (10, 12, 14 and 16–20 weeks). Data points indicate individual PSV values according to the different gestational age categories.

Figure 5 Individual data and centiles (p10, p50, p90) for heart rate variability relative to gestational age
The slope after the calculated breakpoint (i.e. 15.2 ± 1.0 weeks) equals 0.08 ± 0.2 beats/min per week. Note the logarithmically transformed vertical axis.

Figure 6 Individual data and centiles (p10, p50, p90) for PSV variability relative to gestational age (r = 0.6, P 0.001)
Note the logarithmically transformed vertical axis.

been established in the descending aorta and umbilical artery at 10–15 weeks, reflecting a significant reduction in fetoplacental vascular resistance at this early stage of gestation. Placental microangiogenesis is probably the mechanism for these resistance changes [15]. The change in umbilical artery flow velocity before and after 16 weeks of gestation is unrelated to the measurement technique. No difference between transvaginal and transabdominal umbilical artery flow velocity recordings could be established at 12–13 weeks of gestation.
In late pregnancy, auditory stimulation increases heart rate and decreases ventricular stroke volume without changing ventricular output [17]. Thus, the Frank-Starling mechanism and not heart rate is the major regulator of cardiac output in the human fetus. Similar findings have been found in the fetal lamb [18] and chick embryo [19]. In our study we were unable to measure blood volume flow, but the inverse relationship between umbilical artery PSV and FHR suggests that the Frank-Starling mechanism regulates fetal cardiovascular control as early as the early second trimester of pregnancy. If the Frank-Starling mechanism is indeed operational as early as 10–15 weeks of gestation, then the pronounced rise in umbilical artery peak systolic and time-averaged velocity may not only reflect a fetal growth-determined rise in volume flow, but also an increase in cardiac stroke volume due to an increase in diastolic filling time related to the lower FHR. The less marked increase in TAV at 16–20 weeks may be mainly growth-related since heart rate remains rather constant at that time.

No correlation existed between FHR variability and umbilical artery PSV variability, suggesting that the gestational age-related increases in FHR variability and PSV variability are mediated by two separate control mechanisms. Maturation of the parasympathetic nervous system mediates the increase in FHR variability [2,3]. A cardiovascular feedback mechanism probably increases variability in PSV as has been demonstrated in the chick embryo. In the chick, short-duration modulations in aortic blood flow and vascular impedance are a haemodynamic control during early development [20,21]. Several oscillating physiological mechanisms arising from respiration, baroreceptor activity and vasomotor activity may influence heart rate variability. Whether all these mechanisms influence heart rate variability in the early human fetus is not known. Power spectral analysis of longer lasting umbilical artery waveform recordings will be needed to investigate which mechanisms are present this early in pregnancy.

In the fetal lamb, vagal blockade by atropine increases FHR and decreases heart rate variability [22]. In the human fetus, atropine administered to the mother after 15 weeks of pregnancy results in a rise in FHR that correlates with advancing gestation [3]. Parasympathetic maturation is considered responsible for the gestational age-related decrease in FHR; these changes occur in parallel with the appearance of FHR variability [23]. However, the present study has shown that at 10–15 weeks the fall in FHR is not associated with an increase in FHR variability. Therefore, an alternative explanation for the reduction in FHR must be considered.

There is evidence that cardiac muscle cells are immature at 9–10 weeks of gestation. During the subsequent weeks myofibrils, which form the contractility apparatus, appear in large numbers. The maturation of these myofibrils may affect the performance of the myocardium to load resulting in more efficient contractions [13]. Developmental changes in the myocardial contractile system demonstrate that, in 18- and 21-day-old rabbit fetuses, the myofibrils are scarce and disorganized compared with 28-day-old rabbits [24]. According to the data of Sissman [25], 18- and 21-day-old rabbit fetuses are comparable with 10–12-week-old human fetuses and 28-day-old rabbit fetuses are comparable with 18-week-old human fetuses. Thus, improvements in myocardial contractility may be responsible for the early decrease in heart rate in the human fetus.

FHR variability data from the present study are at variance with earlier data indicating a decrease with advancing gestational age [26]. We suggest that the difference relates to the reconstruction method used to estimate the velocity waveform. Recently we found that the mode reconstruction method (i.e. frequencies with the highest intensity within the power spectra) is particularly sensitive to noise, non-uniform insonation and wall filter settings [7] with emphasis on the 10–14-week gestation period. Therefore, the previous method generated a greater variability in heart rate compared with the reconstruction method used in the present study.

In umbilical artery flow velocity coincides with a decline in FHR at 10–15 weeks of gestation. These observations suggest that the Frank-Starling mechanism regulates cardiovascular function during this early stage of human pregnancy. The pregnancy period of 15–20 weeks is characterized by an increase in both FHR variability and umbilical artery PSV variability. The latter may be mediated by maturation of the parasympathetic nervous system, and the latter by the activation of a haemodynamic feedback mechanism.

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