Evolution of the Fetal Atrioventricular Interval from 6 to 40 Weeks of Gestation

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Doppler-based methods of estimating the atrioventricular interval are commonly used as a surrogate for the electrical PR in fetuses at risk of conduction abnormalities; however, to date, normal values for the fetal atrioventricular interval and an understanding of the evolution of its components in the late first trimester are lacking. We sought to investigate changes in the fetal atrioventricular interval from the first trimester to 40 weeks gestational age, and to explore functional and electrophysiological events that potentially impact its evolution. We prospectively examined healthy pregnancies by fetal echocardiography from 6 to 40 weeks' gestational age. The atrioventricular interval, heart rate, isovolumic contraction time, and A-wave duration were measured from simultaneous ventricular inflow-outflow Doppler tracings. Regression analysis was used to examine relations with gestational age, and linear relations with heart rate were assessed by Pearson's correlation coefficient. Data were collected in 305 fetuses from 279 pregnancies. Atrioventricular interval demonstrated an inverse relation with heart rate (r = −0.45, p <0.0001), dramatically decreasing before 10 weeks and slowly increasing thereafter. Between 6 and 9 weeks, isovolumic contraction time acutely decreased approaching 0, thereafter minimally increasing to term. In contrast, from 6 weeks, the A-wave duration linearly increased through gestation, and negatively correlated with heart rate (r = −0.62, p <0.0001). In conclusion, we have established normal measures of the atrioventricular interval from 6 to 40 weeks' gestational age. Before 10 weeks, a prolonged atrioventricular interval in healthy fetuses largely reflects the lengthened isovolumic contraction time which is likely influenced by the evolution of ventricular function and afterload. **(Am J Cardiol 2019;123:1709−1714)**

Electrocardiography and magnetocardiography are not routinely available for the assessment of fetal rhythm. Consequently, Doppler signals are largely relied on to measure the atrioventricular (AV) interval as a proxy for electrophysiological AV conduction. The AV interval measured by tissue Doppler correlates best with the PR interval; however, this technology is not readily available or feasible at earlier gestations; therefore, pulsed Doppler has mainly been used.[1] Several studies have reported the evolution of the AV interval based on Doppler flow signals from the mid trimester, but none have assessed this from the first trimester.[1−4] We sought to establish normative AV interval values from 6 weeks to term. We also aimed to determine the relation between AV interval and heart rate and how its components change with gestation and contribute to AV interval evolution. Our goal was to explore how these changes contribute to our understanding of the evolution of electrical conduction, cardiac function, and loading conditions throughout pregnancy, and particularly in late embryonic and early fetal development.

Methods

This investigation was a prospective, cross-sectional study. We recruited healthy pregnancies from 6 to 40 weeks of gestation to undergo fetal echocardiography between January 2009 and December 2015. Pregnancies were considered healthy if there was no maternal, placental, or fetal

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disease, and there was confirmation of a healthy neonatal outcome. Singleton and multiple gestation pregnancies were included. All participants provided informed consent. The University of Alberta Research Ethics Board approved this study.

Fetal echocardiography was performed using the Siemens S2000 (Mountainview, CA) or the General Electric Voluson E8 (Boston, MA). For transabdominal imaging, 4 to 9 MHz curved or linear array transducers were used, and for transvaginal imaging a 9 to 12 MHz endocavity probe was used. All echocardiograms at ≤12 weeks were attempted transabdominally with additional transvaginal ultrasound imaging only when transabdominal imaging was inadequate.

Gestational age was based on the first day of the last menstrual period for most. Gestational age was based on fetal size if at ≤15 weeks, the crown rump length (measured in all pregnancies <12 weeks), biparietal diameter and femur length (pregnancies of ≥12 weeks suggested the pregnancy was > or <1 week, or for pregnancies >15 weeks, if the biparietal diameter and femur length suggested the pregnancy to be < or >2 weeks).[5] All pregnancies had a normal fetal echocardiogram ≥17 weeks.

Pulsed Doppler interrogation of simultaneous left ventricular inflow and outflow was acquired for all pregnancies. At <9 weeks of gestation, it was not always possible to determine whether the signal was from the left ventricle but signals acquired were comparable to ventricular inflow-outflow signals observed in 10 to 14-week gestation fetuses. The AV interval and A-wave duration were measured from the onset of the A wave, including when E and A waves were partially merged (Figure 1). Doppler tracings were analyzed both on- and offline to measure (in milliseconds) the following: cardiac cycle duration, AV interval, isovolumic contraction time, and A-wave duration (Figure 1). All measurements were made from 3 cardiac cycles, consecutive where possible, and averaged. All measurements were generated by 1 author (DG) and assessment of inter- and intraobserver variability was performed by a second (LKH). Medical records were used to verify normal pregnancy outcome. Only pregnancies with high-quality left ventricular inflow-outflow pulsed wave Doppler tracings were included.

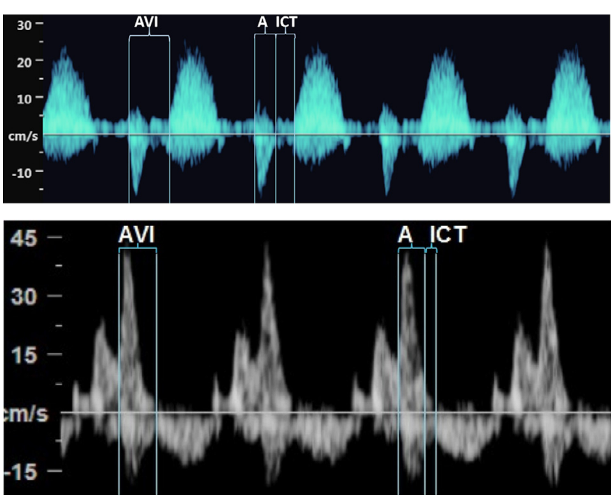

Figure 1. Assessment of the fetal AV interval (AVI) and its components (ICT-isovolumic contraction time and A wave during atrial systole) from simultaneous left ventricular inflow-outflow tracings at 8 (*A*) and 14 (*B*) weeks of gestation. Note the uniphasic Doppler ventricular inflow pattern typically seen before 10 weeks of gestation. At 14 weeks, Doppler inflow patterns are consistently biphasic in the normal fetus.

Regression analysis was used to investigate the evolution of the AV interval and its components across gestational ages. We fitted regression lines between dependent and independent variables by applying fractional polynomials or simple linear regression techniques. Fractional polynomial regression was used when a curved relation between dependent and independent variables was suggested by exploratory analysis of the data. We assessed the appropriateness of the final fitted models by examining residual plots and reported the significance of the final model (p value and adjusted R-squared), the regression coefficients and related statistics (eg, 95% confidence intervals) and the corresponding scatter-plots including the fitted lines and corresponding 95% confidence interval area. We estimated the association between heart rate and AV interval, A-wave duration, or isovolumic contraction time using Pearson's correlation coefficients (r). We also reanalyzed the data excluding repeated measures in the same fetus to determine whether repeated measures had a significant impact. Interobserver variability was assessed on a random sample of ~10% of the study group (overall 30 echocardiograms, 10 from each of the following gestational age groups: 6 to 10^{+6}, 11 to 16^{+6}, and 17 to 40) using % difference: (absolute difference between measurement by Observer 1 and measurement by Observer 2)/([measurement by Observer 1 + measurement by Observer 2]/2). We performed statistical analysis by using Stata v13.

Results

Two hundred seventy-four women with 279 pregnancies were enrolled and underwent fetal echocardiography between 6^{+1} weeks and 39^{+2} weeks of gestation. Of the 279 pregnancies, 248 were singleton, 28 were twin and 3 were triplet gestations. Three hundred thirteen fetuses had attempts at assessment of AV interval of which in 305 measurements could be made. Inadequate tracings were found at all age groups. Four hundred thirty-three AV interval measurements were performed in total.

From 6^{+1} weeks, the fetal heart rate increased to a peak at 10 weeks then slowly decreased to term (p <0.001; Figure 2). Ventricular inflow patterns were biphasic in none before 9^{+0} weeks, in 20% at 9^{+0} to 9^{+6} weeks, in 85% from 10^{+0} to 10^{+6} weeks, and in all thereafter. The fetal AV interval dramatically decreased from 6 to 10 weeks and gradually increased thereafter to term (p <0.001; Figure 3). AV interval demonstrated a negative linear correlation with heart rate (r = −0.45, p <0.0001; Figure 4). Normal ranges for the AV interval and AV interval-RR interval by gestational age group are shown in Table 1. Regression coefficients for regression models using gestational age as an explanatory variable are shown in Table 2. Testing for interobserver variability indicated a 4% difference for AV interval measurements (without major differences between gestational age groups).

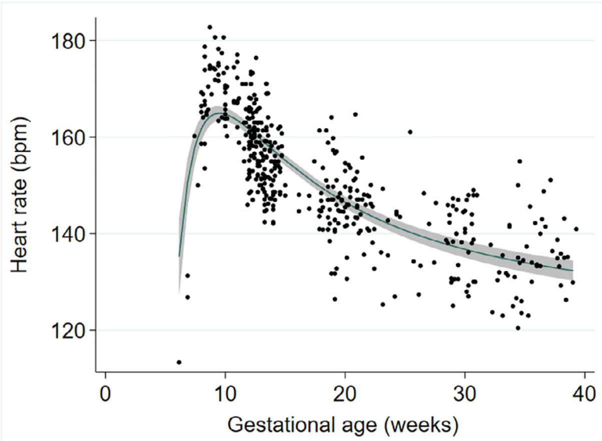

Figure 2. Heart rate as a function of gestational age (p <0.001; adjusted R-squared = 0.62). Fitted line and its 95% confidence intervals (shaded area) are shown. Regression coefficients are reported in Table 2.

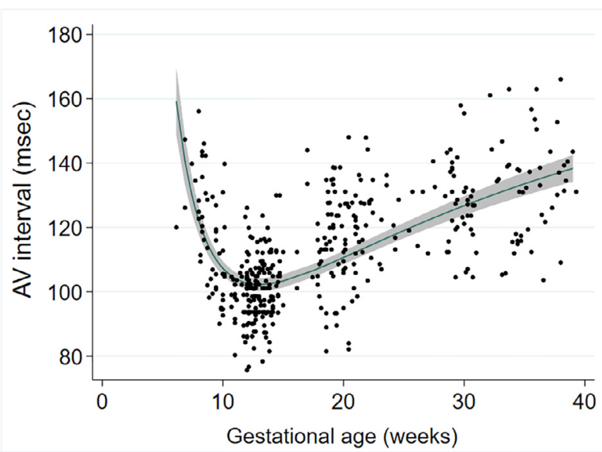

Figure 3. Atrioventricular (AV) interval as a function of gestational age (p <0.001; adjusted R-squared = 0.43). Fitted line and its 95% confidence intervals (shaded area) are shown. Regression coefficients are reported in Table 2.

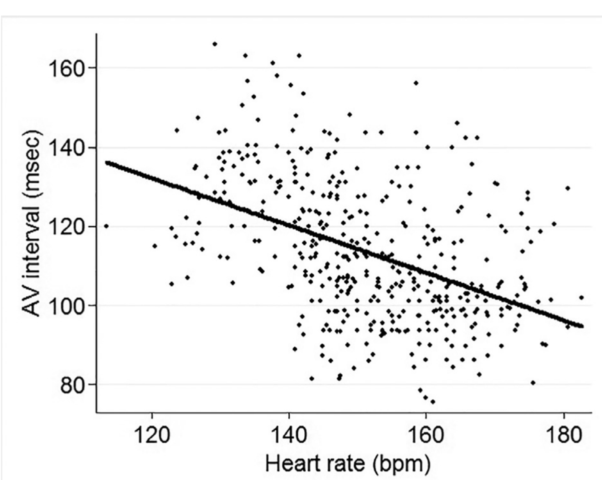

Figure 4. Atrioventricular (AV) interval as it relates to heart rate. There is a negative linear correlation (r = −0.45, p <0.001).

The individual components of the AV interval changed significantly with gestation. The A-wave duration (p <0.001; Figure 5) and the A wave/R-R interval (p ≤0.001, not shown) increased linearly with gestation, and the A-wave duration negatively correlated with heart rate (r = −0.62, p <0.0001; Figure 5). In contrast, isovolumic contraction time was highest at 6 weeks, acutely decreased through to 10 weeks, then remained fairly stable approaching 0 for the rest of gestation (p <0.001; Figure 6). Isovolumic contraction time weakly inversely correlated with heart rate (r = −0.18, p = 0.02, not shown).

When the results were analyzed excluding cases with repeat measures in the same fetus at different gestations, there was no impact on the results, except that isovolumic contraction time no longer inversely correlated with heart rate (p = 0.08).

Discussion

The conduction system begins to develop shortly after the heart undergoes morphogenesis in the third week of gestation.[6−10] The AV node is identifiable histologically from 5 weeks.[10,11] Using Doppler, the human heart beat can be demonstrated from 5 weeks and AV synchrony has been demonstrated from 6 weeks onward.[12]

The first report of normal values for fetal AV interval was in a small cohort from 17 weeks to term and this suggested that the AV interval did not change with gestational age or heart rate.[13] Shortly thereafter, however, another group demonstrated in a larger cohort that the AV interval increases with gestational age from the mid trimester and inversely correlates with heart rate, findings subsequently confirmed by other investigators.[2,3,14] We have confirmed that pulsed Doppler can demonstrate AV synchrony in essentially all fetuses from 6 weeks. We found an acute decrease in AV interval from 6 to 10 weeks then a gradual increase thereafter. The AV interval inversely mirrors heart rate which progressively increases to 10 weeks and then gradually decreases.[15] Our findings in the mid and third trimester are comparable to those reported by others and suggest that the inverse correlation between AV interval and heart rate exists even from 6 weeks of gestation.[2,3]

The pulsed Doppler-based AV interval excludes atrial electromechanical delay, but includes ventricular electromechanical delay and isovolumic contraction time and is longer than the PR interval.[16] Isovolumic contraction is so brief beyond 11 weeks that it has minimal impact on the AV interval, rendering it a satisfactory proxy for PR interval (in the setting of normal heart function) from then onwards. Although the dramatic reduction in the AV interval from 6 to 10 weeks' gestation could be in part due to faster AV conduction, our findings suggest that the AV interval may be less reflective of the PR interval in early gestations due to prolonged isovolumic contraction. As isovolumic contraction occurs following ventricular depolarization, its inclusion in the assessment of AV conduction may be inappropriate especially at earlier gestations.

Prolonged isovolumic contraction occurs when there is increased afterload or reduced systolic function.[17,18] The embryonic circulation has high placental resistance initially, which falls late in the first trimester with trophoblast

Table 1
Normal ranges for AVI and AVI-RR interval by gestational age group

		AVI (milliseconds)				AVI-RR interval (milliseconds)			
GA range (weeks)	n	Median	IQ range	Mean	SD	Median	IQ range	Mean	SD
6 to 8	26	127	22	128	15	353	59	345	44
9 to 10	32	105	15	107	12	299	30	305	36
11 to 15	172	101	12	101	10	265	37	265	23
16 to 20	74	115	21	115	15	280	49	282	39
21 to 25	37	122	13	122	11	298	42	292	30
26 to 30	44	127	15	127	13	292	39	294	30
31 to 35	28	132	23	130	17	295	86	291	47
36 to 40	20	136	14	136	16	306	40	310	32
Total	433	112	26	113	17	280	50	284	39

AVI = atrioventricular interval, GA = gestational age, IQ = interquartile, SD = standard deviation.

Table 2
Regression coefficients for regression models using gestational age as explanatory variable

Variable	Type-curve	Parameter	Power (p)	Coefficient	p Value	95% confidence intervals
Heart rate	Polynomial*	*bo*	–	122.76	0.000	[119.82, 125.69]
		b1	−2	−13,404.71	0.000	[−15,246.03, −11,563.39]
		b2	−2	7,644.54	0.000	[6,721, 8,567.16]
AV interval	Polynomial*	*bo*	–	0.22	0.000	[0.21, 0.24]
		b1	−1	2.45	0.000	[2.07, 2.83]
		b2	−1	−1.56	0.000	[−1.79, −1.34]
A-wave duration	Linear	*bo*	–	0.066	0.000	[0.062, 0.070]
		b1	–	0.0012	0.000	[0.0010, 0.0014]
Isovolumic contraction time	Polynomial*	*bo*	–	0.06	0.000	[0.04, 0.08]
		b1	−1	1.46	0.000	[0.99, 1.94]
		b2	−1	−0.78	0.000	[−1.07, −0.49]

See Stata reference manual for interpretation: StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC.
* The fractional polynomial model has the form: $y^{(p1,\ p2,..pm)'}\beta = \beta_0 + \beta_1 x^{(p1)} + \beta_2 x^{(p2)} + \ldots + \beta_m x^{(pm)}$.

invasion.[19] Simultaneous with the dramatic fall in isovolumic contraction time, changes in the myocardium, which likely influence function, occur. For example, animal studies suggest rapid growth of embryonic tissue causing relative myocardial hypoxia and stimulating ingrowth of coronary vasculature.[20,21] Concomitantly, the myocardium compacts likely influencing diastolic function, and the 3 layers of the left ventricular myocardium evolve and mature, which may improve twist.[22,23] If these changes augment ventricular contractility, this would shorten isovolumic contraction. Changes in the early fetal heart rate may be influenced by the evolution of fetal heart function as

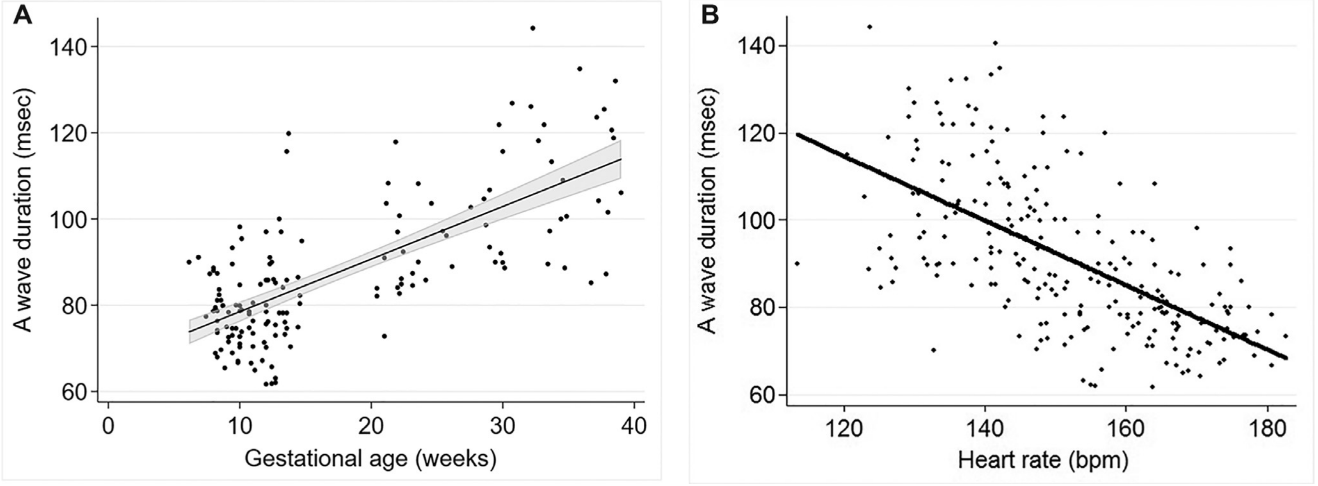

Figure 5. A-wave duration as a function of gestational age (*A*) and heart rate (*B*). A-wave duration increases linearly and progressively throughout gestation ($p < 0.001$; adjusted R-squared = 0.51). Fitted line and its 95% confidence intervals (shaded area) are shown. Regression coefficients are reported in Table 2. A-wave duration inversely correlated with heart rate ($r = -0.62$, $p < 0.0001$).

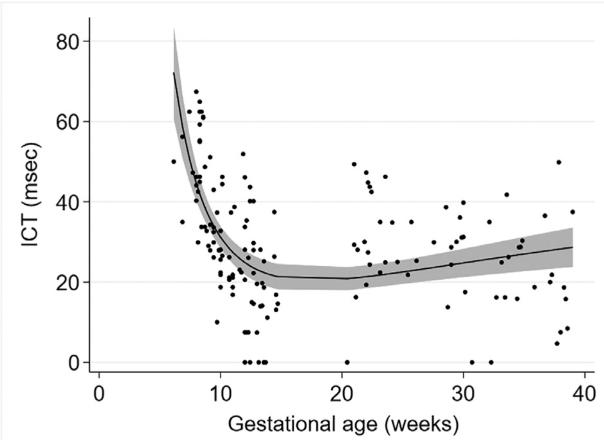

Figure 6. Isovolumic contraction time (ICT) as a function of gestational age ($p < 0.001$; adjusted R-squared = 0.29). Regression coefficients are reported in Table 2.

growth of the fetus may demand a greater cardiac output than can be achieved by increasing stroke volume alone.

Previous investigations also suggest that the AV interval is influenced by forces beyond AV conduction. In mothers with anti-Ro/La autoantibodies, the transiently increased fetal AV interval observed in many is secondary, at least in part, to increased isovolumic contraction time.[24] Clinicians using AV intervals to assess conduction should be aware that a prolonged isovolumic contraction may lead to false-positive diagnoses of AV conduction disease.

The right ventricular Aa-IV interval measured by tissue Doppler, which excludes isovolumic contraction time, more tightly correlates with, but is shorter than the PR interval.[1] For pulsed Doppler measurements, use of the A-wave duration could eliminate overestimation of the PR interval related to prolonged isovolumic contraction both in the early and late fetus. A-wave duration may be more akin to the TDI-based Aa-IV. However, the A wave represents flow and does not take into account electrophysiological-mechanical and mechanical-hemodynamic delays. Furthermore, A-wave duration could be influenced by ventricular diastolic properties, atrial function, AV valve function, and atrial and ventricular preload. Bergman et al compared A-wave duration and other pulsed Doppler techniques of assessing AV interval in the mid-trimester with the PR interval on the neonatal electrocardiogram.[24] Their findings suggested that the A-wave duration had a lower sensitivity and negative predictive value for first degree AV block, but higher specificity than the simultaneous mitral-aortic Doppler technique, suggesting it may be less likely to overcall conduction abnormalities, but may underestimate the PR interval in those with true PR prolongation. A weakness of the latter study was the time delay between AV interval measurement and electrocardiogram acquisition.

Although AV block does not typically evolve before 17 weeks in pregnancies with maternal autoantibodies, other conditions are associated with earlier alterations in AV conduction, such as corrected transposition, single ventricles with L-ventricular looping or heterotaxy syndrome.[25] AV block has been reported as early as 11 weeks in heterotaxy.[26] Our normative data for AV interval and A-wave duration from 6 to 40 weeks should facilitate detection of AV conduction abnormalities.

In conclusion, we have established normative values for the AV interval from 6 to 40 weeks' gestation. As the AV interval includes the period of isovolumic contraction, its interpretation as a marker of cardiac conduction disease should be used with caution in early gestation and in fetuses with altered loading and/or ventricular dysfunction. Utilization of A-wave duration alone may better reflect the PR interval and requires further evaluation. Evolution of the AV interval and isovolumic contraction time in the late embryonic and early fetal periods suggests dramatic changes in cardiac function and/or afterload occur during these developmental stages.

Disclosures

The authors have no conflicts of interest and no relevant financial relationships related to this article to disclose.

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