Original Article

Normal Reference Values of Fetal Atrioventricular (AV) and Ventriculoatrial (VA) Time Intervals and VA:AV Ratio Assessed by Pulse Wave Doppler

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Objective: To identify the normal reference ranges of the atrioventricular (AV) time interval, ventriculoatrial (VA) time interval, and VA:AV ratio in fetuses between 18 and 37 weeks of gestational age (GA) and to establish the relationship between AV and VA time intervals and VA:AV ratio with GA and fetal heart rate (FHR).

Materials and Methods: A prospective cross-sectional study was conducted at Rajavithi Hospital between December 2019 and June 2020. AV and VA time intervals and VA:AV ratio were obtained by pulse wave Doppler over inflow and outflow tract of left ventricle. The correlation of the measurement values with GA and FHR were analyzed by Spearman's rank correlation.

Results: Three hundred seventy pregnant women were enrolled in the present study with 343 participants included in the analysis. The average values of AV and VA time intervals and VA:AV ratio, along with their 5th, 10th, 50th, 90th, and 95th percentiles were calculated from the measurement values. A correlation between each measurement value and GA was demonstrated to be linear [AV time intervals = 91.74+1×GA(weeks) (R^2=0.516, p<0.001); VA time intervals = 2.58E2+1.39×GA(weeks) (R^2=0.151, p<0.001); and VA:AV ratio = 2.74–8.99E–3×GA(weeks) (R^2=0.063, p<0.001)]. A correlation between each measurement value and FHR was also linear [AV time intervals = 1.79E2–0.41×FHR (R^2=0.181, p<0.001); VA time intervals = 6.21E2–2.23×FHR (R^2=0.811, p<0.001); and VA:AV ratio = 3.9–9.64E-3×FHR (R^2=0.150, p<0.001)].

Conclusion: Both AV and VA time intervals are positively correlated with GA but VA:AV ratio is negatively correlated with GA. All measurement values have negative correlation with FHR. The normal reference values of AV, VA time intervals, and VA:AV ratio from the present study may be useful for diagnosis of fetal arrhythmia.

Keywords: normal reference value, atrioventricular time intervals, ventriculoatrial time intervals, VA:AV ratio

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Fetal cardiac arrhythmia occurs in about 2% of all pregnancies. There are three types of cardiac arrhythmia including irregular cardiac rhythm, bradyarrhythmia, and tachyarrhythmia. The most common fetal cardiac rhythm disturbance is premature atrial contraction (PAC), which is typically detected by irregular cardiac rhythm in the second and third trimesters. Most cases resolve spontaneously and do not require any antiarrhythmic drug. However, some conditions of cardiac arrhythmia cause heart failure, fetal hydrops, and fetal demise such as atrioventricular (AV) block, supraventricular tachycardia (SVT), ventricular tachycardia (VT), atrial fibrillation (AF), and atrial flutter[1]. The AV block is suspected in fetus whose heart rate is below 100 beats per minute. Approximately 40% of cases are associated with structural heart abnormalities, especially left atrial isomerism (LAI) and transposition of great arteries (TGA). The remaining often occur in cases with maternal connective tissue disease with anti-SS-A (Ro) or anti-SS-B (La) antibodies[2,3]. Therefore, detectable SS-A or SS-B antibodies are an indication that AV time intervals should be examined by fetal echocardiography in pregnant women between 18 and 26 weeks of gestational age (GA) to detect any early sign of AV block[4]. Nowadays, the normal range of AV time interval is 120±20 milliseconds in all GA[2]. Fetal tachyarrhythmia is when the fetal heart rate (FHR) is more than 180 beats per minute. Finding the cause of tachycardia is important because some conditions may require antiarrhythmic therapy. Short ventriculoatrial (VA) time intervals help distinguish

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re-entry SVT from sinus tachycardia, ectopic atrial tachycardia, and permanent junctional reciprocating tachycardia[5]. Accordingly, measurement of AV time intervals, VA time intervals, and VA:AV ratio can help in diagnosing the types of fetal arrhythmia.

There are four techniques of pulse wave Doppler ultrasound to evaluate fetal cardiac rhythm including the left ventricular inflow and outflow tract, the superior vena cava and the ascending aorta, the pulmonary vein and pulmonary artery, and the renal vein and renal artery[2]. The pulsed Doppler ultrasound over the left ventricular inflow and outflow tract is commonly used to evaluate the fetal cardiac rhythm abnormalities due to its easy approach. Mosimann et al determines the reference ranges for AV and VA time intervals and AV:VA ratios by pulsed Doppler over left ventricular in- and outflow tract in Swiss population[6]. In Thailand, there is only nomogram of AV time intervals published[7] but the diagnosis of fetal cardiac rhythm abnormalities required the AV, VA time intervals, and VA:AV ratio.

The primary objective of the present study was to establish normal reference values of fetal AV, VA time intervals, and VA:AV ratio by pulsed wave Doppler in fetuses between 18 and 37 weeks of gestation. The present study also aimed to evaluate the correlation of AV and VA time intervals and VA:AV ratio with GA and FHR.

Materials and Methods

The present study was a prospective cross-sectional study performed at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Thailand, between December 2019 and June 2020. The study was approved by the Ethics Committee of Rajavithi Hospital (No.181/2562) and all participants had given informed consent.

Singleton pregnant women between the GA of 18 and 37 weeks underwent a routine obstetric ultrasound at the antenatal care unit with no fetal structural anomaly detected and normal rhythm of FHR were enrolled. GA was calculated from the last menstrual period (LMP) and confirmed by the first or second trimester ultrasonography. The GA 18^{+0} to 18^{+6} weeks were described as GA 18 week. Pregnant women who had a history of autoimmune diseases, positive anti SS-A or anti SS-B, beta-adrenergic agonist drug use and fetal complications including intrauterine growth restriction (IUGR), large for gestational age (LGA), chromosomal abnormality in cases where prenatal diagnosis was performed, preterm birth, or stillbirth were excluded. Maternal characteristics such as age, parity, pre-pregnancy BMI, and obstetric outcomes including GA of delivery, birth weight, and fetal abnormality after birth were recorded.

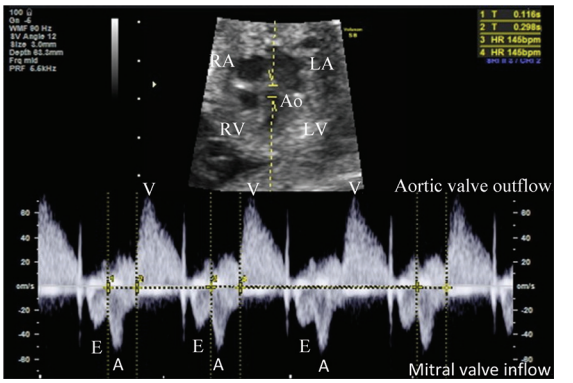

Figure 1. The two-dimension pulsed wave Doppler of mitral valve and aortic valve in five chamber view showing E (early diastolic filling), A (atrial contraction), and V (ventricular contraction) wave; the AV time intervals which were measured from the onset of the A wave to the onset of the V wave; the VA time intervals which were measured from the onset of the V wave to the onset of the A wave, and FHR which was measured with both atrial rate and ventricular rate.

RA=right atrium; LA=left atrium; RV=right ventricle; LV=left ventricle; Ao=aorta

All parturients underwent a two-dimensional ultrasound using a Voluson S8 (GE Healthcare, USA) with an abdominal 2 to 5 MHz transducer. The procedure was performed by a single operator and only one measurement was performed for each participant. First, the ultrasound was done to evaluate the fetal growth, anomaly scan, and fetal echocardiogram for exclusion criteria assessment. The next step was measurement of AV and VA time intervals and FHR by focusing on the fetal heart in five-chamber view, then magnified to 50% to 75% of the image. At least three to five cardiac cycle of pulsed wave Doppler was recorded during fetal apnea, keeping insonating angle at less than 30 degree from direction of blood flow while the Doppler sample volume was placed to cover the mitral and aortic valve and the Doppler cursor was adjusted parallel to the blood flow direction[2,7]. The AV time intervals were measured from the onset of the A wave (atrial contraction) to the onset of the V wave (ventricular contraction). Similarly, the VA time intervals were measured from the onset of the V wave to the onset of the A wave during the same cardiac cycle. FHR was measured for both atrial and ventricular heart rate to confirm that the fetus has normal cardiac rhythm, as shown in Figure 1. All measurements were performed three times from three cardiac cycles. The mean

Table 1. Normal reference value of atrioventricular time intervals by gestational age groups

GA (weeks)	n	Mean	±SD	±2SD	±3SD	AV time intervals at percentiles				
						5th	10th	50th	90th	95th
18 to 19	35	109.43	±5.52	±11.04	±16.56	101.20	102.00	110.00	115.80	119.60
20 to 21	34	111.65	±4.78	±9.56	±14.34	104.75	106.00	111.00	120.00	120.75
22 to 23	36	114.81	±6.09	±12.18	±18.27	102.00	104.10	115.50	122.00	123.15
24 to 25	33	116.88	±4.51	±9.02	±13.53	109.10	111.00	117.00	123.00	123.00
26 to 27	34	118.47	±5.30	±10.60	±15.90	110.75	111.00	119.00	124.00	129.75
28 to 29	34	120.53	±6.14	±12.28	±18.42	110.00	112.00	120.00	129.50	133.00
30 to 31	33	121.82	±7.50	±15.00	±22.50	108.00	111.00	123.00	131.20	133.00
32 to 33	34	124.18	±5.63	±11.26	±16.89	113.25	116.00	124.00	132.00	133.00
34 to 35	35	126.23	±5.81	±11.62	±17.43	113.80	115.80	127.00	133.00	133.40
36 to 37	35	128.17	±5.80	±11.60	±17.40	119.20	120.00	129.00	136.00	136.40

GA=gestational age; SD=standard deviation; AV=atrioventricular

values were recorded for analysis. The intra-observer variability was calculated from 20 participants. The correlation coefficient was 0.98 (95% CI 0.951 to 0.992, $p<0.001$).

The sample size was calculated from the previous study[7] by using this formula[8]

$$N/group = \frac{(Z_{\alpha/2})^2 \times (SD)^2}{d^2}$$

N=sample size; $\alpha=0.05$; $Z_{\alpha/2}=1.96$; SD=5.8; d=2

The subjects were 33 per group plus 10% drop-out rate, finally the total number of sample size was 37 per group. The participants were divided into 10 groups according to the GA including 18 to 19, 20 to 21, 22 to 23, 24 to 25, 26 to 27, 28 to 29, 30 to 31, 32 to 33, 34 to 35, and 36 to 37 weeks of GA. The statistical data analyses were performed by IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). The baseline characteristics of pregnant women and obstetric outcomes were reported as mean ± standard deviation (SD). The AV and VA time intervals and VA:AV ratio were reported as mean ± SD, ± 2SD, ± 3SD and values at 5th, 10th, 50th, 90th, and 95th percentile ranking. The correlation of GA and FHR with the measurement values were reported by Spearman's rank correlation coefficient.

Results

Three hundred seventy participants were initially enrolled in the present study, but twenty-seven participants were excluded as eleven of them were lost to follow-up and thus the obstetric outcomes were unknown, eleven had preterm births, three were IUGR, and two were LGA. Therefore, 343 participants were included in the analyses. All babies were healthy, and no abnormalities were detected in postnatal examination. The mean maternal age was 30.58±6.74 years, the mean of pre-pregnancy body mass index (BMI) was 23.58±5.04 kg/m², the mean GA of delivery was 38.36±1.05 weeks and the mean of birthweight was 3017.62±399.62 grams. The normal reference values of AV and VA time intervals and VA:AV ratio are shown in Table 1-3.

Both AV and VA time intervals positively correlated with GA ($R^2=0.516$ and $R^2=0.151$ respectively, $p<0.001$) whereas VA:AV ratio weakly negatively correlated with GA ($R^2=0.063$, $p<0.001$); the equations assuming linear correlation are shown in Table 4. Moreover, the VA time intervals had the strongest negative correlation with FHR ($R^2=0.811$, $p<0.001$) while AV time intervals and VA:AV ratio had a low level of negative correlation ($R^2=0.181$ and $R^2=0.150$, respectively, $p<0.001$) (Table 4).

Discussion

The present study has established the reference values of AV and VA time intervals and VA:AV ratio in normal singleton pregnancy in Thai population. Moreover, the study also demonstrated the relationship of AV and VA duration as well as VA:AV ratio with GA and FHR.

The AV time interval measurement by pulsed wave Doppler is widely used to detect first-degree AV block since it is the easiest method and examination of the left ventricular outflow tract is a part of routine fetal cardiac screening. AV time intervals of 140 milliseconds or longer has been used as a fixed cut-off value for diagnosis of a first-degree AV block, which may progress to a second-degree AV block and

Table 2. Normal reference value of ventriculoatrial time intervals by gestational age groups

GA (weeks)	n	Mean	±SD	±2SD	±3SD	VA time intervals at percentiles				
						5th	10th	50th	90th	95th
18 to 19	35	286.03	±13.29	±26.58	±39.87	262.40	265.20	286.00	303.80	309.00
20 to 21	34	289.91	±16.19	±32.38	±48.57	265.75	271.00	289.00	312.00	325.25
22 to 23	36	287.31	±14.18	±28.36	±42.54	266.55	267.00	287.00	308.20	311.75
24 to 25	33	285.88	±16.10	±32.20	±48.30	258.90	265.60	283.00	307.00	315.60
26 to 27	34	292.32	±19.11	±38.22	±57.33	260.50	268.50	293.00	322.50	331.75
28 to 29	34	294.21	±14.95	±29.90	±44.85	262.00	266.00	295.50	314.00	315.50
30 to 31	33	306.85	±27.80	±55.60	±83.40	266.50	270.60	304.00	351.80	367.20
32 to 33	34	306.59	±22.80	±45.60	±68.40	268.75	272.50	308.00	341.00	349.00
34 to 35	35	303.89	±20.84	±41.68	±62.52	272.00	274.00	302.00	335.00	341.80
36 to 37	35	308.63	±22.90	±45.80	±68.70	271.40	277.20	308.00	336.80	353.40

GA=gestational age; SD=standard deviation; VA=ventriculoatrial

Table 3. Normal reference value of VA:AV ratio by gestational age groups

GA (weeks)	n	Mean	±SD	±2SD	±3SD	VA:AV ratio at percentiles				
						5th	10th	50th	90th	95th
18 to 19	35	2.61	±0.20	±0.40	±0.60	2.26	2.36	2.60	2.90	2.90
20 to 21	34	2.60	±0.20	±0.40	±0.60	2.25	2.40	2.60	2.90	3.00
22 to 23	36	2.51	±0.22	±0.44	±0.66	2.20	2.27	2.40	2.80	3.00
24 to 25	33	2.45	±0.13	±0.26	±0.39	2.24	2.30	2.50	2.60	2.70
26 to 27	34	2.47	±0.19	±0.38	±0.57	2.08	2.25	2.50	2.60	2.93
28 to 29	34	2.45	±0.18	±0.36	±0.54	2.10	2.20	2.40	2.70	2.73
30 to 31	33	2.53	±0.28	±0.56	±0.84	2.17	2.20	2.50	2.96	3.03
32 to 33	34	2.47	±0.20	±0.40	±0.60	2.10	2.20	2.45	2.70	2.75
34 to 35	35	2.41	±0.21	±0.42	±0.63	2.10	2.16	2.40	2.80	2.80
36 to 37	35	2.42	±0.20	±0.40	±0.60	2.08	2.20	2.40	2.70	2.72

GA=gestational age; SD=standard deviation; VA=ventriculoatrial; AV=atrioventricular

Table 4. Correlation of AV, VA, and VA:AV ratio with gestational age and fetal heart rate

	Equation	Correlation coefficient	R^2	p-value
Gestational age (X)				
AV	Y=91.74+1×X	0.718*	0.516	<0.001
VA	Y=2.58E2+1.39×X	0.378*	0.151	<0.001
VA:AV	Y=2.74–8.99E-3×X	–0.255*	0.063	<0.001
Fetal heart rate (X)				
AV	Y=1.79E2–0.41×X	–0.425*	0.181	<0.001
VA	Y=6.21E2–2.23×X	–0.899*	0.811	<0.001
VA:AV	Y=3.90–9.64E-3×X	–0.350*	0.150	<0.001

VA=ventriculoatrial; AV=atrioventricular

p-value from Spearman correlation coefficient

* Correlation is significant

eventually become a third-degree AV block, which is an irreversible condition and requires permanent pacemaker after birth[2]. As a result, accurate diagnosis and early treatment of a first-degree AV block is an important factor in preventing a complete heart block[3]. However, when AV time intervals were considered in each gestation age group, the authors found the mean ± 2SD AV time intervals or those at 95th percentile of normal reference range identified in the present study were all lower than 140 milliseconds throughout gestation, especially during earlier GA. The result suggests that obstetricians might misdiagnose a first-degree AV block especially in the early gestation if still using a fixed cut-off of AV times. In contrast, falsely positive abnormality of AV prolongation may be encountered in second or third

trimester. Accordingly, GA specific AV time intervals may be more appropriate for prenatal diagnosis of first-degree AV block. The AV time intervals of the present study at GA 18 to 29 weeks were similar to those reported in the previous study in Thailand[7], but the AV duration at GA 30 to 37 weeks were longer. Nii et al reported positively correlation of both AV times and fetal cardiac cycle length with GA[9]. Additionally, several previous studies not only demonstrated that AV times gradually increased with advancing GA but also decreased as the FHR[6-7,10-13] increased, as the authors have also found in the present study. The increasing of cardiac size and parasympathetic tone with advancing gestation are probably related to the prolongation of AV conduction[9].

Accurate diagnosis of fetal tachyarrhythmias ensures the proper option of medical therapy to decrease morbidity and mortality of the fetus. Both VA time interval and VA:AV ratio help in the differential diagnosis of fetal tachycardia especially re-entry SVT, which has short VA interval or a VA:AV ratio of less than 1. On the other hand, a long VA interval is found in sinus tachycardia, ectopic atrial tachycardia, and permanent junctional reciprocating tachycardia[2]. The Mosimann et al study has established the reference ranges for VA time intervals and AV:VA ratio in the European population as a median and interquartile range as well as reported that the VA time interval is about two to five times longer than AV time interval[6]. However, the present study has measured shorter VA duration and the VA:AV ratio is 2.41 to 2.61 in normal pregnancy in the Asian population. The VA time interval in the present study has weakly positive correlation with GA and significantly negative correlation with FHR, similar to the data in prior research[6]. Meanwhile, the VA:AV ratio has been shown to have low negative correlation with both GA and FHR, which may be explained by unequal increasing proportion of AV and VA time in advancing GA whereas a faster heart rate shortens cardiac cycle.

The strengths of the present study are that it provides the first nomogram of VA time intervals and VA:AV ratio in Asian population and all participants were followed until delivery to confirm that they gave birth to healthy babies. The authors' nomogram of AV and VA time intervals were different from European population, suggesting that ethnicity influences this value, and this ethnicity-specific reference range could be useful in prenatal care of Asian population. Additionally, the low intra-observer variation indicates a reliable measurement value. Nonetheless, the limitations of the current study are that all measurements were conducted by one operator and the data were not collected in a longitudinal cohort study to evaluate the AV and VA time intervals and VA:AV ratio of the same fetus in different GA.

In conclusion, the AV and VA time intervals increased in advancing GA but the VA:AV ratio decreased with increasing GA. All measurement values were negatively correlated with FHR. Furthermore, the appropriate reference values of AV and VA time intervals and VA:AV ratio are important for early diagnosis and differential diagnosis of fetal arrhythmias; however, the actual values need to be considered with ethnicity in mind as well.

What is already known on this topic?

The AV and VA time intervals and VA:AV ratio are useful for diagnosis of fetal arrhythmias. Currently, the normal reference range of AV time interval is 120±20 milliseconds in all GA, but there are no reference value of VA time intervals and VA:AV ratio. The GA specific reference values may be more appropriated for diagnosis fetal arrhythmia.

What this study adds?

The AV and VA time intervals increased in advancing GA while the VA:AV ratio decreased with increasing GA. In consequence, the appropriate reference values of AV and VA time intervals and VA:AV ratio are important for early diagnosis and differential diagnosis of fetal arrhythmias.

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Conflicts of interest

The authors declare no conflict of interest.

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