Significance of cardiac defects in the developing fetus: a study of spontaneous abortuses

PHILIP C. URSELL, M.D., JULIANNE M. BYRNE, PH.D.,* AND BARBARA A. STROBINO, PH.D.

ABSTRACT We investigated the impact of heart defects on the developing human fetus by examining 412 hearts from consecutive spontaneous abortuses. In each case, the cardiac morphology was correlated with the autopsy findings and the karyotype (unavailable in 115 hearts not successfully cultured). Of the 412 hearts, 10 (2.4%) contained structural defects (six ventricular septal defects, one atrial septal defect with ventricular septal defect, and one coarctation, atroventricular septal defect, and tetralogy of Fallot). Only one of 10 had major extracardiac malformations. Of the 277 fetuses with normal karyotype, three (1.1%) had heart defects. Of the 20 fetuses with abnormal karyotype, four (20%) had heart defects. In the remaining three fetuses with heart defects, the karyotype was not obtained. Thus (1) 57% of spontaneous abortuses with congenital heart defects contained major chromosomal abnormalities, (2) the spectrum of heart defects among spontaneous abortuses was similar to that among liveborns, and (3) since the prevalence of heart defects among fetuses without other major abnormalities was similar to that among liveborns, heart defects alone may not jeopardize the survival of a developing fetus. Circulation 72, No. 6, 1232–1236, 1985.

THE SIGNIFICANCE of heart defects in the developing fetus is uncertain. Major structural malformations of the heart that cause shunting and/or obstruction could be detrimental to the fetus. Studies have documented a higher prevalence of heart defects among stillborn infants than among liveborns.1-3 However, it has never been clear from such studies whether the heart defect per se was responsible for death. In this regard, physiologic studies performed in animal preparations suggest that cardiac defects have little effect in utero.4 Thus, cardiac defects may be a part of some other abnormal developmental process that results in death of the fetus.

We investigated the impact of heart defects on the developing human fetus by examining hearts from consecutive spontaneous abortuses. Analysis of the products of conception from spontaneous abortions provides an efficient means of evaluating the importance of morphologic and chromosomal anomalies to the survival of the fetus.5 We correlated the cardiac pathology in each case with the karyotype and pathology manifest in the remainder of the fetus. Our objectives in this study were (1) to determine the prevalence and nature of cardiac defects among spontaneously aborted fetuses, and (2) to develop insight into the significance of these defects in the developing fetus.

Materials and methods

Hearts examined in this study were obtained from a large epidemiology-cytopathological-pathology study of consecutive spontaneous abortions identified at three New York City hospitals between 1976 and 1983. Approximately 4000 specimens were examined as a part of the larger study. However, because most products of conception from spontaneous abortions do not contain an organized fetus6 and some hearts are not large enough to study, only 412 hearts could be eviscerated and subsequently examined. In each of the 412 cases, a complete autopsy of the fetus and placenta was performed.7 Developmental age was determined by crown-rump length.8 Histologic sections of the major organs, placenta, and umbilical cord were examined. The hearts were from relatively nonmacerated fetuses from 8 to 28 weeks of gestation. They were preserved in formaldehyde for subsequent study.

Dissection of the hearts was performed according to standard autopsy techniques. Each heart was opened along the path of blood flow. All observations and measurements were made under 10-fold magnification with a dissecting microscope. Measurements of the circumference of valve annuli and the aorta at the isthmus were made with a small flexible ruler or with a...
PATHOPHYSIOLOGY AND NATURAL HISTORY—CONGENITAL HEART DISEASE

piece of thread and the ruler. The morphologic characteristics of these fetal hearts were described according to the scheme of Tynan et al. A heart defect was defined as any developmental malformation of cardiac structure (and proximal great vessels) that is known to be attended by significant morbidity after birth. In addition to clear-cut abnormalities such as septal defects, more subtle changes due to relative stenoses or dilatations were judged to be true defects if measurements were more than two standard deviations from the mean of those of the normal hearts in the corresponding developmental age range. A secundum atrial septal defect was diagnosed if the untorn primum membrane covered less than one-half of the fossa ovalis. Although all ductus arteriosus vessels were patent, histologic inspection of ductal tissue was not performed.

Karyotypes were determined by tissue culture of fetal tissue and subsequent staining by the G-banding method as described previously. A fetal karyotype was determined from 297 (72%) of the 412 specimens. In the remaining 115 hearts either no fetal tissue was set up in culture, or the specimen was set up but failed to grow.

A chi-square test was used to determine the significance of associations.

Results

The distribution of developmental ages of the 412 fetuses included in this study is shown in figure 1. Of the 412 hearts, 10 (2.4%) contained structural defects. The developmental age, type of defect, karyotype, and other accompanying major malformations are listed for each abortus with a heart defect in table 1. The developmental age of the youngest of the fetuses was 11 weeks, well beyond the period when cardiac morphogenesis is complete.

Ventricular septal defect was the most common cardiac anomaly among the 10 fetuses with heart defects. In each of the six cases of isolated ventricular septal defect, the defect was perimembranous and the diameters of the defects ranged from 50% to 100% of the diameter of the corresponding aortic valve anulus (figure 2). In one other case of ventricular septal defect there was a wide defect of the midportion of the interatrial septum with virtually no membrane covering it. Coarctation of the aorta was diagnosed in one heart in which the circumference of the aorta at the isthmus fell two standard deviations below the mean for fetuses of similar developmental age. There was no discrete "shelf" present in the aorta at the level of the ductus, but the distal portion of the aortic segment between the left subclavian artery and the ductus contained several irregular ridges of tissue that compromised the lumen. The coarctation was present in association with a bicuspid aortic valve. This association is seen in liveborns. Only two of the 10 hearts showed complicated lesions: atrioventricular septal defect and tetralogy of Fallot (figure 3). There were no cases of more complex heart defects. Other major malformations were present in only one of the 10 fetuses with heart defects. This fetus had hydrocephalus and lung hypoplasia.

Karyotypes were documented in 297 fetuses; 277 were normal and 20 were abnormal. Of the 277 fetuses with normal karyotype, three (1.1%; 95% confidence limits 0.0% to 2.3%) had heart defects. Of the 20 fetuses with abnormal karyotype, four (20%; 95% confidence limits 2.5% to 37.5%) had heart defects. Thus, although the numbers are small, heart defects were more common in chromosomally abnormal than in chromosomally normal fetuses ($\chi^2 = 21.4, p < .001$). As shown in table 1, the chromosomal anomalies included trisomy 21, trisomy 3 with a normal cell line, and two cases of triploidy.

![FIGURE 1](http://circ.ahajournals.org/)

**FIGURE 1.** Histogram showing the distribution of developmental ages of fetuses from which hearts were obtained for this study. An asterisk denotes a fetus with a cardiac defect.

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<th>Table 1 Fetal characteristics</th>
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<td><strong>Fetus developmental age (weeks)</strong></td>
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VSD = ventricular septal defect; AVSD = atrioventricular septal defect; ASD-2° = ostium secundum-type atrial septal defect; BAV = bicuspid aortic valve; + = hydrocephalus and hypoplastic lungs present.
two series may be impossible for several reasons. First, although “unselected,” the British series of hearts may not have been derived from consecutive spontaneous abortions, as ours was. In any epidemiologic study, careful control over inclusion of specimens (preferably at one institution) is critical to ensure an unbiased sample. Second, although cardiac malformation is not specifically defined, the British series included hearts with several minor malformations, such as bilateral superior caval veins and pericardial defects, which were excluded in our series. On the other hand, there is a preponderance of relatively complex cardiac defects — such as valve atresias, transpositions and double-outlet ventricles — in the British series. It is unlikely that histologic analysis (a difference between the two studies) would have yielded many more cardiac malformations in our series, since these structural defects are readily identifiable grossly under the dissecting microscope. By not examining tissue histologically, we may have missed abnormal ductus tissue, a precursor for patent ductus arteriosus. However, from the report it appears that ductus tissue

FIGURE 2. Under the dissecting microscopic, a perimembranous ventricular septal defect (arrows) is easily appreciated directly inferior to the aortic valve (V). The defect occupies roughly 10% of the septal surface (S), and the diameter of the defect is 50% of the diameter of the aortic valve anulus.

Discussion

Several studies of stillborn infants have determined the prevalence of cardiovascular defects to be in the range of 1.2% to 5.4%. Our finding of heart defects in 2.4% of spontaneous abortuses of developmental ages 8 to 28 weeks is in accord with these other studies. It is important to recognize, however, that these prevalence figures include fetuses with heart defects and possibly other major malformations or chromosomal abnormalities. Thus, conclusions as to the effect of heart defects alone on the developing fetus should not be made from these data.

Recently, a series of cardiac malformations in spontaneous abortions has been published by Gerlis. Using standard autopsy dissection techniques on larger hearts as well as histologic examination of small hearts, he found the prevalence of cardiac defects to be 15.4% within the gestational age range examined (less than 24 weeks). While this prevalence is considerably higher than what we found, a direct comparison of the

FIGURE 3. The anatomy of tetralogy of Fallot is clearly evident in this view from the opened right ventricle (V). The ventricular septal defect (arrow) is present directly anterior to the tricuspid valve (T) and is separated from the stenotic infundibulum (i) by the conal septum.
was not examined in the British study either, and so this cannot explain the discrepancy in prevalence rates found in the two studies. Instead, we suspect that the British series does not reflect the entire population of spontaneous abortuses — that the heart specimens were unwittingly selected by the referring hospitals for examination by the cardiac pathologist. That cardiac malformations are not so common among spontaneous abortuses in Great Britain is supported by another study in which the prevalence was found to be 0.4%. Problems such as inadvertent introduction of a bias, different observers, and varying definitions of terms commonly plague epidemiologic studies and often make direct comparison difficult.

We have attempted to focus on the significance of cardiac disease in the fetus by separating out fetuses with other conditions that may jeopardize survival. It is generally accepted that certain anatomic malformations are detrimental to the developing fetus, although there are scant data in support of this. For example, an increased frequency of malformation of the central nervous system among spontaneous abortuses has been reported, suggesting that these defects are detrimental in utero. Certain other major malformations may also be harmful to the fetus. In our study, only one fetus with cardiac defects had other major malformations, but it also had an abnormal karyotype.

In contrast to gross structural malformations, chromosomal anomalies were more common in fetuses with heart defects (57.1%), in excess of their frequency among fetuses without heart defects (5.5%) (p < .001). The association of heart defects with specific chromosomal anomalies is well known. Trisomy 21 is associated with a 53% frequency of congenital heart disease, while trisomy 13 and trisomy 18 are associated with even higher frequencies of 83% and 95%, respectively. In addition to one case of trisomy 21 with ventricular septal defect, within our group of fetuses with heart defects there were two examples of triploidy with ventricular septal defect. A variety of heart defects, including ventricular septal defects, has been reported in stillbirths and infants with triploid karyotype. The precise manner by which extra chromosomes lead to heart defects has never been determined. Nevertheless, clinically it is important to recognize that a high percentage of patients with heart defects (liveborn infants as well as fetuses) has chromosomal abnormalities, a factor that may influence the prognosis.

In the present study of spontaneous abortuses, three of 277 (1.1%) fetuses with normal karyotypes had heart defects. As best we can determine by our methods (complete autopsy and documentation of karyotype), these three demonstrate no other significant disease processes. In studies of stillborn infants and neonates, the autopsy, including gross and histologic examination, and the determination of karyotype appear sufficient to detect the great majority of abnormalities. We believe that the same should be true for fetuses. However, it is possible that in our study subtle abnormalities were not discovered. For example, cardiac arrhythmias contributing to fetal demise would not have been detected. In this regard, histology of the conduction system may provide clues as to functional abnormality (such as complete heart block), but other more sophisticated techniques would be required to document the dysfunction.

Many investigations have addressed the question of the prevalence of congenital heart defects among liveborn infants. Although the results vary widely (in part due to the variety of investigative techniques), most intensive studies show the true prevalence of congenital heart defects, excluding bicuspid aortic valve, to approach 1%. We have used this figure from the literature as a basis for comparison in the present study. That this prevalence among liveborns is similar to what we found among our population of chromosomally normal spontaneous abortions suggests that heart defects per se may not jeopardize the survival of the developing fetus within the developmental age range studied.

In autopsy series such as ours, associations may be established but conclusions as to cause and effect may not follow. For example, the association between cardiac defects and abnormal karyotype emphasizes that other abnormal developmental processes may be present in fetuses with defects. Even in those fetuses with cardiac defects and normal karyotype, an unknown process (for which heart defects may or may not be a marker) may be operant. In those with a normal karyotype, minor chromosomal alterations beyond the resolution of current techniques may be present and affect cardiac development. Similar alterations can be expected to adversely affect the entire developing fetus. Clearly, genetics is a critical influence in cardiac and general fetal development, but environment may be equally, if not more, important. Unfortunately, specific environmental teratogens are difficult to identify. Environmental risk factors associated with spontaneous abortion include cigarette smoking, fever, and alcohol consumption by the mother during pregnancy. The latter is associated with a syndrome that may include heart defects. Ultimately, the interaction between genetics and environment may be most im-

Vol. 72, No. 6, December 1985

1235
important not only in cardiac morphogenesis but also general fetal development. In light of the above, the British study\textsuperscript{12} appears incomplete: neither a complete autopsy nor karyotyping was done on the spontaneous abortuses. Without more complete data it is difficult to evaluate the significance of the cardiac defects in developing fetuses. Thus, the statement made in the accompanying editorial\textsuperscript{31} that in some cases the heart defect itself leads to fetal loss appears to be a hasty conclusion. Our data suggest that this is not true.

The conclusion that the impact of heart defects on the fetus may be minimal has been derived from physiologic studies performed in a sheep preparation during the last one-half of gestation.\textsuperscript{4} Because of the nature of the circulation in the fetus, pressures and oxygenation in the four chambers of the fetal heart are relatively homogeneous. Thus, most lesions resulting in abnormal shunting and/or obstruction may be expected to have minimal effect. One abnormality, constriction of the ductus arteriosus in utero, may affect the developing fetus by diminishing blood return to the placenta.\textsuperscript{4} We did not find this lesion among any of our specimens.

It is possible, although unlikely, that more complex heart malformations adversely affect the survival of the fetus. Since we did not identify any such lesions among the spontaneous abortuses, our data neither support nor refute this thesis. In light of the rarity of complex cardiac defects, an epidemiologic analysis would require much larger numbers than those provided by our study.

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References
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