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Multicentre study of fetal cardiac time intervals using magnetocardiography

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Objective A database with reference values of the durations of the various waveforms in a magnetocardiogram of fetuses in uncomplicated pregnancies is assessed. This database will be of help to discriminate between pathologic and healthy fetuses. A fetal magnetocardiogram is a recording of the magnetic field in a location near the maternal abdomen and reflects the electric activity within the fetal heart. It is a non-invasive method, which can be used with nearly 100% reliability from the 20th week of gestation onward.

Design Durations of the waveforms were assembled from averaged magnetocardiograms and statistically processed.

Setting Fetal magnetocardiograms were measured with different magnetocardiographs. All measurements were carried out in magnetically shielded rooms.

Sample Fetal magnetocardiograms were obtained for 582 healthy patients.

Method The durations of the waveforms were extracted from fetal magnetocardiograms measured at the cooperating centres. The variables collected included the duration of the P-wave, the PR interval, the PQ interval, the QRS complex, the QT interval and the T-wave and QTc value. The results were compared with values extracted from electrocardiograms of fetuses measured via electrodes attached to the maternal abdomen, from electrocardiograms measured during labour using a scalp electrode, and from electrocardiograms recorded in newborns, that were found in the literature.

Main outcome measures Values of the durations are given as a function of gestational age including the regression line as well as the bounds marking the 90%, 95% and 98% prediction interval.

Results The durations of the P-wave, the PR interval, the QRS complex, the QT interval and QTc value increase linearly with gestational age. The durations of the PQ interval and the T-wave are independent of fetal age.

Conclusion The values found agree with those found in the literature. The scatter of the data is wide due to the variation in normal physiology, the measuring system and signal processing and the subjectivity of the researcher. However, the system can define normal ranges and may be used in diagnosis.

INTRODUCTION

One way of monitoring the fetal heart is by electrocardiography using electrodes attached to the maternal abdomen. However, a fetal electrocardiogram does not allow measurement of its components due to the fact that currents are confined within the uterus. This problem does not arise with fetal magnetocardiography and this technique seems to be a good alternative for monitoring the fetal heart. Fetal magnetocardiograms are recordings of the magnetic field generated by the electric activity within the fetal heart. The magnetic fields are measured near the maternal abdomen by means of very sensitive magnetometers using special sensors, so-called SQUID. Fetal magnetocardiography allows the non-invasive measurement of cardiac waveforms from the 20th week of gestation onward. The durations of the P-wave, PR interval, PQ interval, QRS complex, QT interval and T-wave can be determined. Consequently, fetal magnetocardiograms can be used to classify arrhythmias, to study congenital heart diseases and to observe fetal wellbeing in growth restriction and twin pregnancy. In order to discriminate between pathological and healthy fetuses, reference values of the components of superconductive quantum interference devices of the cardiogram are needed. In this paper, cardiac time intervals extracted from 582 fetal magnetocardiograms are

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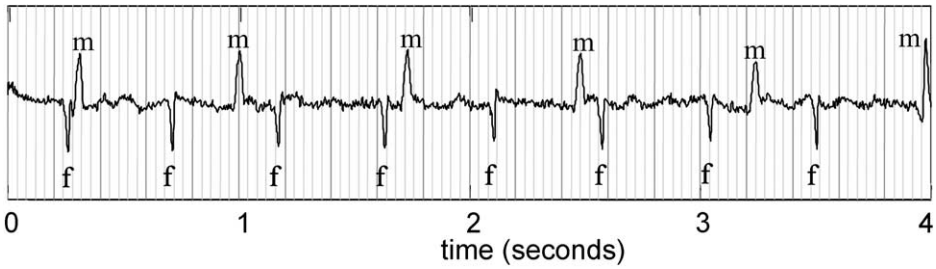


Fig. 1. Example of a fetal magnetocardiogram time trace. The maternal QRS complexes are indicated by an m, and the fetal QRS complexes by an f.

presented, discussed and compared with values found in the literature. The magnetocardiograms were recorded in uncomplicated pregnancies. The time intervals were extracted from fetal magnetocardiograms that were measured at the various cooperating centres; thus, they were obtained under different conditions.

The durations of the various intervals were compared with the durations found in the literature, although knowledge of the variables describing the fetal PQRST waveform is scarce. Apart from fetal magnetocardiograms, these variables were obtained from electrocardiograms obtained in pregnancy, in labour and in the newborn period.

METHODS

Fetal magnetocardiograms were obtained in normal pregnancies, following written informed consent from the women. The hospitals' ethics committee approved the study in accordance with the Helsinki guidelines. All 582 measurements were carried out in magnetically shielded rooms. The magnetometer systems used varied from multichannel magnetometer systems to a one-channel vector magnetometer system. With a multichannel system, a magnetic field vector (usually the component perpendicular to the maternal abdomen with the mother in the supine position underneath the magnetometer system) is measured simultaneously at several positions over the maternal abdomen. With a one-channel vector magnetometer, all three vectors of the magnetic field are measured simultaneously at one position over the maternal abdomen. The system is repositioned in order to identify the optimal measuring position, which usually is the position where a prominent QRS complex is seen in the time trace. This is not necessarily a good position to measure the P- or T-wave.

The following biomagnetometer systems were used: at the University of Erlangen, two different 37-channel systems (Siemens Krenikon and BTi MagnesII); at the Biomagnetism Centre in Bochum, a 37-channel system (Siemens Krenikon) and more recently, a 67-channel system (BTi 1300 C); at the University of Tsukuba, both a 32-channel system measuring two vectors of the magnetic

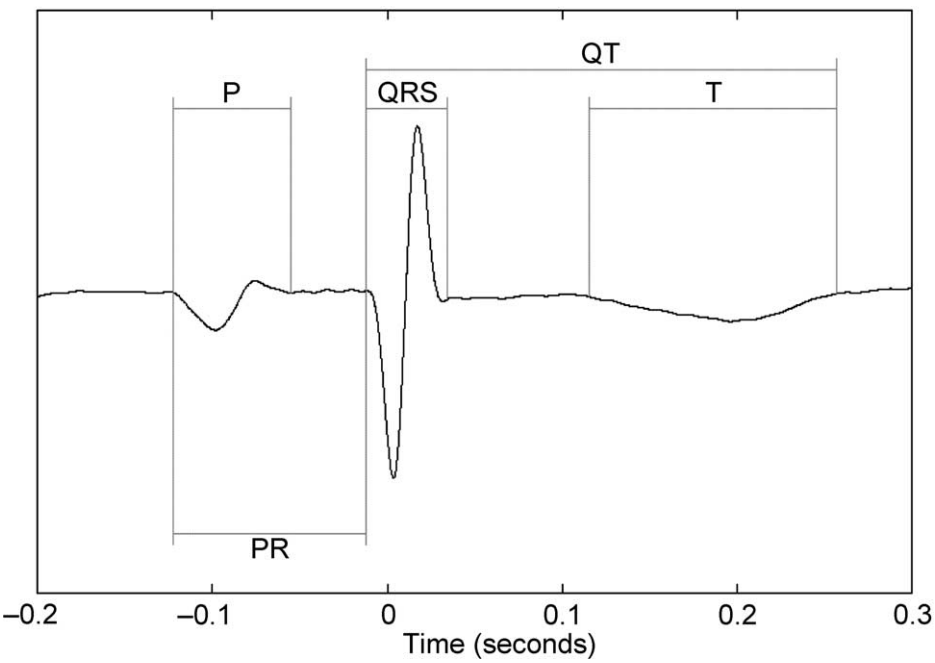


Fig. 2. Identification of fetal cardiac time intervals from a measured averaged fetal magnetocardiogram.

field at 16 positions as well as a nine-channel system to measure three vectors (both self-constructed); at the Friedrich Schiller University in Jena, a 31-channel system (Philips); at the University of Twente, a self-constructed 19-channel system or a one-channel vector magnetometer. Generally, the data were sampled at 1 kHz and were band pass filtered. In the acquired signal, maternal activity was identified and digitally subtracted.

An example of a fetal magnetocardiogram is shown in Fig. 1. The times of the fetal R-peaks were used to construct an averaged fetal magnetocardiogram. First, the PQRST waveforms were extracted from the magnetocardiogram traces; these were subsequently aligned along their R-peaks. Next, the waveforms, which displayed a high degree of similarity, were added to obtain their sum. This sum was divided by the number of complexes used to obtain an averaged fetal magnetocardiogram (usually > 100 complexes). The duration of the various time intervals was determined from this averaged signal. The time intervals are determined by the onset and termination of the various waves, as shown in Fig. 2. On the basis of the experience gathered to date, the centres involved have agreed on the criteria for the definition of the onset and the termination of a component of the magnetocardiogram: the onset is the first and the termination is the last visible defection from the zero line in any channel.

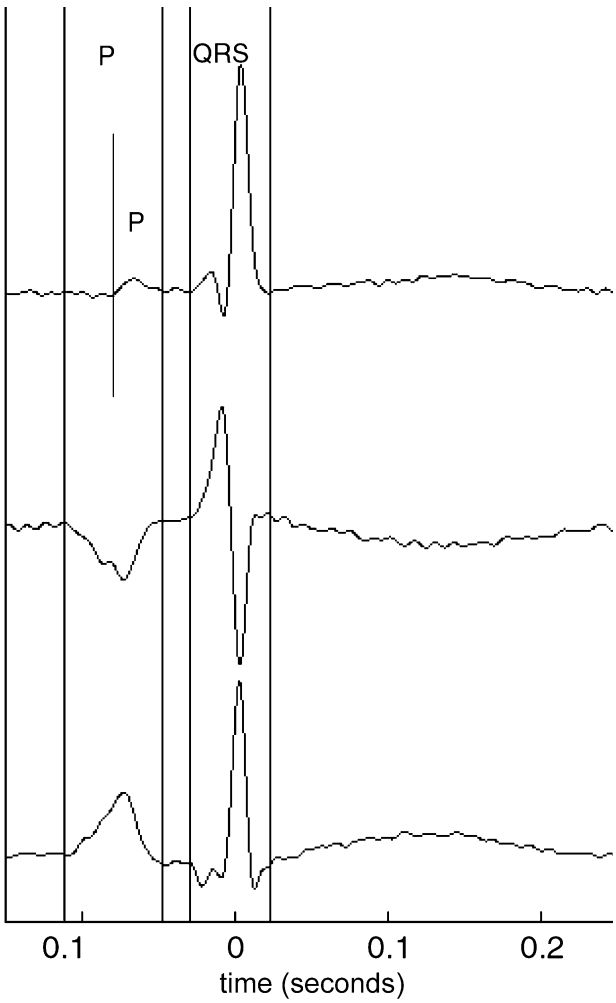


Fig. 3. Three fetal magnetocardiograms measured simultaneously based on three different components of the magnetic field, measured at the same position over the maternal abdomen.

As the duration of the QT interval is known to be dependent on the RR interval, the QTc value is also given. Empirically, it has been found that the QTc value is independent of the heart rate[1]. According to Bazett's formula, the QTc value is defined as the duration of the QT interval divided by the square root of the preceding RR interval. In our case, it is defined as the value of the QT interval divided by the square root of the mean value of the RR-interval.

Values are given as means and standard deviations (SD) or standard errors (SE). The dependency of the time intervals on gestational age was examined by simple linear regression. In order to estimate the effect of the cooperating centre, the dependency of the time intervals on gestational age and on centre was calculated using analysis of covariance (ANCOVA). P values <0.05 were considered statistically significant.

RESULTS

The P-wave and the QRS complex could easily be identified in averaged fetal magnetocardiograms, whereas the detection of the T-wave was difficult. The relatively clear onset and termination of the QRS complex allowed its reliable determination. On the other hand, the beginning of the P-wave was sometimes difficult to define, as it could be biphasic and its shape varied as a function of the measuring position, as demonstrated in Fig. 3. The onset and termination of the T-wave were difficult to identify and often only a drift in the signal was discernible. Accordingly, all intervals including the T-wave must be interpreted with caution. Some centres did not determine all such intervals.

Scatter plots of the duration of the time intervals *versus* the gestational week are shown in Fig. 4. A clear dependency on fetal age is apparent for the QRS complex and the P-wave, whereas the PR interval, the QT interval and the QTc value show a weaker relationship. The duration of the PQ interval and the T-wave appears to be independent of gestational age. This was confirmed by simple linear regression analysis (Table 1). Figure 4 includes the regression lines as well as the bounds marking the 90%, 95% and 98% prediction interval. The prediction interval, sometimes referred to as the reference interval, is the range in which a new observation is expected. Hence, this interval can be used to define what is normal and what is not.

Investigating the effect of centre using ANCOVA, we found that there were also systematic differences between centres for some intervals (Table 2). The values for the

individual centres, corrected to the 32nd week of gestation in Table 3, indicate higher values for the P-wave in Bochum, for the PR interval in Bochum and Jena and for the PQ interval in Jena; and lower values for the QRS complex in Jena, for the QT interval in Erlangen and Jena and for QTc for Erlangen and Tsukuba.

Despite the statistically significant slopes of most of the intervals, the majority of the variability is not explained by the fetal age and centre as shown by the r^2 statistics (Table 2). For instance, for the QRS complex, only 47% of the variance can be accounted for, and for the P wave only 45%. For the PQ interval and the T-wave, the values are low, indicating insignificant dependency on gestational age and higher variance, most likely due to measurement errors.

For comparison, data obtained from the literature are shown in Figs. 5a–5d. In Fig. 5a, the duration of the QRS complex found by us is compared with data obtained from fetal electrocardiography measured at the maternal abdomen by Brambati and Pardi[2] ($N = 421$) and Abboud *et al.*[3] ($N = 21$); with data obtained from electrocardiography in immature newborns by Van Wezel-Meijler *et al.*[4] ($N = 28$); and with data obtained from fetal magnetocardiography reported by Quinn *et al.*[5] ($N = 68$) and Leuthold *et al.*[6] ($N = 145$). All the measurements show reasonable agreement; only the regression line describing the duration of the QRS interval measured by Leuthold *et al.*[6] is appreciably different from ours. In Fig. 5b, the duration of the PR interval found by us is compared with that in the literature. The data obtained by Quinn *et al.*[5] and by Leuthold *et al.*[6] are appreciably different from ours. In Figs. 5c and 5d, the QT interval and the value of QTc are compared with data obtained from fetal electrocardiography measured in 21 fetuses by Abboud *et al.*[3]. These data agree within one standard deviation with our findings. However, the duration of the QT interval measured by Quinn *et al.*[5] by fetal magnetocardiography is considerably lower.

In Table 4, the values of the various intervals for fetuses between 38 and 41 weeks of gestation in our

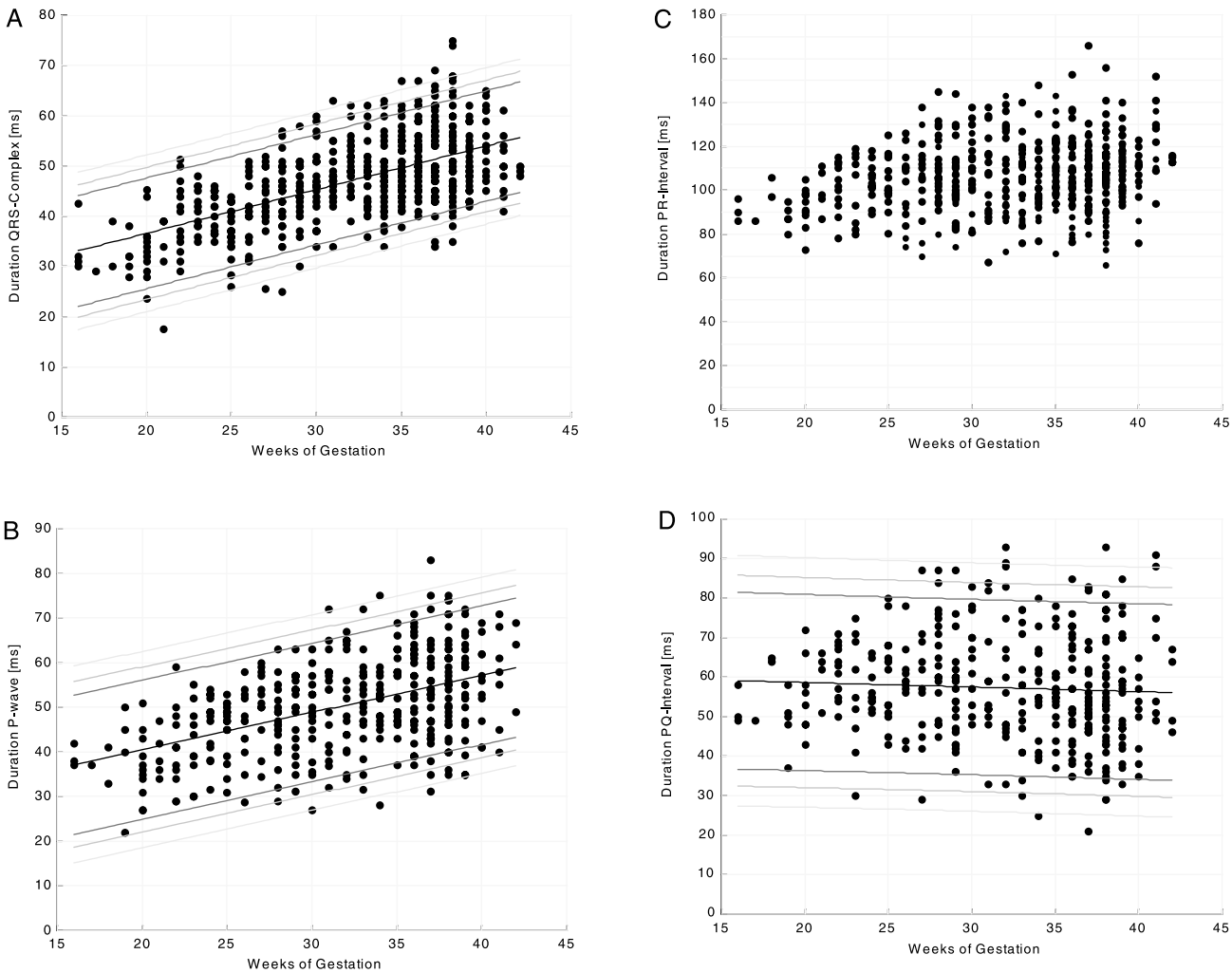
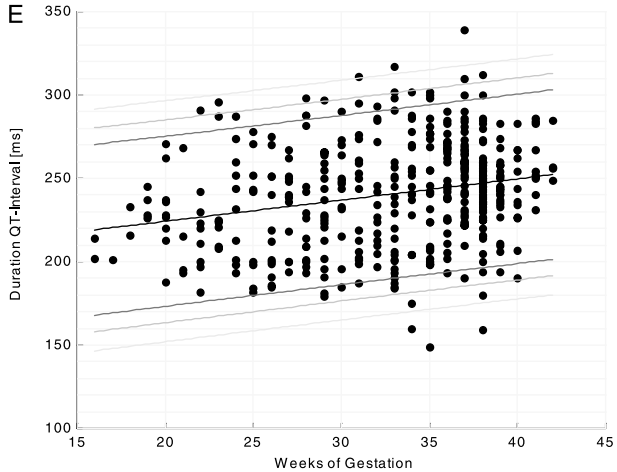
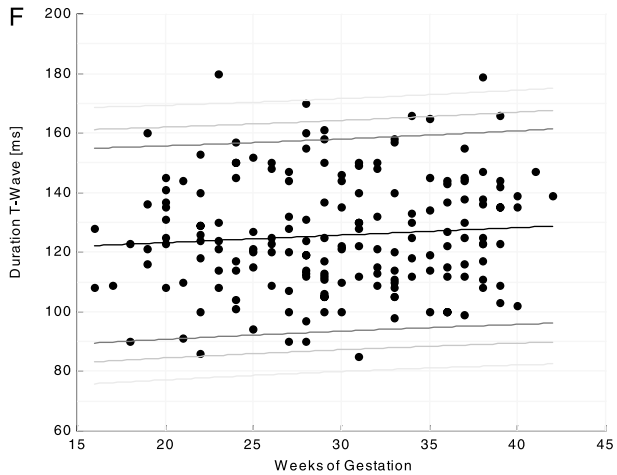


Fig. 4. The duration of the various fetal cardiac time intervals as a function of the week of gestation. The black line is the least squares fit; the three grey lines indicate a prediction interval of 90%, 95% and 98%.





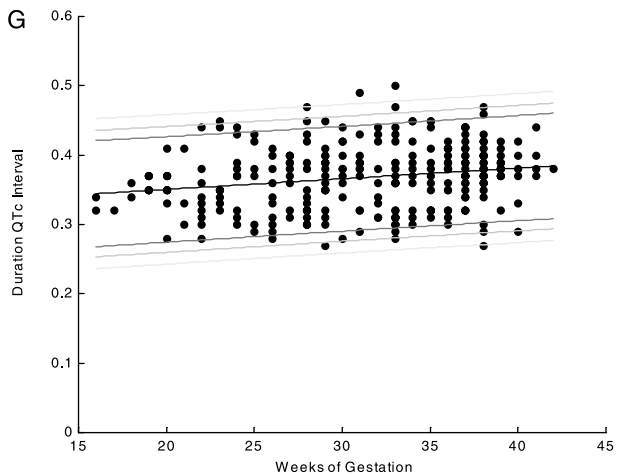


Fig. 4. (*continued*)

study are compared with the values obtained by electrocardiography in pregnancy at term and in the newborn period[7–9]. The time intervals agree within one standard deviation.

DISCUSSION

The time intervals of the magnetocardiogram. There are three possible explanations: (a) the physiologic considerations; (b) acquisition of the data; and (c) measurement by the observer.

The duration of the P-wave, like the duration of the QRS complex, increases from the 20th week of gestation to term by a factor of about 1.4. The increase can be explained by the increase in myocardial mass and cardiac dimensions with gestational age. This increase is very variable. Left ventricular mass increases linearly by about a factor 9, from 0.86 g (SD 0.09) at 20 weeks to 7.47 g (SD 2.43) at term[10]. The minimum thickness of the left ventricle in diastole increases linearly by about a factor 1.7, from 2 mm at week 20 to 3.5 mm at term[10]. Brambati and Pardi[2] found a linear relationship between the duration of the QRS complex and the weight at birth. The average birthweight may differ between the cooperating centres, as it depends on the sex of the infant, the ethnic group of the mother, smoking, high altitude and many other factors[11]. A positive relationship between birthweight and the durations of the P-wave and the QRS complex was also found in a study of immature newborns[12].

The conduction time in the ventricles is reflected by the duration of the QRS complex. Our findings show that the rate of increase of the conduction time is less than the rate of increase of the cube root of the heart weight. This was also found by Brambati and Pardi[2] and Van Wezel-Meijler *et al.*[4]. The latter found in immature infants that hearts weighing 6–10 g have conduction times half of that of the adult heart, which weighs 50 times as much. In all mammals, the weight of the heart is about 0.6% of the body weight. At 20 weeks of gestation, the mean total body weight of a fetus is 300 g, and the heart weighs about 1.8 g; at 40 weeks, the mean total body weight is 3500 g, and the heart weighs about 21 g. The weight of the heart increases by a factor of about $12 \approx (2.3)^3$. The thickness of the ventricular wall therefore presumably increases by a factor 2.3. However, the duration of the QRS complex (i.e. the

Table 1. Simple linear regression model for each cardiac time interval with gestational age as independent variable (beta values (SE)), including the square of the correlation coefficient *r*, level of significance and minimum and maximum interval values (ms).

	n	Constant	Age	r^2	*P*	Min	Max
P	400	23.9 (2.5)	0.83 (0.08)	0.23	<0.001	22	83
PR	534	87.6 (3.8)	0.57 (0.12)	0.04	<0.001	66	166
PQ	351	60.9 (3.7)	−0.12 (0.12)	0.00	NS	21	93
QRS	579	19.2 (1.5)	0.87 (0.05)	0.37	<0.001	18	75
T	179	118 (7)	0.25 (0.23)	0.01	NS	85	180
QT	412	199 (9)	1.27 (0.26)	0.06	<0.001	149	339
QTc	274	0.326 (.015)	0.002 (.000)	0.04	<0.001	0.270	0.502

NS = not significant.

Table 2. Results of the ANCOVA for each interval, showing the constant term, the coefficients for fetal age and centre and their levels of significance (P) and the square of the correlation coefficient r.

	Constant	Age	Bochum	Erlangen	Jena	Tsukuba	Twente	r^2
P	10.0	1.08 (0.001)	12.0 (0.001)	−2.3 (NS)	3.8 (NS)	–	*	0.45
PR	73.1	0.79 (0.001)	12.7 (0.001)	5.4 (NS)	9.6 (0.01)	−0.4 (NS)	*	0.15
PQ	61.1	−0.25 (0.05)	2.1 (NS)	–	6.8 (0.05)	–	*	0.03
QRS	18.5	0.97 (0.001)	−0.3 (NS)	−3.1 (NS)	−6.5 (0.001)	−0.5 (NS)	*	0.47
T	123.9	0.21 (NS)	−4.8 (NS)	–	–	–	*	0.01
QT	201.7	1.67 (0.001)	−10.5 (NS)	−28.0 (0.05)	−22.8 (0.05)	−16.3 (NS)	*	0.09
QTc	0.343	0.002 (0.001)	−0.022 (NS)	−0.052 (0.01)	–	−0.029 (0.05)	*	0.07

* = redundant; NS = not significant; – = no data on this interval for this centre.

conduction time through the ventricles) increases by a factor of only 1.4.

Wilson and Hermann[13] found for an adult heart that the duration of the QRS-complex (in ms) is $12.5 \times \sqrt[3]{\text{ventricular weight (g)}}$. Left and right ventricular wall weights are the same (i.e. 30% of the total heart weight), the left ventricular mass consists of the septum plus the left ventricular mass. The left ventricular mass increases linearly by about a factor 9 from 0.86 g at 20 weeks to 7.47 g at term[10]. So the ventricular mass is less than 2×0.86 g at week 20 and less than 2×7.47 g in week 40. If the relationship given by Wilson and Hermann would be true for the fetus, one would expect duration of the QRS-complex at 20 weeks that is smaller than $12.5 \times \sqrt[3]{2 \times 0.86} = 14$ ms and at 40 weeks a duration that is smaller than $12.5 \times \sqrt[3]{2 \times 7.47} = 30$ ms at week 40. According to our findings in Fig. 4, the duration of the QRS complex increases from week 20 to week 40 from 36 to 54 ms. We conclude that the dependence of electric conduction on the increase in weight of the ventricles and the duration of the QRS complex given by the relationship of Wilson and Hermann[13] does not hold for fetuses.

A difficult confounding problem is whether a pregnancy is uncomplicated or not. Leuthold *et al.*[6] included mothers with diabetes, gestational diabetes and low amniotic fluid volume where the birthweight was normal. However, the thickness of the cardiac walls increases more quickly in fetuses of diabetic mothers than in normal fetuses irrespective of fetal size; the duration of the QRS complex may increase at a faster rate with gestational age than normally[14].

The PR interval and the QT interval also increase proportionally with gestational age, as is the case during normal development after birth. The PR interval of children normally increases with age and decreases with increasing heart rate. The mean PR interval changes from 100 ms at week 20 to 110 ms at week 40. Janse *et al.*[15] measured the duration of the PR interval in three isolated hearts of fetuses in the 12th–16th weeks of gestation. Their values of 85–100 ms agree with ours. About 20–30 ms is due to the propagation of electric activity in the atria and a maximum of 10 ms is due to the conduction in the His–Purkinje system. The relative contribution of the AV node to the total AV conduction increases with diminishing heart size. A common cause for a short PR interval in a normal heart is a low right atrial pacemaker. The PR interval fluctuates as a result of variations in the conduction time of the AV node[16]. These fluctuations give rise to 'trigger jitter', which in turn affects the morphology of the averaged fetal magnetocardiogram in the same way as a low-pass filter[17,18]. Under normal physiologic conditions, it is found that the RR and the PR intervals are positive related[19].

The fetal heart rate is characterised by a normal baseline frequency of 110–150 beats per minute. A baseline variability of more than 10 beats per minute and the presence of accelerations in relation to fetal movements are regarded as signs of fetal wellbeing[20].

Table 3. Mean (SE) fetal age (in weeks) and duration of cardiac time intervals (ms) for each centre. Values for the time intervals are corrected to a gestational age of 32 weeks.

	Bochum		**Erlangen**		**Jena**		**Tsukuba**		**Twente**	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Fetal age	171	29.2 (0.4)	69	30.7 (0.7)	162	34.3 (0.4)	162	33.4 (0.4)	18	34.0 (1.3)
P	171	56 (2)	49	42 (2)	162	48 (2)	–	–	18	44 (3)
PR	171	111 (4)	51	104 (4)	162	108 (4)	132	98 (4)	18	98 (5)
PQ	171	55 (3)	–	–	162	60 (3)	–	–	18	53 (5)
QRS	171	49 (2)	69	46 (2)	162	43 (2)	159	49 (2)	18	49 (2)
T	167	126 (6)	–	–	–	–	–	–	12	131 (10)
QT	167	245 (9)	15	227 (12)	131	232 (9)	87	239 (9)	12	255 (13)
QTc	167	0.38 (0.01)	12	0.35 (0.02)	–	–	84	0.37 (0.01)	11	0.40 (0.02)

– = no data on this interval for this centre.

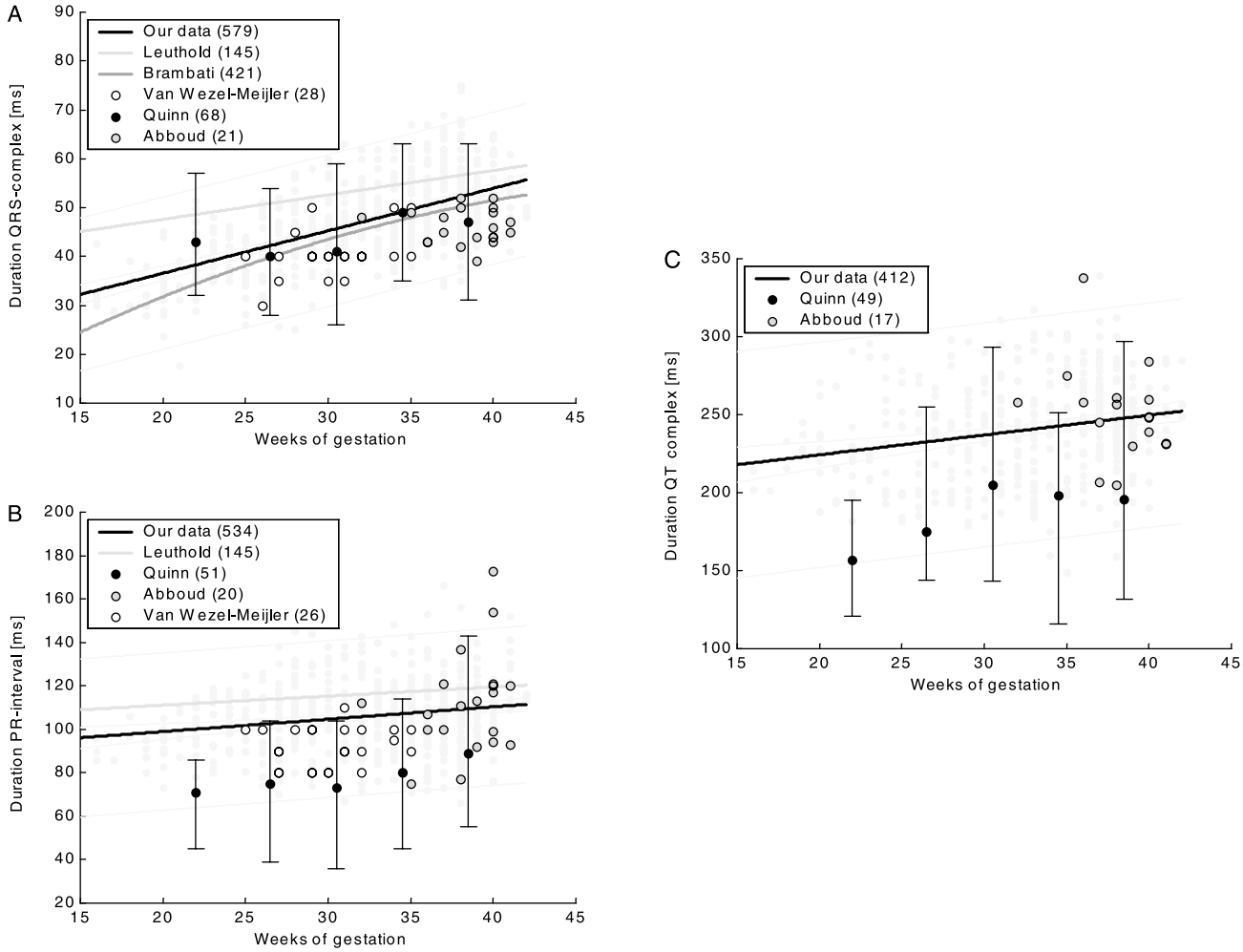


Fig. 5. Comparison of the duration of the various fetal cardiac time intervals. The regression line that is fitted to our data is given by the black line, the 98% prediction interval and the 98% confidence interval for our data are given by thin grey lines. The second order polynomial is a best fit to the fetal electrocardiographic data of Brambati and Pardi[2]. The grey circles are individual data obtained from fetal electrocardiograms by Abboud *et al.*[3]. The open circles are individual measurements obtained from electrocardiograms of premature infants by Van Wezel-Meijler *et al.*[4]. The black points are mean values obtained from fetal magnetocardiograms by Quinn *et al.*[5]. The endings of the bars through these points indicate maximum and minimum values.

Factors that may influence the fetal heart rate are fetal age, the behavioural state and the fact that the mother is in the supine position. During quiet sleep, the fetal heart rate hardly changes (bandwidth 7 beats per minute); the bandwidth increases during breathing movements. The measurements in this paper were extracted during epochs when the fetal heart rate was at its basal level. Movements of the fetus may lead to a different magnetocardiogram as the distance to the fetal heart may change. In the early weeks of gestation, the fetus is able to move freely within the uterus.

Besides physiologic considerations, the variation in the results can be ascribed to the various methods of measurement. The magnetometer systems used in this study differ in the type of sensor, the number of channels and the signal-to-noise ratio. In deriving a fetal magnetocardiogram, a gradiometer is used in which the magnetic flux measured at some distance from the maternal abdomen is subtracted from the magnetic flux measured near the abdomen. This improves the signal-to-noise ratio as the fetal signal is largest near the abdomen and is diminished at a distance from the abdomen, while the noise is very much the same at both distances. Burghoff *et al.*[21] compared a magnetocardiographic measurement recorded with different gradiometers and found an influence of the gradiometer on the duration of the QRS complex of an adult heart patient. This effect can be explained by the fact that at a certain position the magnetic flux may be zero or practically zero (i.e. having a signal-to-noise ratio much smaller than one). Consequently, the P-wave or QRS complex may start or end at a different time instant at different measurement positions and thus the duration of a certain time interval may vary. This effect is illustrated in Fig. 3, demonstrating the necessity to measure at different positions or orientations above the maternal abdomen. Moreover, a large number of channels simplify the measurement because it is easier to detect an appropriate measuring

Table 4. Comparison of mean values of fetal cardiac time intervals (ms).

	MCG fetus[a]		ECG mature newborn		ECG during labour	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
P	84	56 (10)	un	46 (7)[b]	37	52 (9.5)[c]
					37	52 (6.3)[d]
PR	110	109 (16)	34,442	113 (23)[e]		
PQ	73	57 (16)				
QRS	113	52 (8)	34,442	57 (7)[e]		
T	21	131 (20)				
QT	100	243 (27)	34,442	274 (28)[e]		
QTc	46	0.370 (0.042)	34,442	0.400 (0.020)[e]		

un = unknown; MCG = magnetocardiogram; ECG = electrocardiogram.

[a] MCG of fetuses in the 38th to 41st week of gestation reported in this study.

[b] ECG of mature newborn infants one to seven days after delivery adapted from Hastreiter and Abella[8].

[c] ECG adapted from Marvell *et al.*[9] recorded during the first 20 minutes of labour.

[d] ECG adapted from Marvell *et al.*[9] recorded during delivery.

[e] ECG of mature newborn infants, recorded on the third or fourth day of life adapted from Schwartz *et al.*[7].

position. The dependence of the time intervals on the number of channels used has been studied by van Leeuwen *et al.*[22], who concluded that the minimum number of measurement positions necessary for the reliable determination of time intervals is seven. All the measurements reported here are based on many more measurement positions or orientations than seven.

Several sources of variation may be found in the steps leading to the determination of the cardiac time intervals. These include the subtraction of the maternal artefact, the number, morphology and RR duration of fetal beats included in the average, and inconsistency in the definition of the intervals. If the magnetocardiogram of the mother is not removed before averaging, then channels with a strong maternal signal produce spurious effects in those channels in the averaged fetal signal. Thus, subtraction of the maternal artefact should generally be performed in multi-channel systems, and in single- and few-channel systems when the recording is corrupted by the maternal signal. By increasing the number of fetal beats averaged, the signal-to-noise ratio is improved. On the other hand, restricting the number of beats by selectively averaging on the basis of similarity in the signal shape and duration will improve the precision of the waveforms. Differences in these procedures in the centres contributing to this study may well have led to some of the variation in the durations of the cardiac intervals. Finally, variation in the definitions of the onset and termination of the various intervals may have occurred between the centres. Efforts have recently been made among the collaborating groups to apply a uniform definition with respect to the onset and termination of cardiac electric events. Comparing the results obtained by different observers adhering to the definitions given in the methods section, van Leeuwen *et al.*[22] reported a median difference of only 1 ms in the identification of the onset or termination of a cardiac event.

Although the data given in this paper are not precise, the results can nevertheless be used to establish normal ranges. In normal fetuses, the duration of the QRS complex at 29 weeks is 45 (SD 6) ms. Thus, a QRS duration of 68 ms at a gestational age of 29 weeks can be expected in less than 1% of fetuses. This value was reported by Pardi *et al.*[23] for a fetus severely affected by rhesus disease. In another study, a pronounced tendency towards prolonged QRS durations in pregnancies complicated by rhesus haemolytic disease was found[24]. In a case of right heart hypoplasia, the prolonged QRS complex suggested bundle branch block due to the morphologic anomaly[25]. Hamada *et al.*[26] and Menéndez *et al.*[27] diagnosed the long QT syndrome by fetal magnetocardiogram. The QTc values were 0.51–0.57, which, compared with the data in Fig. 4, are clearly prolonged. Measurements carried out by van Leeuwen *et al.*[28] in fetuses ($N = 9$) with intrauterine growth restriction showed values for the PQ interval that are decreased compared with our reference values. Fetal magnetocardiograms of four fetuses with severe congenital heart disease were abnormal when compared with reference values reported in a recent study[29]. These preliminary results show that the database may assist in the detection of heart anomalies early in pregnancy and in the monitoring of the disorder.

The data in the present paper is accessible on Internet so that every user can submit and extract data: http://bct.tn.utwente.nl/database.

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