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Cardiac structure and function in fetuses of mothers infected with HIV: The prospective P²C²HIV multicenter study

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Abstract

Background—This study was designed to determine if vertically transmitted HIV infection and maternal infection with HIV are associated with altered cardiovascular structure and function in utero.

Methods—Fetal echocardiography was performed in 173 fetuses of 169 HIV-infected mothers (mean gestational age, 33.0 weeks; SD = 3.7 weeks) at 5 centers. Biparietal diameter, femur length, cardiovascular dimensions, and Doppler velocities through atrioventricular and semilunar valves and the umbilical artery were measured. Measurements were converted to *z* scores based on published normal data.

Results—Fetuses determined after birth to be HIV-infected had similar echocardiographic findings as fetuses later determined to be HIV-uninfected except for slightly smaller left ventricular diastolic dimensions ($P = .01$). The femur length ($P = .03$) was also smaller in the fetuses postnatally identified as HIV-infected. Differences in cardiovascular dimensions and Doppler velocities were identified between fetuses of HIV-infected women and previously published normal fetal data. The reason for the differences may be a result of maternal HIV infection, maternal risk factors, or selection bias in the external control data.

Conclusions—Vertically transmitted HIV infection may be associated with reduced left ventricular size but not with altered cardiac function in utero. Fetuses of HIV-infected mothers may have abnormal cardiovascular structure and function and increased placental vascular resistance, regardless of whether the fetuses are subsequently found to be infected with HIV.

The percentage of patients with acquired immunodeficiency syndrome (AIDS) who are female has increased from an estimated 8% during the period of 1981 to 1987 to 18% from 1993 to 1995.¹ Almost half of the 35 to 40 million HIV-infected people living in the world are women, and 1600 babies are born with HIV infection every day.² In developed nations, highly active antiretroviral therapy is also prolonging and improving the lives of many of these women. Consequently, there is an ever-growing population of infants at risk for vertically transmitted HIV infection. Although perinatal zidovudine and alternatives to breast-feeding are reducing vertical HIV transmission rates, fetuses may still be exposed in utero to adverse effects of maternal HIV infection. Knowing the effects of maternal HIV infection and of vertically transmitted HIV infection, both before and after birth, is important for understanding the pathogenesis of HIV infection and for developing effective management strategies for the mother and fetus during pregnancy and for the infant after birth.

In 1989, the multicenter, prospective Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus (HIV) Infection Study (P²C²HIV Study) was initiated by the National Heart, Lung, and Blood Institute.³ A study objective was to determine the incidence, course, and outcome of cardiovascular abnormalities associated with vertically transmitted HIV infection in a cohort of infants and children, many of whom were to be enrolled prenatally. As part of the P²C²HIV study, echocardiography was performed on fetuses of HIV-infected women. For this article, we analyzed these fetal echocardiograms to determine whether vertically transmitted HIV infection or maternal HIV infection was associated with any alterations in fetal cardiovascular structure and function.

Methods

Pregnant women with HIV infection were prospectively enrolled at 5 clinical centers. Antibody titers against HIV were measured by an enzyme-linked immunosorbent assay with confirmation by Western blotting. Informed consent, approved by the local institutional review boards, was obtained from all participants.

Maternal health-related factors during pregnancy were determined from interviews and medical records. Data collected included smoking history, illicit drug and alcohol use,

hemoglobin levels at the time of delivery, hospitalizations, zidovudine use, and pregnancy-induced hypertension. Urinary cytomegalovirus and oropharyngeal Epstein-Barr virus specimens for culture and serology were obtained once in all mothers during pregnancy. Lymphocyte phenotypes were determined during pregnancy with the AIDS Clinical Trials Group (ACTG) consensus protocol.

Fetal echocardiography was performed in the second or third trimester of pregnancy. The gestational age was determined from the date of the last menstrual period or from the biparietal diameter if the date of the last menstrual period was unavailable. Doppler interrogation of the atrioventricular valves, semilunar valves, and umbilical artery was performed when the fetus was not active and respiration was suspended. The presence or absence of pleural or pericardial effusions, ascites, and skin edema was documented.

To ensure uniformity of measurements, videocassette recordings of the fetal echocardiograms were analyzed by a single reviewer (L.K.H.) who was blinded to the gestational age and postnatal HIV infection status. From each echocardiogram, an attempt was made to measure several cardiovascular dimensions from 2-dimensional images in an axial plane, as previously described.^{4,5} From Doppler spectra obtained at an angle of incidence of $<30^\circ$, the peak tricuspid and mitral valve E and A waves, and the peak aortic valve, pulmonary valve, and umbilical arterial systolic and diastolic velocities were digitized. Period time, measured as the time from peak to peak ventricular outflow velocity (equivalent to an R-R interval), was measured and the heart rate calculated.

Pregnancy outcomes and postnatal courses were documented. All infants underwent postnatal echocardiograms within the first months of life. HIV cultures were obtained in infants at birth and at 3 and 6 months of age. Infants were considered HIV-infected if 2 cultures were positive and HIV-uninfected if 2 cultures were negative (1 of which was at or after 5 months). An enzyme-linked immunosorbent assay was performed at 15 months of age in infants believed to be uninfected to confirm the absence of HIV infection.

Statistical analysis

Measurements from postnatally HIV-infected and HIV-uninfected fetuses were compared by analysis of covariance. In the 2 twin pregnancies and 2 repeat singleton pregnancies, each fetus was treated independently. An adjusted mean was calculated for each fetal measurement. The adjusted mean for a subgroup was defined as the predicted response value obtained by evaluating the regression equation for the subgroup at the mean gestational age for the 2 subgroups.

The relations between maternal factors recorded in the medical history and fetal cardiac and noncardiac measurements were also investigated by analysis of covariance. The maternal factors were compared for mothers of postnatally HIV-infected and postnatally HIV-uninfected fetuses by the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. Reported *P* values are 2-sided.

Cardiac and noncardiac measurements obtained in fetuses of HIV-infected women were compared with previously published normal fetal data⁴⁻¹² or with data from 43 normal

pregnancies studied at the Children's Hospital in Boston (ventricular wall thickness only) with z scores. The published normal data (Table II) were chosen for comparison with the study data because they were available in raw form or were presented as regression equations with the residual standard deviations, which permitted calculation of z scores. For several cardiac dimensions, normal values from 2 different sets of published normal data were used for comparison with the study population. When more than 1 normal dataset was available, the measurement was considered abnormal only if it was abnormal compared with both normal datasets and in the same direction.

A z score adjusted for gestational age was calculated for each echocardiographic measure as the difference between the observed value for a study fetus and the normal predicted value from the regression equation divided by 1 SD for the regression. The z score standardization for gestational age was necessary to adjust for the changes in size associated with growth. The Wilcoxon signed rank test was used to determine whether the z scores differed from zero (normal).

Because we used previously published normal data, we assessed interobserver variability for 2-dimensional measurements with 12 fetal echocardiograms completed at 1 clinical center. The mean difference and SD of the difference were calculated for each measurement. Mean differences were compared with zero by a 1-sample t test. The intraclass correlation coefficient (ICC) calculated from the variance components from an analysis of variance was also used to measure interrater agreement. An ICC near 1.0 would indicate high interrater agreement. Interobserver variability for intracardiac Doppler velocities in the fetus has been previously demonstrated to be low.^{8,13}

Results

One hundred sixty-nine mothers participated in the study (mean age 27.1 years, SD = 5.3 years, median gravidity 3.0, median parity 2.0), and 173 fetuses were examined echocardiographically. There were 2 pregnancies with twin gestation, and 2 women participated during 2 separate singleton pregnancies. Most of the mothers were black ($n = 72$, 42.6%) or Hispanic ($n = 62$, 36.7%). The mean gestational age at fetal echocardiography was 33.0 weeks (SD = 3.7 weeks, range 20 to 42 weeks).

Approximately one third of the mothers received zidovudine during pregnancy (37.9%, 64 of 169). During pregnancy, 34.5% (58 of 168) of the mothers reported a history of anemia, 35.9% (60 of 167) reported smoking regularly, 14.4% (24 of 167) reported using alcohol, and 19.2% (32 of 167) reported using illicit intravenous drugs. A urine screen for cocaine or crack was performed in 70 women, with 17 (24.3%) testing positive. In 28 of the 172 pregnancies with live births (16.3%), the mothers were hospitalized. Preeclampsia was uncommon (5.2%, 9 of 172). Most of the women tested for cytomegalovirus were culture-negative (6.6% positive [8 of 122]) but 74.8% (101 of 135) of those tested for Epstein-Barr virus were culture-positive. The median maternal CD4 T-cell counts and percent were 452 cells/mm³ and 29%, respectively.

Pregnancy and postnatal outcome

One fetus died in utero at 33 weeks of gestation shortly after intrauterine exposure to cocaine. No acute event was identified as the cause. The fetus was not growth-retarded, and no abnormalities were found at autopsy. The placenta showed older infarcts, but of an amount insufficient to cause fetal death. The other 172 fetuses were delivered at a mean gestational age of 38.9 weeks ($SD = 2.1$ weeks). Six infants died in the first year of life before HIV infection status could be confirmed (range 35 to 325 days). Autopsy in 4 revealed no significant cardiac abnormality. In 2 without autopsy, hepatic cirrhosis was diagnosed in 1 and the cause of death was unknown in the other.

HIV status was determined for 165 infants; 25 (15.2%) were HIV-infected and 140 HIV-uninfected. The postnatal HIV status was not determined for 8 fetuses: 1 died in utero, 1 lost to follow-up, and 6 died in infancy. There was no significant difference in the maternal demographic and health-related characteristics between the HIV-infected and HIV-uninfected subgroups.

A large ventricular septal defect and valvular pulmonary stenosis were diagnosed postnatally in 1 HIV-uninfected infant whose prenatal data were excluded from the analysis. The data for 15 others with hemodynamically insignificant structural cardiac abnormalities not identified antenatally were included in the analysis. The lesions included a small ventricular septal defect in 4 (2 HIV-infected, 2 HIV-uninfected), mild valvular or supra-aortic pulmonary stenosis in 5 (all HIV-uninfected, 1 with patent ductus arteriosus), a bicuspid aortic valve in 2 (both HIV-uninfected), and a patent ductus arteriosus that persisted beyond the first month of life in 5 (4 HIV-uninfected, 1 of undetermined status). No neonate had a major congenital extracardiac defect.

HIV-infected versus uninfected fetuses

When fetuses who were postnatally identified as HIV-infected were compared with the HIV-uninfected subgroup, the only cardiovascular difference was in the left ventricular end-diastolic dimension, which was smaller in the HIV-infected group ($P = .01$, Figure 1 and Table I). The adjusted mean for end-diastolic dimension was 11.5 mm for 15 HIV-infected fetuses and 12.7 mm for the 78 HIV-uninfected fetuses. However, Figure 1 shows that all fetuses, regardless of HIV infection status, fell within the normal range, so the mean difference of 1.2 mm was probably not clinically important. Furthermore, the results from the first 2 postnatal echocardiograms did not suggest a difference in mean end-diastolic dimension based on the HIV status (18.9 mm and 23.4 mm at birth and 4 months, respectively, for the HIV-infected cohort, and 19.0 mm and 22.9 mm for the HIV-uninfected cohort, respectively). Although the biparietal diameter was similar for the 2 subgroups, femur length was smaller in the HIV-infected subgroup ($P = .03$).

Association with maternal variables

When fetal cardiac and noncardiac measurements were analyzed for association with maternal factors, a relation was found only between maternal hemoglobin and fetal left ventricular end-diastolic dimension. The Pearson correlation coefficient in the 91 patients for whom both measures were available was 0.24 ($P = .02$). Among 36 fetuses having an

echocardiogram after 33 weeks of gestation, the correlation was stronger ($r = 0.44$, $P = .007$) than in those with an echocardiogram before 33 weeks ($r = .13$, $P = .36$; $n = 52$). A statistical model including postnatal HIV-infection status, menstrual age, and maternal hemoglobin at delivery suggests all 3 factors were related to fetal left ventricular end-diastolic dimension ($P = .003$ for HIV status; $P = .002$ and $.01$, respectively, for the linear and quadratic menstrual age terms; $P = .005$ for maternal hemoglobin at delivery). The infrequent occurrence of each maternal risk factor made it hard to explore further the relations between maternal factors and fetal cardiac and noncardiac measurements.

Other echocardiographic features

Several other abnormalities were found in the fetuses of HIV-infected mothers. Color flow mapping showed tricuspid regurgitation in 19 (2 HIV-infected, 14 HIV-uninfected, 3 undetermined). In 5, the regurgitant jet extended to the mid-right atrium, and in 14 the jet extended less than halfway into the right atrium. Mild mitral regurgitation was present in 1 postnatally HIV-infected fetus, 1 HIV-uninfected fetus, and 1 of undetermined status. The fetus that died in utero had both mitral and tricuspid regurgitation and a small pericardial effusion documented echocardiographically. Pleural effusions, ascites, and skin edema were not identified in any of the fetuses.

Fetuses of HIV-infected mothers

Several differences in cardiovascular dimensions and Doppler velocities between fetuses of HIV-infected women and previously studied normal populations (Table II) were identified (Table III). Fetuses of HIV-infected women had significantly thicker left and right ventricular walls and lower left and right ventricular shortening fractions. They had lower heart rates and longer average period times than the normal populations. The peak aortic and pulmonary flow velocities were higher. The mitral peak A waves and the mitral and tricuspid A/E wave velocity ratios were higher, and E/A wave ratios were lower. The umbilical systolic-diastolic velocity ratios were also higher in the study population. Differences identified in the diameter of the ascending aorta were not consistent, and some of the Doppler velocity data were significantly different from normal controls when compared with one reference and not significantly different when compared with another reference. For noncardiac dimensions, the femur length was smaller and the biparietal diameter was larger in the fetuses of HIV-infected women; however, the weight, length, and head circumference at birth did not differ from those in the normal populations.¹⁴

Regarding the potential for interobserver variability, there was no significant difference between right and left ventricular diastolic dimensions and wall thicknesses measured by the 2 reviewers. The mean difference and SD in measurements for right and left ventricular diastolic dimension was 1.13 ± 2.2 mm ($P = .11$, ICC = 0.37) and 0.66 ± 1.3 mm ($P = .12$, ICC = 0.73), respectively, and for right and left ventricular wall thickness, 0.168 ± 0.63 mm ($P = .51$, ICC = 0.27) and 0.083 ± 0.38 mm ($P = .53$, ICC = 0.76), respectively. There was also no significant difference in measurements of the femur length (mean difference 0.050 ± 0.12 mm; $P = .36$; ICC = 0.99) and biparietal diameter (mean difference 0.69 ± 1.34 mm; $P = .16$; ICC = 0.97) between the 2 observers.

Discussion

Vertically transmitted HIV infection was not associated with significant alterations in any measure of cardiovascular structure and function in most second and third trimester fetuses except for left ventricular dimension. This may be the result of the timing of HIV transmission. Abnormalities of cardiovascular function associated with prenatally acquired HIV infection might not be expected, even in the early or middle third trimester, because most transmission is thought to occur perinatally.^{15,16} Additionally, the small number of HIV-infected infants with an adequate prenatal echocardiogram in our study may not be sufficient to show more subtle antenatal changes or trends in cardiovascular structure and function.

Fetuses of HIV-infected mothers

Our study found statistically significant differences in cardiovascular structure and function between normal fetuses and fetuses developing in HIV-infected mothers, regardless of their ultimate HIV status. The reason for the differences may be a result of maternal HIV infection, maternal risk factors, or selection bias in the external control data. Because of these limitations, the magnitude and the clinical importance of the observed differences are more difficult to interpret. Nevertheless fetuses of HIV-infected mothers had thicker right and left ventricular walls and lower biventricular fractional shortening, a lower heart rate, higher peak mitral A wave and mitral and tricuspid A/E wave ratios, higher right and left ventricular outflow velocities, and higher umbilical artery systolic-diastolic flow velocity ratios. Each of these differences was supported by comparing P²C²HIV study fetuses with data from 2 normal datasets.

The thicker ventricular walls in fetuses of HIV-infected mothers have also been observed in children with HIV infection.¹⁷ The thicker walls could be the result of increased circulating catecholamines or elevated placental vascular resistance, the latter suggested by the high umbilical systolic-diastolic blood flow velocities.^{11,18,19} The wall thickness may also be a secondary effect of altered circulating maternal factors, such as cytokines.^{20–22} Interleukin-1, for instance, which is elevated during HIV infection,²¹ induces hypertrophy of neonatal cardiomyocytes in vitro.²³

The low left and right ventricular shortening fractions in fetuses of HIV-infected mothers might also be the effect of circulating maternal cytokines, particularly tumor necrosis factor- α , interleukin-1 β , and interleukin-6, which are elevated in adult patients with HIV-associated cardiomyopathy, and that have been shown to have negative inotropic effects.²⁴ The abnormalities in ventricular function persist after birth; infants of HIV-infected mothers have been found to have reduced left ventricular shortening fractions and depressed contractility.²⁵

Blood flow velocity and heart rate abnormalities further suggest altered cardiovascular function in fetuses of HIV-infected mothers. The high ratio of peak late to early ventricular inflow velocities indicates abnormal biventricular diastolic function, possibly caused by the increased ventricular wall thickness. Although average heart rates were lower, a finding usually associated with a low peak A-wave velocity and low A/E wave ratio,⁸ in these

patients the A/E wave ratio was high, further supporting the interpretation that ventricular filling was abnormal.

Limitations

Study limitations arise from the control data used. The use of fetal data from other laboratories creates uncertainty related to interobserver variability, although we found no significant difference in cardiac dimensions between the 2 independent reviewers. The control samples of uninfected women represented populations different from the study population. Tan et al⁴ recruited mostly health care workers. Reed et al^{6,7} used subjects from an urban obstetrical program with many Native Americans. The inconsistencies we identified in some of the Doppler velocity data and the ascending aorta diameter may be attributable to differences in study populations. Maternal factors not controlled for, including socioeconomic status, availability of health care, living conditions, and race, could have played a role in the observed cardiovascular differences. These confounders limit certainty of our conclusions about the influence of maternal HIV infection on fetal cardiovascular structure and function. Additionally maternal HIV RNA data were not available. However, our findings do suggest that fetal cardiac structure and function may be altered in an abnormal intrauterine environment. A study of fetuses of mothers without HIV infection during pregnancy but at high risk of HIV infection would be necessary to distinguish conclusively between the effects of HIV infection and other potential risk factors in this population.

Recent rapid changes in HIV therapy, survival, and perinatal transmission rates in some countries may impose other limitations on this study. It is unknown how our study, conducted on fetuses of women whose primary HIV therapy was zidovudine, will generalize to fetuses of women taking highly active antiretroviral therapy. However, these costly drug regimens are available to only a minority of infected women, and infection rates among women continue to rise. In addition, in developed countries it is likely that the number of uninfected infants of HIV-infected mothers will grow, in part because of HIV therapy that is prolonging patients' life and health and because zidovudine and alternatives to breast feeding are reducing vertical transmission rates. Thus our results are likely to be applicable to a growing infant population.

Conclusion

Clinically important differences were not identified when fetuses who were postnatally identified as HIV-infected were compared with the HIV-uninfected cohort. Furthermore, our data suggest that fetuses of HIV-infected mothers may have altered cardiovascular structure and function and increased placental vascular resistance. These abnormalities may be the direct or indirect consequences of maternal HIV infection or of other maternal variables or study population differences.

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Appendix

A complete list of study participants can be found in reference 25.

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Figure 1.

Scatterplot and fitted regression lines from analysis of covariance of end-diastolic dimension (in millimeters) vs gestational age (weeks) for 15 HIV-infected fetuses (*solid line, solid circles*) and 78 HIV-uninfected fetuses (*dotted line, open circles*). *Dashed lines* are fitted regression line and 95% prediction intervals from 337 normal fetuses.⁵

Table 1

Descriptive statistics by HIV status for fetal echocardiogram measurements, controlling for gestational age with analysis of covariance

Measurement	Subgroup	n	Adjusted mean $\pm$ SEM*	P value	Equation	Mean square error
LV wall thickness (mm)	HIV-infected	18	3.61 $\pm$ 0.10	.28	$\hat{Y} + = 0.997 + 0.0789X$	0.185
	HIV-uninfected	89	3.74 $\pm$ 0.05		$\hat{Y} - = 1.120 + 0.0789X$	
RV wall thickness (mm)	HIV-infected	18	3.61 $\pm$ 0.12	.25	$\hat{Y} + = 0.357 + 0.0989X$	0.263
	HIV-uninfected	86	3.76 $\pm$ 0.06		$\hat{Y} - = 0.513 + 0.0989X$	
LV end-diastolic dimension (mm)	HIV-infected	15	11.5 $\pm$ 0.4	.01	$\hat{Y} + = -20.4 + 1.62X - 0.0195X^2$	2.75
	HIV-uninfected	78	12.7 $\pm$ 0.2		$\hat{Y} - = -19.2 + 1.62X - 0.0195X^2$	
RV end-diastolic dimension (mm)	HIV-infected	15	13.4 $\pm$ 0.5	.35	$\hat{Y} + = -13.8 + 1.35X - 0.0158X^2$	3.14
	HIV-uninfected	72	13.9 $\pm$ 0.2		$\hat{Y} - = -13.3 + 1.35X - 0.0158X^2$	
LV fractional shortening (%)	HIV-infected	15	25.1 $\pm$ 2.2	.31		0.00690
	HIV-uninfected	77	27.4 $\pm$ 0.6		$\hat{Y} + = -0.0200 + 0.0198X$	
RV fractional shortening (%)	HIV-infected	14	24.5 $\pm$ 1.5	.76	$\hat{Y} - = 0.0109 + 0.0198X$	0.0104
	HIV-uninfected	74	25.0 $\pm$ 0.7		$\hat{Y} + = 0.0519 + 0.0220X$	
Ascending aortic diameter (mm)	HIV-infected	18	0.63 $\pm$ 0.02	.67	$\hat{Y} - = 0.0499 + 0.0220X$	0.260
	HIV-uninfected	102	0.64 $\pm$ 0.01		$\hat{Y} + = -3.97 + 0.576X - 0.00607X^2$	
Main pulmonary artery diameter (mm)	HIV-infected	18	0.77 $\pm$ 0.02	.94	$\hat{Y} - = -4.03 + 0.576X - 0.00607X^2$	
	HIV-uninfected	106	0.77 $\pm$ 0.01			
Biparietal diameter (cm)	HIV-infected	19	8.33 $\pm$ 0.12	.66		
	HIV-uninfected	106	8.28 $\pm$ 0.05			

Measurement	Subgroup	n	Adjusted mean $\pm$ SEM*	P value	Equation	Mean square error
Femur length (mm)	HIV-infected	15	58.3 $\pm$ 1.3	.03	$\hat{Y} + = 15.3 + 1.31X$	24.6
	HIV-uninfected	75	61.6 $\pm$ 0.6		$\hat{Y} - = 18.5 + 1.31X$	
Umbilical systolic/diastolic velocity ratio	HIV-infected	21	2.95 $\pm$ 0.17	.67	$\hat{Y} + = 14.59 - 0.631X + 0.00831X^2$	0.565
	HIV-uninfected	106	3.03 $\pm$ 0.07		$\hat{Y} - = 14.67 - 0.631X + 0.00831X^2$	
MV peak A/E wave velocity	HIV-infected	18	1.40 $\pm$ 0.06	.92	$\hat{Y} + = 1.896 - 0.0151X$	0.0698
	HIV-uninfected	96	1.41 $\pm$ 0.03		$\hat{Y} - = 1.903 - 0.0151X$	
TV peak A/E wave velocity	HIV-infected	15	1.40 $\pm$ 0.07	.96	$\hat{Y} + = 2.05 - 0.0196X$	0.0702
	HIV-uninfected	85	1.40 $\pm$ 0.03		$\hat{Y} - = 2.05 - 0.0196X$	
Peak aortic velocity (m/s)	HIV-infected	18	0.92 $\pm$ 0.05	.81		
	HIV-uninfected	104	0.91 $\pm$ 0.02			
Peak pulmonary velocity (m/s)	HIV-infected	8	0.83 $\pm$ 0.05	.66		
	HIV-uninfected	83	0.86 $\pm$ 0.03			
Heart rate (beats/min)	HIV-infected	20	136 $\pm$ 1.8	.09		
	HIV-uninfected	10	140 $\pm$ 1.1			

* Mean is adjusted for gestational age for all measurements except left ventricular fractional shortening, right ventricular fractional shortening, heart rate, peak aortic velocity, and peak pulmonary velocity. LV, Left ventricular; RV, right ventricular; MV, mitral valve; TV, tricuspid valve; A, atrial systole; E, early ventricular diastole; X, gestational age in weeks; $\hat{Y} +$, fitted value from the regression for the HIV-infected subgroup; $\hat{Y} -$, fitted value from the regression for the HIV-uninfected subgroup.

Table II

References and regression analysis summary for normal control data

Measurement	n	Equation	Mean square error *	Intercept [#]	Slope [#]	Covariance [#]	Reference [†]
Cardiac and noncardiac dimension data							
LV wall thickness (cm)	100	$\hat{Y} = -0.214 + 0.0255X - 0.000295X^2$	0.00109				Tan et al ⁴ (a)
LV wall thickness (cm)	43 [‡]	$\hat{Y} = -0.362 + 0.104X$	0.0262				Hornberger (unpublished) (c)
RV wall thickness (cm)	100	$\hat{Y} = -0.232 + 0.0268X - 0.000316X^2$	0.00116				Tan et al ⁴ (a)
RV wall thickness (cm)	43 [‡]	$\hat{Y} = -0.326 + 0.103X$	0.0187				Hornberger (unpublished) (c)
LV end-diastolic dimension (cm)	100	$\hat{Y} = -0.948 + 0.109X - 0.00115X^2$	0.040				Tan et al ⁴ (a)
Log (LV dimension) [§]	337	$\hat{Y} = -3.48 + 0.208X - 0.00285X^2$	0.022				Sharland and Allan ⁵ (b)
RV end-diastolic dimension (cm)	100	$\hat{Y} = -0.987 + 0.108X - 0.00104X^2$	0.032				Tan et al ⁴ (a)
Log (RV dimension) [§]	337	$\hat{Y} = -3.28 + 0.186X - 0.00229X^2$	0.0214				Sharland and Allan ⁵ (b)
Ascending aortic diameter (cm)	45	$\hat{Y} = -0.052 + 0.020X$	0.00656				Tan et al ⁴ (a)
Log (ascending aortic diameter) [§]	298	$\hat{Y} = -2.29 + 0.0583X$	0.0255				Sharland and Allan ⁵ (b)
Main pulmonary artery diameter (cm)	84	$\hat{Y} = -0.152 + 0.0279X$	0.0121				Tan et al ⁴ (a)
Log (main pulmonary artery diameter) [§]	313	$\hat{Y} = -2.25 + 0.0605X$	0.0243				Sharland and Allan ⁵ (b)
Bipartietal diameter (cm)	533	$\hat{Y} = -2.34 + 0.367X - 0.0000449X^2$	0.0582				Hadlock et al ⁹ (d)
Femur length (mm)	338	$\hat{Y} = -39.3 + 4.38X - 0.0374X^2$	8.88				Hadlock et al ¹⁰ (e)
Doppler velocity data							
Umbilical systolic/diastolic velocity ratio	127	$\hat{Y} = 3.58 - 0.029X$	0.203				Schulman et al ¹¹ (f)

Measurement	n	Equation	Mean square error [*]	Intercept [#]	Slope [#]	Covariance [#]	Reference [†]
Heart rate (beats/min)	104	$\hat{Y}=158.5 - 0.483X$	87.5				Reed et al ⁷ (h)
Average period time (ms)	40 ^f	$\hat{Y}=380.2+1.33X$	484.0				Van der Mooren et al ⁸ (g)
Peak MV E-wave velocity (cm/s)	40 ^f	$\hat{Y}=34.4+0.758(X - 30)$	11.9	5.51	0.078	0.485	Van der Mooren et al ⁸ (g)
Peak MV E-wave velocity (cm/s)	106	$\hat{Y} = - 3.00+2.21X - 0.0356X^2$	32.3				Reed et al ⁷ (h)
Peak MV A-wave velocity (cm/s)	40 ^f	$\hat{Y}=47.4+0.17(X - 30)$	12.9	5.35	0.060	0.715	Van der Mooren et al ⁸ (g)
Peak MV A-wave velocity (cm/s)	106	$\hat{Y}=6.55+2.96X - 0.0574X^2$	57.4				Reed et al ⁷ (h)
Peak TV E-wave velocity (cm/s)	40 ^f	$\hat{Y}=39.6+0.852(X - 30)$	10.7	4.50	0.088	0.498	Van der Mooren et al ⁸ (g)
Peak TV E-wave velocity (cm/s)	102	$\hat{Y} = - 16.8+3.0268 - 0.0434X^2$	36.8				Reed et al ⁷ (h)
Peak TV A-wave velocity (cm/s)	40 ^f	$\hat{Y}=54.1+0.315(X - 30)$	12.6	3.85	0.062	0.453	Van der Mooren et al ⁸ (g)
Peak TV A-wave velocity (cm/s)	102	$\hat{Y} = - 0.676+3.19X - 0.0536X^2$	74.4				Reed et al ⁷ (h)
MV Peak A/E wave	106	$\hat{Y}=1.99 - 0.0194X$	0.0370				Reed et al ⁷ (h)
MV Peak E/A wave	40 ^f	$\hat{Y}=0.730+0.014(X - 30)$	0.00490	0.0011	0.000014	0.00017	Van der Mooren et al ⁸ (g)
TV Peak A/E wave	102	$\hat{Y}=1.93 - 0.0193X$	0.0181				Reed et al ⁷ (h)
TV Peak E/A wave	40 ^f	$\hat{Y}=0.744+0.0132(X - 30)$	0.00221	0.0006	0.0000024	0.00000	Van der Mooren et al ⁸ (g)
Peak aortic velocity (cm/s)	40 ^f	$\hat{Y}=74.8+1.35(X - 30)$	21.8	13.95	0.077	1.215	Van der Mooren et al ⁸ (g)
Peak pulmonary velocity (cm/s)	40 ^f	$\hat{Y}=60.1+1.19(X - 30)$	10.4	6.88	0.05	90.921	Van der Mooren et al ⁸ (g)

Abbreviations as in Table I.

* Mean square error is the residual variance estimate (ie, the variance among fetuses all having the same value of X).

[†]The letter in parentheses after the reference number corresponds with Table III to identify the source of normal control data.

[‡] 43 pregnancies with 92 echocardiograms. The between-fetus variance estimate is 0.00374 for left ventricular wall thickness and 0.00605 for right ventricular wall thickness.

[§] Natural logarithmic transformation performed before fitting the regression model.

[#] Variance Estimates of the Random Effects.

[¶] 40 pregnancies with 233 echocardiograms.

z Scores for fetal echocardiogram measurements among 173 fetuses of HIV-infected women compared with fetuses developing in mothers without HIV

Table III

	n	Mean ± SEM for P ² C ² HIV data [*]	Mean <i>z</i> score [†]	SD	Median <i>z</i> score	<i>P</i> value
Cardiac and noncardiac dimensions						
LV wall thickness (mm)	114	3.70 ± 0.04	1.99 (a)	1.3	1.97	<.001
			3.70 (c)	2.6	3.80	<.001
RV wall thickness (mm)	111	3.73 ± 0.05	2.06 (a)	1.5	1.80	<.001
			4.35 (c)	3.2	4.32	<.001
LV end-diastolic dimension (mm)	98	12.5 ± 0.2	-0.61 (a)	0.9	-0.71	<.001
			-0.09 (b)	0.9	-0.08	.34
RV end-diastolic dimension (mm)	91	13.9 ± 0.2	-0.18 (a)	1.0	-0.12	.12
			-0.24 (b)	1.0	-0.23	.03
LV fractional shortening (%)	97	27.1 ± 0.62	-3.42	3.2	-3.42	<.001
RV fractional shortening (%)	91	25.0 ± 0.64	-3.25	2.6	-3.47	<.001
Ascending aortic diameter (mm)	129	0.64 ± 0.01	0.36 (a)	1.0	0.28	<.001
			-0.54 (b)	1.0	-0.51	<.001
Main pulmonary artery diameter (mm)	133	0.77 ± 0.01	0.07 (a)	0.9	-0.01	.66
			-0.07 (b)	1.1	-0.11	.40
Biparietal diameter (cm)	135	8.26 ± 0.04	0.79 (d)	2.3	0.61	<.001
Femur length (mm)	97	60.8 ± 0.5	-0.94 (e)	1.9	-1.13	<.001
Doppler velocity data						
Umbilical systolic/diastolic velocity ratio	135	3.03 ± 0.07	0.88 (f)	1.8	0.46	<.001
Heart rate (beats/min)	138	140 ± 0.9	-0.30 (h)	1.1	-0.19	.004
Average period time (ms)	138	432 ± 2.9	0.36 (g)	1.5	0.12	.04
Peak MV E-wave velocity (cm/s)	123	38.1 ± 0.9	1.31 (h)	1.8	1.07	<.001
			0.32 (g)	2.2	0.05	.34
Peak MV A-wave velocity (cm/s)	123	52.0 ± 0.8	1.40 (h)	1.3	1.15	<.001
			0.85 (g)	1.9	0.84	<.001
Peak TV E-wave velocity (cm/s)	115	41.8 ± 1.2	1.07 (h)	2.1	0.75	<.001
			-0.03 (g)	2.9	-0.40	.16
Peak TV A-wave velocity (cm/s)	112	55.1 ± 1.0	1.08 (h)	1.2	1.08	<.001

	n	Mean $\pm$ SEM for P ² C ² HIV data [*]	Mean z score [†]	SD	Median z score	P value
MV peak A/E wave velocity	123	1.41 $\pm$ 0.02	0.03 (g)	2.3	0.11	.87
MV peak E/A wave velocity	123	0.74 $\pm$ 0.01	0.26 (h)	1.3	0.17	.05
TV peak A/E wave velocity	105	1.41 $\pm$ 0.03	-0.39 (g)	1.9	-0.60	<.001
TV peak E/A wave velocity	105	0.74 $\pm$ 0.02	0.78 (h)	2.0	0.50	<.001
Peak aortic velocity (m/s)	131	0.90 $\pm$ 0.02	-0.68 (g)	3.5	-0.87	<.001
			1.23	1.2	1.22	<.001
			1.83 (g)	2.8	1.53	<.001
Peak pulmonary velocity (m/s)	97	0.86 $\pm$ 0.02	1.96	1.7	1.58	<.001
			5.14 (g)	5.6	3.92	<.001

Abbreviations as in Table I.

^{*}Mean $\pm$ SEM for P²C²HIV study subjects. The mean is adjusted for gestational age for all measurements except left ventricular fractional shortening, right ventricular fractional shortening, heart rate, peak aortic velocity, and peak pulmonary velocity.

[†]The letter in parentheses after the mean z score identifies the source of normal control data, as detailed in Table II. The normal control data are from Reed et al⁶ (peak aortic velocity: mean = 0.71, SD = 0.15, n = 88; peak pulmonary velocity: mean = 0.60, SD = 0.13, n = 115) and Rasanen and Kirkinen¹² (left ventricular fractional shortening: mean = 33.5%, SD = 1.88, n = 51; RV fractional shortening: mean = 32.6%, SD = 2.35, n = 51).