ULTRA SONO GRAPHY

Development of a Z-score equation for atrioventricular interval measurement by two-dimensional pulsed Doppler echocardiography in normal fetuses between 16 and 33+6 weeks of gestation

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Purpose: Fetal echocardiography is the primary diagnostic tool for assessing the atrioventricular (AV) time interval. Establishing a reference range for this parameter throughout pregnancy is essential for the early detection of potential abnormalities. The aim of this study was to develop a Z-score equation and establish specific percentiles for the AV time interval in normal fetuses between 16 and 33+6 weeks of gestation.

Methods: A multicenter, prospective, cross-sectional study was conducted between 2018 and 2022. A large sample of pregnant women meeting specific eligibility criteria was included, while cases with potential confounders were excluded. Two-dimensional echocardiography with pulsed Doppler techniques was employed, focusing on the left ventricular inflow and outflow. Data were rigorously analyzed with careful assessment of measurements and normalization procedures.

Results: In total, 1,309 echocardiograms were performed, and 1,183 pregnant women were included after applying the eligibility criteria. Detailed percentiles for each gestational age were determined, and a Z-score equation was formulated. A very weak correlation was observed between AV interval measurement and gestational age ($r=0.16$, $P<0.001$). In addition, the correlation between AV interval measurement and fetal heart rate was weak ($r=-0.21$, $P<0.001$). The Z-score for the AV interval measurement in milliseconds was derived as follows: Z-score=(AV interval measurement−111.3)/8.6.

Conclusion: This study provides a reference range and Z-score equation for the AV interval, which may enhance the accuracy of monitoring fetuses at risk for developing atrioventricular block—especially in pregnant women with specific antibodies—thus facilitating earlier diagnosis and treatment.

Keywords: Fetal heart; Two-dimensional echocardiography; Atrioventricular interval; Reference values

Key points: This study used two-dimensional pulsed Doppler echocardiography to develop Z-score equations and specific percentile curves for measuring the atrioventricular (AV) interval in normal fetuses between 16 and 33+6 weeks of gestation. These reference values are critical for the early detection of AV conduction abnormalities. Fetal AV interval measurement is a valuable tool for assessing cardiac health and detecting congenital AV block, particularly in fetuses of mothers with anti-SSA and anti-SSB antibodies. Accurate identification of AV conduction delays can guide timely therapeutic interventions and improve perinatal outcomes. The study demonstrates the reproducibility and ease of measuring AV intervals using the left ventricular inflow and outflow technique with pulsed Doppler. With a robust sample size and a wide gestational age range, the findings provide a solid foundation for applying Z-score curves, thereby enhancing confidence in diagnosing and managing AV conduction delays in fetuses.

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Introduction

Fetal echocardiography has transformed the diagnosis and management of congenital heart disease (CHD) and fetal arrhythmias since its introduction in the late 20th century [1]. This tool has led to a deeper understanding of fetal cardiac physiology and revolutionized prenatal care by enabling the early detection of cardiac anomalies [1]. Given that postnatal CHD occurs in approximately 1% of cases, early surveillance and diagnosis are essential for timely interventions that can significantly affect pregnancy outcomes and long-term neonatal health [2–4].

Advancements in technology have also propelled fetal cardiology forward. Measurement of the atrioventricular (AV) interval via fetal echocardiography has emerged as a promising indicator of fetal cardiac health. This measurement reflects electrical conduction between the atria and ventricles and may serve as an early marker for detecting cardiac conduction defects [5]. Although existing data support the utility of this parameter in predicting complications such as congenital AV block [5–11], establishing precise reference values remains crucial for its clinical application.

Congenital AV block is a rare but serious arrhythmia affecting approximately 1 in 15–20,000 births [5–11]. It is often caused by the transfer of maternal autoantibodies that lead to inflammation and fibrosis in the fetal myocardium and AV node [5–11]. Risk factors include the use of certain medications, viral infections, structural heart disease, and maternal autoimmune disease [9–11]. Early and accurate identification is crucial, highlighting the importance of AV interval measurement [11].

This article proposes the development of a reference range for the AV interval using a Z-score equation. The goal is to standardize these values and facilitate their practical application, ultimately improving fetal health planning.

Materials and Methods

Compliance with Ethical Standards

All participants provided informed consent in accordance with established guidelines and regulations for research involving human subjects. The study was approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP) (CAAE 91114718.8.0000.5505).

Study Design

This multicenter, prospective, cross-sectional study was conducted between 2018 and 2022 with the objective of developing a Z-score equation for measuring the AV interval in fetal echocardiography.

Eligibility Criteria

This study included singleton pregnancies with live fetuses, with gestational ages between 16 and 33+6 weeks as determined by the date of the last menstrual period and confirmed by an ultrasound examination before 13 weeks of gestation. Fetuses with cardiac or extra-cardiac malformations, suspected arrhythmias, and pregnant women with conditions that could impair the acquisition of quality cardiac images were excluded. Specifically, exclusion criteria comprised the presence of abdominal scars, obesity (body mass index [BMI] >35 kg/m^2), chronic diseases such as arterial hypertension, diabetes mellitus, renal disease, or collagen disorders; as well as pregnant smokers, illicit drug users, hydropic fetuses, and cases of oligohydramnios and/or polyhydramnios (amniotic fluid index >95th percentile or <5th percentile) [12].

Sample Size Calculation

The sample size was determined based on Royston's principle, which recommends 20 cases per week for constructing reference values for fetal biometric parameters covering 90% of the distribution between the 5th and 95th percentiles [13]. As this study analyzed 18 weeks (gestational ages from 16 to 33+6 weeks), the estimated sample size was approximately 360 fetuses. Nonetheless, a larger number per gestational age range was recruited to ensure the robustness of the data.

Interventions

Two-dimensional fetal echocardiography using pulsed Doppler was performed. The AV interval was measured as the time between the onset of the mitral valve A wave and the onset of the aortic valve systolic flow, with both measurements obtained from the same tracing (Fig. 1).

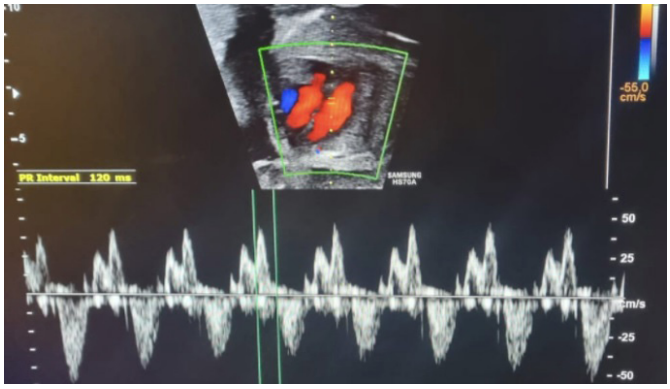

Fig. 1. Measurement of the atrioventricular interval using pulsed Doppler on fetal echocardiography.

Statistical Analysis

Data were managed using REDCap (Vanderbilt University, Nashville, TN, USA) and analyzed with STATA/IC 16.1 (Stata Corp., College Station, TX, USA). Initially, an exploratory analysis of the echocardiographic data was conducted using scatter plots and summary tables to identify any discrepancies in the database; any discrepancies were re-evaluated and corrected, facilitated by the storage of all echocardiographic images on DVDs.

A descriptive analysis of the study population was performed, reporting absolute and relative numbers for qualitative variables and means with their variabilities (standard deviation and/or range) for quantitative variables. Skewness and kurtosis were evaluated to assess data normalization. The Z-score equation was developed using the mean and standard deviation of the original study measurements. From the echocardiographic data, the 10th, 50th, 90th, and 95th percentiles were determined for each gestational age in whole weeks [14]. Pearson correlation coefficient was also used to analyze the relationship between the AV interval measurement and gestational age and fetal heart rate.

Results

During the data collection period, 1,309 fetal echocardiograms were performed. After applying the eligibility criteria, 1,183 pregnant women were included in the final analysis. The mean age of the participants was 29.7±6 years, with 21% aged 35 years or older. The mean BMI was 27.6 kg/m^2, and the mean gestational age at the time of fetal echocardiography was 26.5 weeks. Approximately 80% of the pregnant women underwent routine screening (Table 1).

Table 1. Baseline characteristics of the pregnant women (n=1,183)

Variable	Value
Maternal age (year)	29.7±5.9
>35 years old	236 (20.0)
Fetal echocardiography-based GA (week), mean (min–max)	26.5 (16–34)
Body mass index (kg/m^2)	27.6±4.1
Education level	
Completed high school	397 (43.6)
Incomplete high school	136 (14.9)
Secondary school	362 (39.7)
Primary school	16 (1.8)
Indications for fetal echo	
Routine	933 (78.9)
Maternal risk factor	78 (6.6)
Fetal risk factor	5 (0.4)
Family risk factor	7 (0.6)

Values are presented as mean±SD or number (%).
GA, gestational age; SD, standard deviation.

A very weak but statistically significant correlation was observed between AV interval measurement and gestational age (r=0.16, P<0.001) (Fig. 2). Similarly, the relationship between AV interval measurement and fetal heart rate was weak (r=–0.21, P<0.001) (Fig. 3).

Based on the fetal echocardiographic measurements, the 10th, 50th, 90th, and 95th percentiles were determined for each gestational age (Table 2).

The Z-score equation for AV interval measurement in milliseconds was derived using the following formula: Z-score=(AV interval

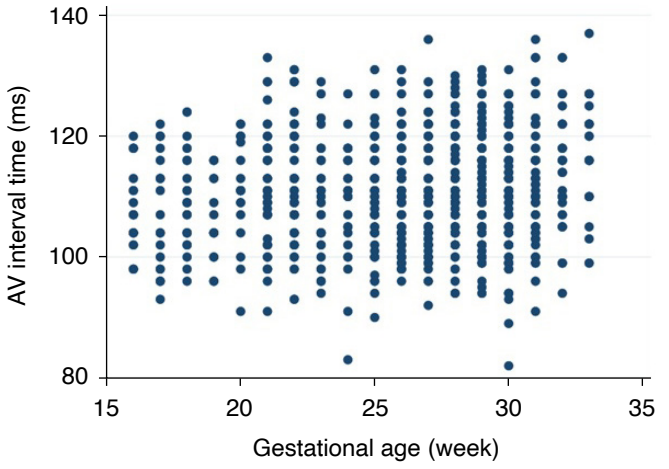

Fig. 2. Pearson correlation coefficient assessing gestational age and atrioventricular (AV) interval – very weak correlation (r=0.16), but statistically significant (P<0.001).

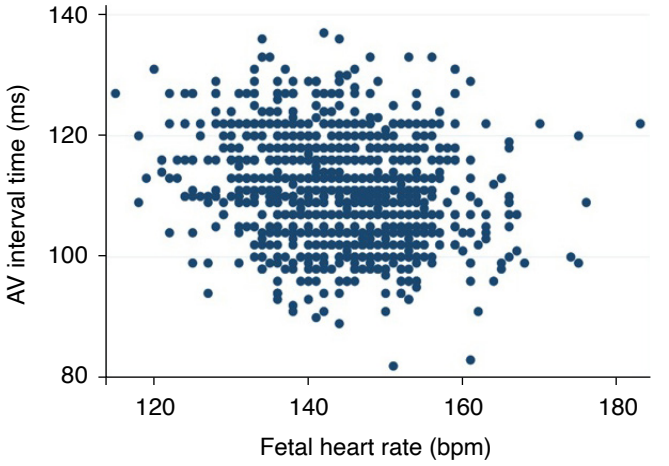

Fig. 3. Pearson correlation coefficient assessing fetal heart rate and atrioventricular interval – weak correlation (r=–0.21), but statistically significant (P<0.001).

measurement−111.3)/8.6.

This equation is based on the mean (111.3) and standard deviation (8.6) of the AV interval measurements obtained during the study. The normal distribution of these measurements, as evidenced by skewness and kurtosis values of 0.07 and 2.7 respectively (and confirmed by the Q-Q plot in Fig. 4), supports the use of this equation without additional transformations. The AV Z-score intervals are provided in Table 3.

Discussion

This study presents a Z-score equation and percentile reference values for fetal AV interval measurement in a large sample covering gestational ages from 16 to 33+6 weeks. These results will aid in monitoring fetuses of pregnant women with anti-SSA and anti-SSB antibodies, thereby facilitating the early diagnosis of AV conduction delay and enabling timely therapy [6–9].

Several studies have sought to define the optimal AV interval cutoff value and to evaluate the benefits of corticosteroids in cases of suspected or confirmed AV block [1,15–18]. Donofrio et

Table 2. The 10th, 50th, 90th, and 95th percentiles of atrioventricular interval measurements (ms) in normal fetuses between 16 and 33+6 weeks of gestation

Gestational age (week)	No.	10th	50th	90th	95th
16	23	98	107	118	118
17	22	96	105	120	122
18	29	100	109	120	124
19	15	96	104	116	116
20	22	100	111	120	122
21	62	100	111	120	126
22	60	101	109	123	131
23	39	96	109	122	127
24	28	98	111	118	122
25	58	100	110	120	127
26	107	100	110	120	122
27	154	100	110	122	122
28	152	104	111	122	125
29	137	100	111	124	127
30	121	99	113	123	127
31	83	103	110	123	129
32	44	105	114	125	127
33	27	103	116	127	127

Table 3. AV intervals Z-scores for gestational age

AV (ms) Z-score	Gestational age (week)																	
	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
−3	86	81	82	82	84	87	84	80	81	84	87	87	90	85	83	85	89	89
−2	93	90	91	89	93	95	93	90	90	93	94	95	98	94	93	94	97	98
−1	100	100	99	97	102	103	102	99	100	101	102	103	105	103	103	104	105	107
0	108	110	108	104	111	112	111	108	109	110	110	111	113	112	112	113	114	117
1	115	119	116	111	120	120	120	117	118	118	117	119	120	121	122	122	122	126
2	122	129	125	119	129	129	129	127	128	127	125	127	128	130	132	131	130	136
3	129	139	134	126	138	137	138	136	137	135	133	134	136	138	141	141	139	145

Atrioventricular (AV) Z-score=(AV interval (ms)−111.3)/8.6.

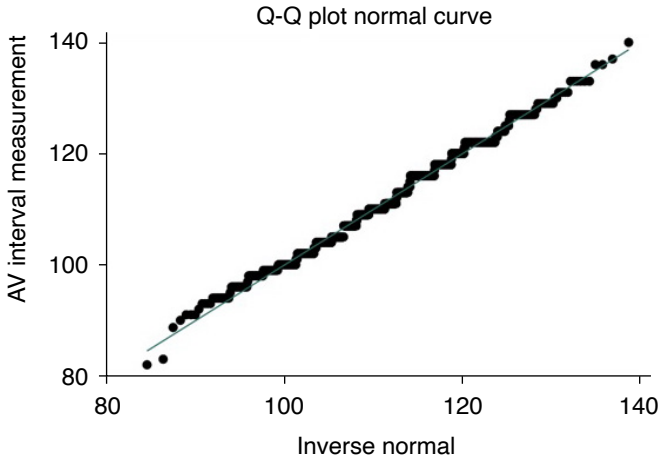

Fig. 4. Quantile-quantile (Q-Q) plot evaluating normality of atrioventricular (AV) interval measurement.

al. [1] compared fetuses from pregnancies positive for anti-Ro/SSA antibodies with a control group by measuring the AV interval (using Doppler of the left ventricular inflow and outflow tracts) and the AV interval (using magnetocardiography). Their study found no significant differences, with AV interval cutoff values for diagnosing first-degree block ranging from 151 to 167 ms between 16.5 and 38.5 weeks—corresponding to Z-scores >+3. Notably, three of the four cases with AV interval and PR Z-scores above +3 exhibited postnatal intra-atrial and intraventricular block despite dexamethasone treatment. Bergman et al. [17] enrolled fetuses from healthy pregnant women with and without positive anti-SSA antibodies between 18 and 24 weeks and, using simultaneous Doppler recordings of left ventricular inflow and outflow as well as superior vena cava a-wave to aortic flow (SVC-Ao), identified abnormal AV interval cutoff values of 134–138 ms and 132–138 ms, respectively. Friedman et al. [19] in the PRIDE study employed a 150 ms cutoff for prolonged AV intervals in fetuses of women with positive anti-SSA antibodies and noted that complete AV block could develop within one week of a normal echocardiogram; they also suggested that tricuspid regurgitation and increased atrial echodensity might serve as markers for complete AV block. In contrast, Eliasson et al. [8] reported that early corticosteroid administration (6–7 days after the onset of block) might reverse AV block in fetuses of anti-SSA–positive mothers.

Discrepancies in the literature regarding the cutoff for diagnosing AV conduction delay and the benefit of corticosteroids in pregnancies with positive anti-SSA and/or anti-SSB antibodies have been noted [6,8,9,18,20–23]. These controversies likely stem from the rarity of the condition, which complicates a comprehensive understanding of its progression from early detection. Establishing a clearer understanding of normal AV interval values is crucial for a more accurate early diagnosis. This study addresses this need by thoroughly evaluating AV interval measurements in a robust sample spanning a wide range of gestational ages [7,16,24].

The reference values developed in this study make it possible to more confidently identify when a fetus is progressing toward AV conduction delay and to direct therapy at the optimal time. Improved early diagnosis allows for prompt treatment and a more reliable evaluation of therapeutic outcomes. The development of Z-score curves based on normal AV interval values facilitates the design of studies investigating corticosteroid use in the prevention of congenital AV block, reducing uncertainty regarding the normality of measurements obtained from fetuses of treated mothers.

Based on the literature, it is proposed that AV interval values can be classified as normal when the Z-score is ≤2.0 and abnormal when the Z-score exceeds 2. Abnormal values may be further stratified into three levels of AV conduction delay: Z-score between 2.0 and 3.0, between 3.0 and 4.0, and greater than 4.0 [8].

A previous study by a Chinese group provided important reference values for the AV interval expressed as Z-scores for gestational age, using three different measurement techniques—Tissue Doppler, SVC-Ao Doppler, and pulmonary vein–pulmonary artery (PV-PA) Doppler. Although their analysis was based on a sample of 227 fetuses, their work significantly contributed to the understanding of fetal AV conduction [25]. This study focused on a standardized measurement technique—pulsed Doppler with simultaneous acquisition of left ventricular inflow and outflow—which ensured methodological consistency. By evaluating a much larger cohort of 1,183 fetuses, this study robustly demonstrated that AV interval measurements follow a normal distribution. This finding strengthens the reliability of the Z-score equation described in this study and enhances its clinical applicability. In addition to providing Z-scores, the present study established percentile-based reference values, offering a comprehensive tool for fetal echocardiographic assessment.

Although fetal AV block can occur suddenly, guidelines recommend weekly or bi-weekly monitoring of the AV interval between 16 and 28 weeks [1,26]. Corticosteroid therapy is generally considered when the AV interval exceeds 150 ms in fetuses of pregnant women with positive autoantibodies [19,20,26]. In this study, the maximum AV interval values observed were 118 ms at 16 weeks and 127 ms at 33+6 weeks of gestation. Consequently, to minimize errors in the early detection of AV block, it is preferable to express AV interval values as percentiles and Z-scores.

The present study also noted differences in the Z-score equation compared to those reported by Donofrio et al. [1] and Pan et al. [25]. Donofrio et al. [1] employed a polynomial regression model incorporating gestational age squared (GA^2) to account for non-

linear variations, whereas Pan et al. [25] used multiple regression models that included both gestational age and fetal heart rate—resulting in more complex equations. In contrast, this study utilized a linear Z-score equation based on the normal distribution of AV interval measurements in a significantly larger cohort. While Donofrio et al. [1] focused on a high-risk population and Pan et al. [25] applied different Doppler-based methods, the aim of this study was to provide a clinically practical and statistically robust reference for routine fetal echocardiography. These methodological differences reflect variations in study design, sample characteristics, and the specific objectives in applying Z-score equations within fetal cardiology.

This study also observed that fetal AV interval measurements tend to exhibit a negative relationship with fetal heart rate and a positive relationship with gestational age, which is consistent with previous findings [15,16,22,27–30]. Given the ease and reproducibility of measuring the AV interval using the left ventricular inflow and outflow technique with pulsed Doppler, the authors advocate for its routine inclusion in all fetal echocardiograms. Employing this normality curve will provide fetal cardiologists with greater confidence in diagnosing AV conduction delay, thereby positively impacting management. Moreover, multidisciplinary collaboration among fetal cardiologists, pediatricians, obstetricians, and other specialists will be essential for early therapeutic intervention and improved outcomes.

A limitation of this study is that the AV interval was measured

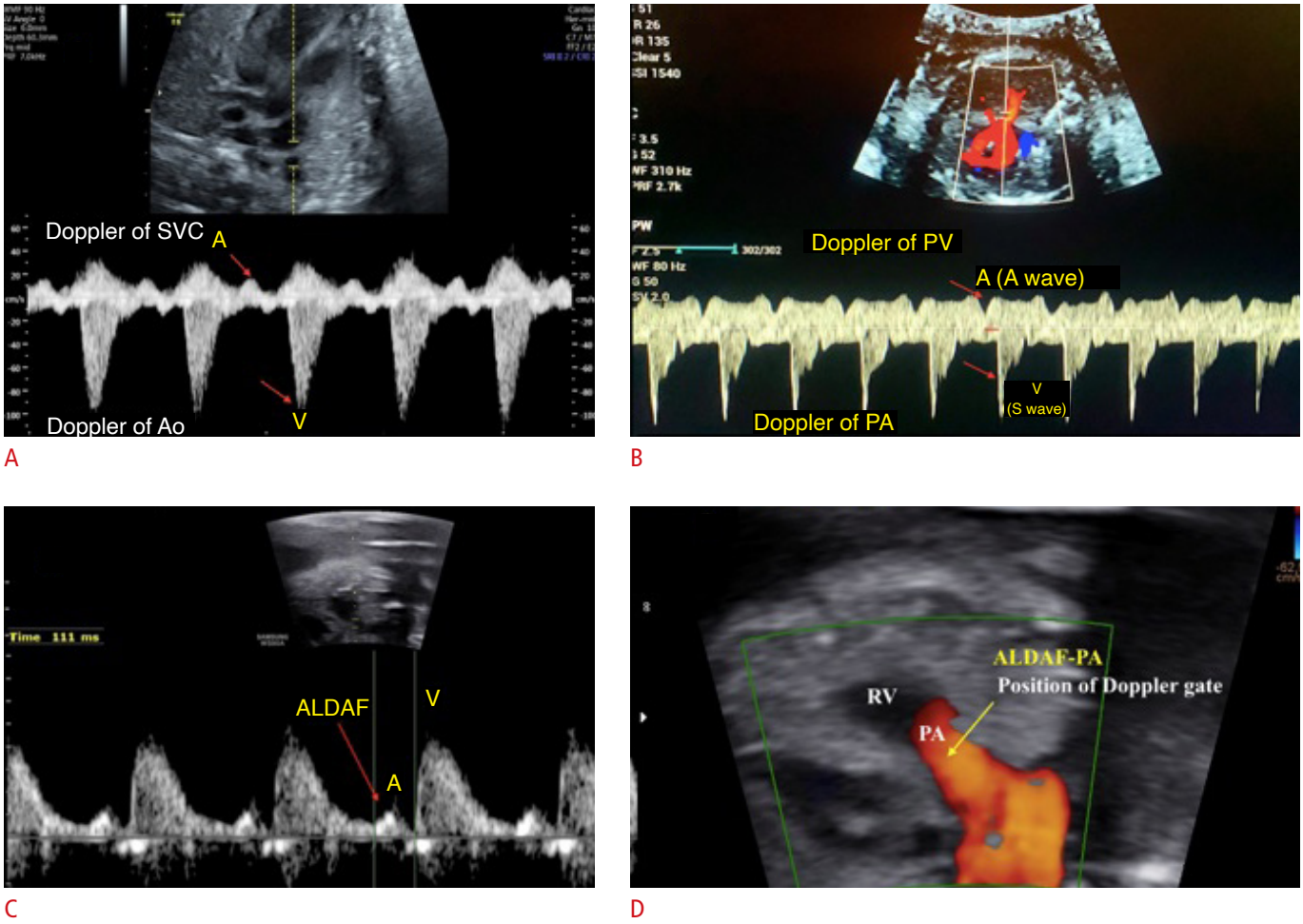

Fig. 5. Fetal echocardiogram showing images of how to measure the atrioventricular (AV) interval using different techniques.
A. Doppler of superior vena cava (SVC)–aorta (Ao) from the onset of the retrograde A-wave of SVC Doppler (A) to the onset of the forward S-wave of aortic flow (V). B. Pulmonary artery (PA)–pulmonary vein (PV) Doppler: note the red line showing the measurement of the AV interval from the beginning of the pulmonary venous A wave to the beginning of the pulmonary arterial ejection flow (S wave). C. Antegrade Late Diastolic Arterial blood Flow (ALDAF): from the beginning of the retrograde A wave (A) to the beginning of the forward S wave in the aortic or pulmonary arterial flow (V). D. This image shows how the Doppler sample should be positioned (red arrow) in the ventricular outflow tract to obtain the ALDAF. A, atrial contraction; V, ventricular contraction; RV, right ventricle.

in a single plane (left ventricular inflow and outflow) without employing additional planes to obtain the spectral curve [6–8,16,24]. However, this approach is recognized as the simplest and most reliable, enabling the measurement of the AV interval in virtually all fetuses [29–31]. In cases where proper identification of the left ventricular inflow E and A waves is challenging—such as in early gestation—alternative methods for AV interval assessment may be required [17,27,28,30]. Examples include simultaneous pulsed Doppler recordings from the SVC-Ao, PV-PA, or antegrade telediastolic arterial flow (Fig. 5) [15,27,28,30]; additionally, tissue Doppler imaging may be used, particularly when fetal positioning is unfavorable [15,22,27]. Another limitation is that not all fetal echocardiograms included more than one measurement per spectral curve; however, the large sample size minimizes this potential bias [15,16,22,27,28,30].

The main strengths of this study are the robust number of participants and the wide range of gestational ages examined. The use of the left ventricular inflow and outflow plane for AV interval measurement is straightforward and reproducible. Advances in technology have yielded devices with excellent image quality and sensitivity for spectral curve acquisition, and this study encountered no technical difficulties in obtaining the spectral curve or measuring the AV interval regardless of gestational age. Given the simplicity and reproducibility of this method—and its positive correlation with gestational age—we strongly support the use of reference curves expressed as percentiles or, ideally, as Z-scores for monitoring AV conduction in fetuses.

A reference range and Z-score equation for AV interval measurement were established. These findings may facilitate more accurate monitoring of fetuses at risk for developing AV block, particularly in pregnant women with anti-SSA and anti-SSB antibodies, thereby enabling earlier diagnosis and treatment.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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