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Results of chromosomal analysis in fetuses with cardiac anomalies as diagnosed by first- and early second-trimester echocardiography

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ABSTRACT

Chromosomal analyses were performed in 36 fetuses with cardiac anomalies diagnosed by echocardiography at 11 + 1 to 15 + 6 weeks of gestation. Karyotyping was successful in 35 cases and 17 (48.6%) had anomalies, including five with Turner's syndrome, seven with trisomy 18, four with trisomy 21 and one with triploidy. The commonest cardiac anomaly observed in trisomy 21 was a complete atrioventricular canal; in trisomy 18 was ventricular septal defect; in Turner's syndrome was a hypoplastic aortic arch in combination with hypoplasia of the left ventricle and left ventricular outflow tract; and in the case of triploidy was a ventricular septal defect. These findings confirm the opinion that, in fetuses with chromosomal anomalies, there is a high incidence of cardiac defects. Furthermore, there is a distinct pattern of cardiac defects associated with each chromosomal anomaly.

INTRODUCTION

High-frequency vaginal ultrasound probes with high resolution enable a detailed identification to be made of the cardiac chambers and in some cases atrioventricular valvular leaflets from the 10th week of gestation[1,2]. Detailed investigation of fetal cardiac anatomy performed in a segmental approach is feasible from 13 weeks of gestation onwards[2–6]. Color-coded Doppler complements classical two-dimensional echocardiography in the first trimester as it especially facilitates demonstration of veins and arteries. This makes visualization of intracardiac blood flow and thus the detection of valvular insufficiencies and stenoses possible[2]. Furthermore, in the presence of complex malformations, diagnostic accuracy and speed of diagnosis are greatly enhanced.

Cardiac defects diagnosed at birth are often associated with chromosomal anomalies[7,8]. Owing to the subsequent high spontaneous abortion rate, the incidence of the latter is even higher in the second trimester of pregnancy[8,9]. An even higher incidence of cardiac anomalies and chromosomal aberrations is thus to be expected in the first trimester[10]. However, this rate is influenced by the referral rate to a particular center and the estimate may be falsely high if the examined patient group includes mainly fetuses with non-immune hydrops, extracardiac malformations and early intrauterine growth restriction.

The aims of this study were to examine the frequency of chromosomal anomalies in fetuses with a cardiac anomaly and to study the diagnostic accuracy of early detection of these cardiac malformations associated with a chromosomal anomaly.

MATERIALS AND METHODS

From January 1990 to January 1996, cardiac anomalies were detected in 36 fetuses by early fetal echocardiography performed between 10 and 15 weeks' gestation. Gestational age was verified by last menstrual period and a compatible crown–rump length measurement. Indications for referral were abnormal sonographic findings in all cases: nuchal edema (n = 1), hygroma colli (n = 2), generalized hydrops (n = 8), brain, abdominal wall or urinary tract defects (n = 6). We used a 5.0-MHz real-time vaginal probe (Acuson 128 XP/10ob, Mountain View, California) and in some cases a high-resolution 5.0-MHz sector probe for an additional transabdominal scan. All scans were performed before karyotyping and the examination was considered complete when the four-chamber view (showing both atria and ventricles and atrioventricular valves), the outflow tracts and the crossing of the great arteries were visualized.

Chromosomal analysis was performed using standard techniques after chorion villus sampling or amniocentesis.

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If termination of pregnancy was indicated, induction was performed by vaginal prostaglandin suppositories allowing gentle extraction and preservation of the fetus. Pathological specimens were examined under stereomicroscopic guidance for verification of the prenatal diagnosis.

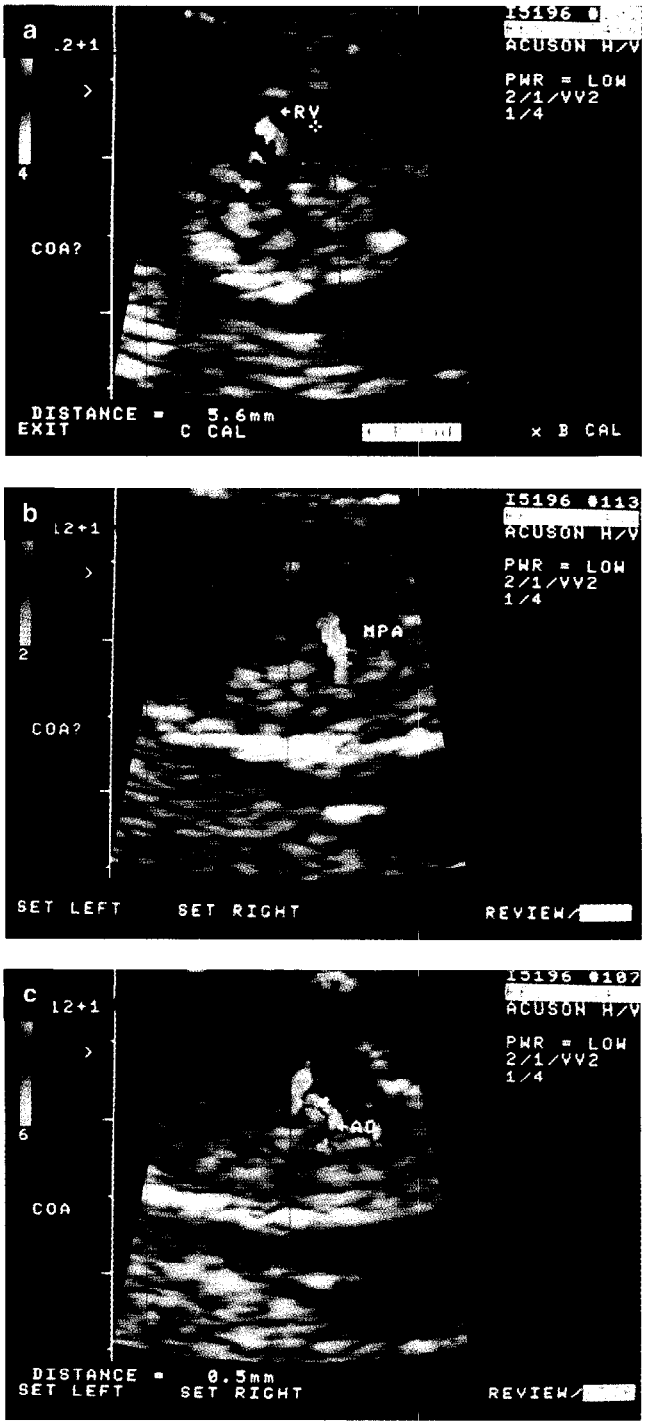
RESULTS

The fetal karyotype was abnormal in 17 cases (Table 1). Fetal echocardiography revealed an atrioventricular septal defect (AVSD) in five cases and in three of these there was holosystolic atrioventricular valvular regurgitation (Figure 1); four of these had trisomy 21; one had trisomy 18. A ventricular septal defect (VSD) was present in six cases; five of these had trisomy 18 and one had triploidy. Four VSDs were diagnosed correctly, but, in two cases with trisomy 18, the diagnosis was missed. In one case (case 9) a VSD was suspected at 12 + 3 weeks' gestation but could not be diagnosed with certainty. Tricuspid regurgitation was demonstrated in both cases of VSD in whom the diagnosis was missed (cases 6 and 9). A tetralogy of Fallot with a dilated overriding aorta was correctly diagnosed at 14 + 5 weeks' gestation in one fetus with trisomy 18 (case 11). Coarctation of the aorta was correctly diagnosed in two cases with Turner's syndrome (Figure 2). In both cases, forward flow through the entire aorta was demonstrated by Doppler sonography. In three other cases with Turner's syndrome, there was hypoplasia of the aortic arch and the ascending aorta which was verified by Doppler sonography by the lack of forward flow through these vessels. These three cases also had a hypoplastic left heart associated with endocardial fibroelastosis in two cases evident at 14 + 4 and 15 + 6 weeks' gestation (cases 12 and 15), respectively.

Table 1 Indication for examination, gestational age and results of fetal echocardiography as well as sonographically detected associated anomalies with results of pathological examination in 17 fetuses with karyotype abnormalities

Case	*Gestational age* (weeks + days)	*Indication for echocardiography*	*Result of echocardiography*	*Associated anomaly*	*Karyotype*	*Cardiac finding at autopsy*
1	11 + 4	generalized edema	AVSD, holosystolic AV valve regurgitation		47,XX,+21	AVSD (type A)
2	14 + 2	generalized edema	AVSD		47,XX,+21	AVSD (type A)
3	15 + 0	bilateral hydronephrosis	AVSD	bilateral hydronephrosis	47,XY,+21	AVSD (type C), LPSCV, moderate CoA
4	13 + 1	hygroma colli	AVSD, holosystolic AV valve regurgitation	hygroma colli, generalized edema	47,XY,+21	AVSD (type A)
5	14 + 4	generalized edema, IUGR	perimembranous VSD		47,XX,+18	perimembranous VSD
6	15 + 2	NIHF	holosytolic TR		47,XY,+18	outlet VSD
7	15 + 5	megacystis	VSD	micrognathia, SUA, megacystis, pleural effusion	47,XY,+18	outlet VSD
8	14 + 2	omphalocele	VSD	omphalocele	47,XY,+18	perimembranous VSD
9	12 + 3	NIHF	early systolic TR, (? outlet VSD)	generalized edema, IUGR	47,XX,+18	outlet VSD
10	14 + 0	megacystis	AVSD, holosystolic AV valve regurgitation	megacystis, SUA, IUGR	47,XY,+18	AVSD (type A) and one muscular VSD
11	14 + 5	megacystis, omphalocele	TOF	megacystis, omphalocele, SUA	47,XY,+18	TOF
12	14 + 5	NIHF, hygroma colli	HLH with LV-EFE, hypoplastic aorta and CoA, no forward flow in AAO		45,X	HLH, LV-EFE, hypoplastic AAO and aortic arch, LPSCV
13	16 + 0	NIHF, hygroma colli	CoA, small LV and aorta		45,X	moderate CoA, ASD (type II)
14	12 + 1	hygroma colli	tubular CoA		45,X	tubular CoA
15	15 + 6	hygroma colli	HLH and LV-EFE, hypoplastic aorta and CoA, no forward flow in AAO		45,X	HLH, LV-EFE, hypoplastic AAO and aortic arch
16	11 + 3	hygroma colli, NIHF	tubular CoA, hypoplastic AAO, small LV, no forward flow in AAO	SUA	45,X	tubular CoA, hypoplastic AAO and aortic arch, hypoplastic LV
17	14 + 6	hydrocephalus	VSD	holoprosencephaly, IUGR	69,XXY	VSD

AAO, ascending aorta; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; EFE, endocardial fibroelastosis; HLH, hypoplastic left heart; IUGR, intrauterine growth restriction; LA, left atrium; LPSCV, left persistent superior caval vein; LV, left ventricle; NIHF, non-immune hydrops fetalis; RA, right atrium; SUA, single umbilical artery; TR, tricuspid regurgitation; TOF, tetralogy of Fallot; VSD, ventricular septal defect. The classification of common AVSD of complete type was subdivided into three types (A, B and C) according to the classification of Rastelli and colleagues[36]



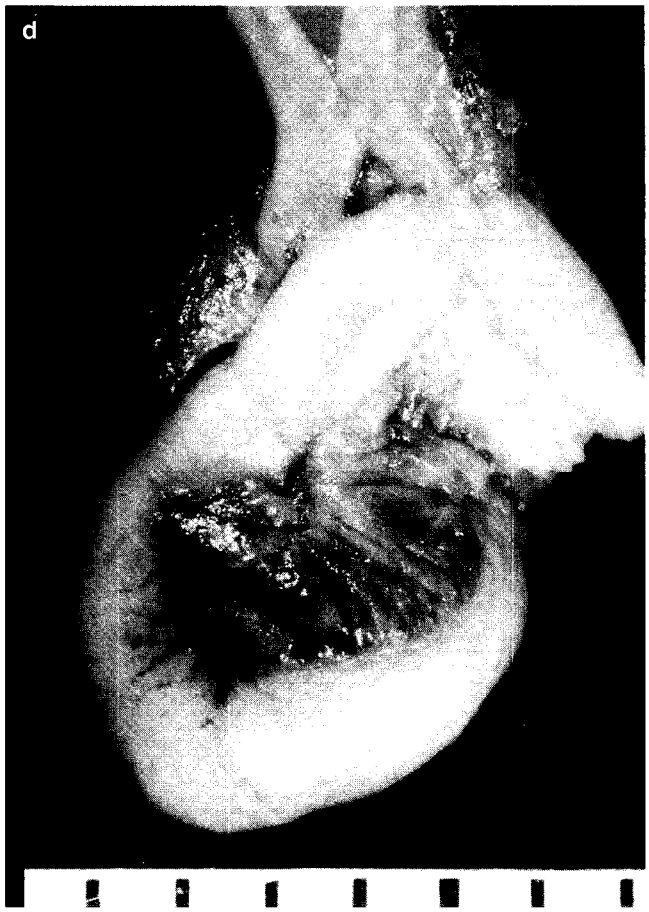


Figure 1 Coarctation of the aorta at 12 + 1 weeks' gestation (case 14). (a) A marked size difference between the two ventricles is demonstrated in the four-chamber view. The inflow into both ventricles is coded in red. (b) The blood flow in the normally developed main pulmonary artery (MPA; 1.1 mm in diameter) is visualized by color-coded Doppler sonography in the short-axis view (coded in blue). (c) The aortic arch (AO) is markedly hypoplastic (diameter 0.5 mm). Color-coded Doppler sonography shows acceleration of blood flow velocities with aliasing. The origin of two vessels supplying the head and neck can be seen as well. The left subclavian artery originates distally to the coarctation (coded in blue). (d) Stereomicroscopic picture of the fetal heart ($5 \times 6 \times 4.5$ mm^3) viewed from the left shows a relatively small ascending aorta and tubular hypoplasia of the transverse arch, the broad pulmonary trunk and ductus arteriosus. The ascending aorta is normal in diameter. The origin of the left subclavian artery is near the aortic ostium of the ductus arteriosus (not visible)

All four fetuses with trisomy 21 had an AVSD. Six fetuses with trisomy 18 had a VSD, in one case as part of the tetralogy of Fallot. One case had an AVSD with an additional muscular VSD. All cases with Turner's syndrome had tubular coarctation of the aorta. In the case of triploidy, a VSD was present.

Stereomicroscopic examination of the heart confirmed the echocardiographic findings in 14 of 17 cases. In two cases of trisomy 18, however, an outlet VSD was demonstrated only by autopsy (cases 6 and 9). In another case with trisomy 18 (case 10), the AVSD was correctly diagnosed prenatally but an additional muscular VSD was missed.

DISCUSSION

Congenital heart disease is common, occurring in 0.4–1.0% of live births[11], and is often associated with malformations of other organ systems. Of infants with congenital heart disease registered between 1981 and 1989 in the Baltimore–Washington infant study, 27.7% had non-cardiac malformations and almost one-half of these (11.9% of the total) had chromosomal defects[7]. Taking the high lethality of chromosomal anomalies into account, their incidence is much higher in midtrimester fetuses in general and especially in the series of fetuses with cardiac anomalies[8]. This has also been confirmed in series of

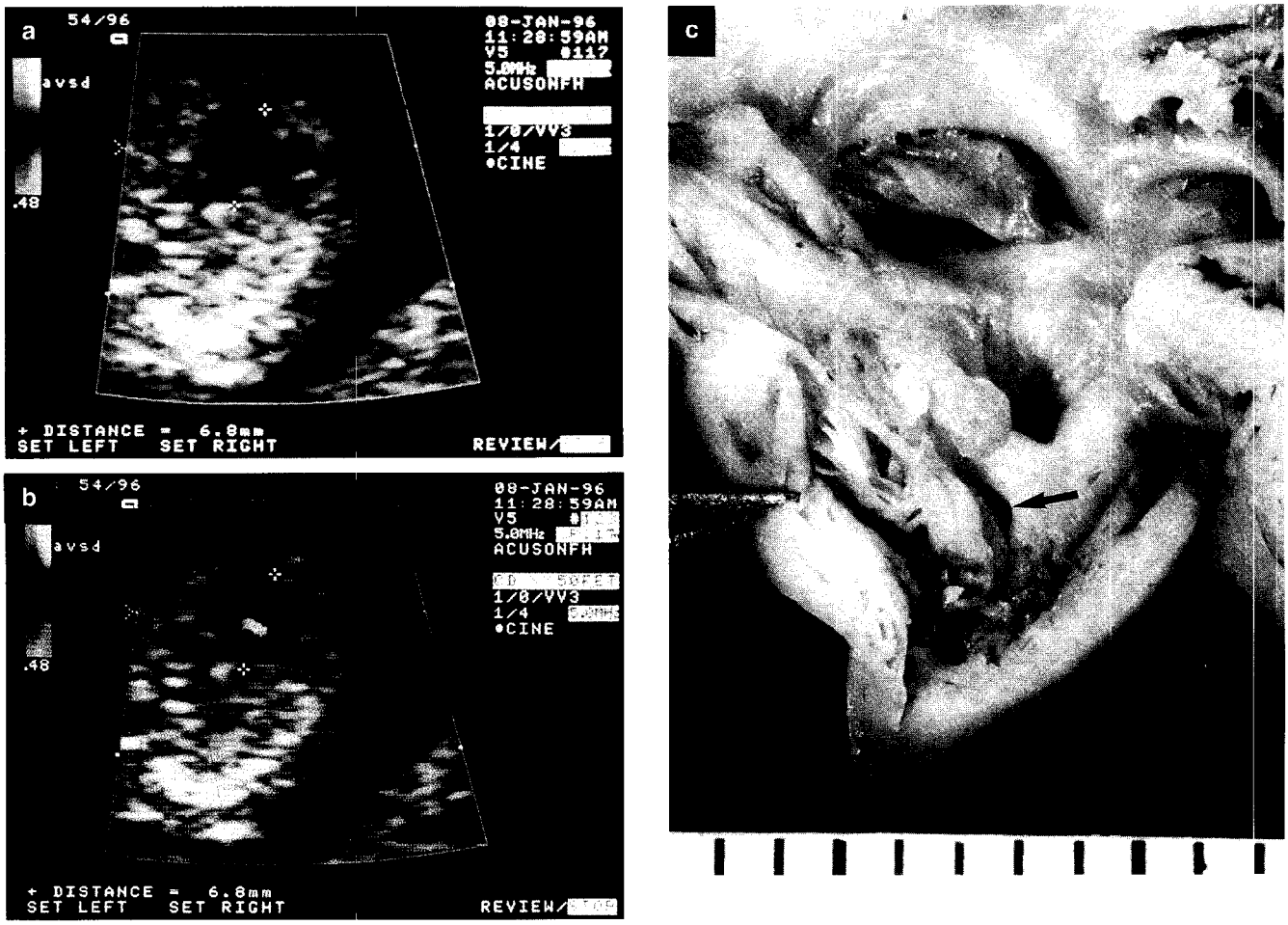


Figure 2 Atrioventricular septal defect (AVSD) in a case with trisomy 18 at 14 + 0 weeks' gestation (case 10). (a) The AVSD is clearly demonstrated by two-dimensional echocardiography in the four-chamber view (atrioventricular diameter of 6.8 mm is marked by the crosses). (b) Holosystolic atrioventricular valvular regurgitation identified by color-coded Doppler sonography. The maximal jet velocity was 2.08 m/s. (c) Stereomicroscopic picture of the fetal heart ($10.5 \times 9 \times 6.5$ mm^3) opened anteriorly through the right atrium and ventricle shows fenestration of the large septum ovale and complete AVSD (type A, according to the anatomical classification of Rastelli and colleagues[36]). The anterior common leaflet is committed almost entirely to the left ventricle and exhibits minimal bridging over the crest of the interventricular septum (on the right side). Below the posterior bridging leaflet there is an additional small muscular ventricular septal defect (arrow)

fetuses with prenatally diagnosed cardiac anomalies which exhibited chromosomal anomalies in 15–50% of cases[12–16]. The very high spontaneous loss rate in fetuses with chromosomal anomalies between 9 and 14 weeks' gestation[10] suggests an even higher rate of chromosomal anomalies in first-trimester fetuses with congenital heart disease. In a series predominantly composed of low-risk pregnancies examined at 12–16 weeks' gestation, 62% of the 47 fetuses with a heart defect had associated extracardiac anomalies and the frequency of chromosomal anomalies was 36%[5]. In our series, 17 of the 36 fetuses with early diagnosed heart defects had chromosomal anomalies and additional anomalies were present in all cases. This may be due to the fact that the extracardiac anomaly was the indication for echocardiography in all cases with chromosomal anomalies. On the one hand, these included nuchal edema, hygroma colli and hydrops which are typical markers of chromosomal anomalies during first-trimester screening[17,18] and, on the other hand, they included malformations such as omphalocele and dilatation of the urinary tract, especially urethral obstruction with megacystis, which are readily diagnosed by ultrasound in early gestation[19,20].

In this first-trimester study, well-known associations of types of cardiac defects with particular chromosomal anomalies were confirmed[7,21]. In all four cases of trisomy 21, a common AVSD of the complete type was diagnosed, which is also the commonest cardiac malformation in liveborn infants with trisomy 21. In a study of pathological examinations of the fetal heart[22], a much higher incidence of atrioventricular and ventricular defects in fetuses with trisomy 21 associated with an increased nuchal translucency thickness at 10–13 weeks' gestation was reported than in liveborn infants with trisomy 21. The incidence of these cardiac defects increased with nuchal translucency thickness[22]. An AVSD can be demonstrated with two-dimensional echocardiography at an early gestational age. An atrioventricular valvular regurgitation can often be demonstrated by color-coded Doppler; this is nearly always present in later gestation, owing to valvular maldevelopment[23]. In cases of AVSD, hydrops fetalis and intrauterine fetal death may be the result of critical

elevation of central venous pressure due to atrioventricular valvular insufficiency[23]. This mechanism may also be operational in fetuses with AVSD and trisomy 21 during the first trimester and may explain the genesis of nuchal edema and generalized edema. Furthermore, it may also explain higher spontaneous loss rates in trisomy fetuses with AVSD compared to those without AVSD.

The commonest cardiac defects in cases with trisomy 18 are VSDs, often of the outlet region of the interventricular septum. Depending on size and location, the prenatal diagnosis of a VSD is much more difficult than that of an AVSD. Visualization of the four-chamber view is insufficient and only the plane showing the outflow part of the septum and the respective great arteries enables the diagnosis of VSDs and other conotruncal malformations[5,24,25]. The diagnosis of tetralogy of Fallot is equally difficult in the first trimester, as the typical picture of the dilated overriding aorta and the flow-related size difference of the great arteries often seems to develop in the following weeks of gestation. This is similar to other cardiac anomalies, in which progressive development of the defect occurs with advancing gestational age[26–29]. We recently demonstrated this in a fetus in which, at 15 weeks' gestation, only an outlet VSD was discernible, whereas dilatation and overriding of the aorta became apparent at 18 weeks' gestation. Because of insufficient spatial resolution and probably also the lack of a significant pressure difference between the two ventricles, color-coded Doppler is not very helpful in the diagnosis of these VSDs[3]. However, in three of the seven fetuses with trisomy 18 we observed tricuspid insufficiency. Two of these had a minor outlet VSD and one a complete AVSD.

The commonest cardiac malformation associated with Turner's syndrome is coarctation of the aorta and, in rarer instances, other obstructions of the left ventricular outflow tract such as aortic atresia and hypoplastic left heart[30,31]. These defects are associated with diminished blood flow through the left ventricle, and are much more common in cases of Turner's syndrome with hygromata colli than in those without hygromata. Clark[32] speculated that increased lymphatic pressure associated with jugular sac obstruction also distends thoracic vessels at the base of the ascending aorta. This compression may result in decreased left-sided blood flow and the subsequent development of the typical left heart defects in Turner's syndrome[30]. Recently, morphometric analyses of the great arteries in the first trimester showed relative narrowing of the aortic isthmus at 11–13 weeks, presumably as a consequence of the rapid growth of the fetal head with a relatively low impedance in the cerebral vessels[33]. Later in pregnancy, with the falling impedance in the ascending aorta and the umbilical arteries, the ratio of the diameter of the aortic isthmus to that of the aortic root increased from 60% at 9 weeks to 80% at 18 weeks[33]. Alterations in distribution of cardiac output could result in the persistence of the narrow aortic isthmus found in early pregnancy. We can speculate according to Clark's hypothesis that increased lymphatic pressure in the thoracic vessels leads to diminished blood flow in the ascending aorta[32]. Maintenance of adequate head growth causes a redistribution of aortic blood flow. With preferential perfusion of the head, blood flow across the aortic isthmus remains low, so that the development of the aortic arch (described by Hyett and co-workers[33]) is disturbed. In addition, the presence of hygromata colli is a very unfavorable prognostic indicator in Turner's syndrome. Intrauterine death with marked hydrops usually ensues in midtrimester in these cases[34], explaining the higher incidence of cardiac anomalies in Turner's syndrome in early gestation than in live births. All five cases of Turner's syndrome in our series had hygromata colli and three of these had generalized hydrops. In two fetuses we found tubular coarctation of the aorta as the predominant cardiac defect. Three cases had a hypoplastic left heart, hypoplastic ascending aorta and aortic arch, which was associated with endocardial fibroelastosis in two cases. This early demonstration of endocardial fibroelastosis at 14 + 5 and 15 + 6 weeks' gestation and a similar case reported by Rustico and colleagues[35] is pathophysiologically a very important observation, indicating that this serious and probably irreversible lesion may exist very early in pregnancy and is not always a progressive disease.

CONCLUSION

The very high rate of cardiac defects in the presence of chromosomal anomalies complicates the use of fetal echocardiography as 'sonographic genetic screening'. Atrioventricular septal defects in trisomy 21 and severe left-sided obstructions in Turner's syndrome may be readily diagnosed even in the four-chamber view, whereas the diagnosis of ventricular septal defects in trisomy 18 is highly dependent on the size and location of the latter. The four-chamber view is insufficient in this regard, as the majority of defects are situated in the outlet portion of the septum. The optimal time period for early fetal echocardiography lies between 13 and 15 weeks' gestation. Since this is also the time period of early screening for fetal malformations in general, fetal echocardiography should be an integral part of this examination. It can be expected that many fetuses with chromosomal anomalies will then be detected by demonstration of a cardiac defect. Currently, the best sonographic marker for fetal chromosomal anomalies is increased nuchal translucency at 10–13 weeks' gestation; this shows a very high detection rate of Down's syndrome and other chromosomal anomalies. Fetal echocardiography at this gestational age is still very difficult, even with the use of high-quality equipment. At best, an atrioventricular septal defect may be diagnosed. There would clearly be no benefit of integrating fetal echocardiography into a screening program at this gestational age. Owing to the often transient character of nuchal translucency and edema, the diagnostic significance of these decreases with advancing gestational age while that of fetal echocardiography steadily increases. Therefore, fetal echocardiography should be an obligatory part of the sonographic examination for exclusion of chromosomal anomalies from the 14th week of gestation onwards.

REFERENCES

1. Blaas, H.-G., Eik-Nes, S. H., Kiserud, T. and Hellevik, L. R. (1995). Early development of the abdominal wall, stomach and heart from 7 to 12 weeks of gestation: a longitudinal ultrasound study. *Ultrasound Obstet. Gynecol.*, **6**, 240–9
2. Gembruch, U., Knöpfle, G., Bald, R. and Hansmann, M. (1993). Early diagnosis of fetal congenital heart disease by transvaginal echocardiography. *Ultrasound Obstet. Gynecol.*, **3**, 310–17
3. Gembruch, U., Knöpfle, G., Chatterjee, M., Bald, R. and Hansmann, M. (1990). First-trimester diagnosis of fetal congenital heart disease by transvaginal two-dimensional and Doppler echocardiography. *Obstet. Gynecol.*, **75**, 496–8
4. Bronshtein, M., Zimmer, E. Z., Milo, S., Ho, S. Y., Lorber, A. and Gerlis, L. M. (1991). Fetal cardiac abnormalities detected by transvaginal sonography at 12–16 weeks' gestation. *Obstet. Gynecol.*, **78**, 374–8
5. Bronshtein, M., Zimmer, E. Z., Gerlis, L. M., Lorber, A. and Drugan, A. (1993). Early ultrasound diagnosis of fetal congenital heart defects in high-risk and low-risk pregnancies. *Obstet. Gynecol.*, **82**, 225–9
6. Achiron, R., Weissman, A., Rotstein, Z., Lipitz, S., Mashiach, S. and Hegesh, J. (1994). Transvaginal echocardiographic examination of the fetal heart between 13 and 15 weeks' gestation in a low-risk population. *J. Ultrasound Med.*, **13**, 783–9
7. Boughman, J. A., Neill, C. A., Ferencz, C. and Loffredo, C. A. (1993). The genetics of congenital heart disease. In Ferencz, C., Rubin, J. D., Loffredo, C. A. and Magee, C. A. (eds.) *Epidemiology of Congenital Heart Disease. The Baltimore–Washington Infant Study 1981–1989. Perspect. Pediatr. Cardiol.*, **4**, 123–67
8. Berg, K. A., Clark, E. B., Astemborski, J. A. and Boughman, J. A. (1988). Prenatal detection of cardiovascular malformations by echocardiography: an indication for cytogenetic evaluation. *Am. J. Obstet. Gynecol.*, **69**, 494–7
9. Hook, E. B. (1983). Chromosome abnormalities and spontaneous fetal death following amniocentesis: further data and associations with maternal age. *Am. J. Hum. Genet.*, **35**, 110–16
10. Snijders, R. J. M., Holzgreve, W., Cuckle, H. and Nicolaides, K. H. (1994). Maternal age-specific risks for trisomies at 9–14 weeks' gestation. *Prenat. Diagn.*, **14**, 543–52
11. Hoffman, J. I. E. (1990). Congenital heart disease: incidence and inheritance. *Pediatr. Clin. North Am.*, **37**, 25–43
12. Allan, L. D., Sharland, G. K., Chita, S. K., Lockhart, S. and Maxwell, D. J. (1991). Chromosomal anomalies in fetal congenital heart disease. *Ultrasound Obstet. Gynecol.*, **1**, 8–11
13. Bromley, B., Estroff, J. A., Sanders, S. P., Parad, R., Roberts, D., Frigoletto, F. D. and Benacerraf, B. R. (1992). Fetal echocardiography: accuracy and limitations in a population at high and low risk for heart defects. *Am. J. Obstet. Gynecol.*, **166**, 1473–81
14. Paladini, D., Calabro, R., Palmieri, S. and D'Andrea, T. (1993). Prenatal diagnosis of congenital heart disease and fetal karyotyping. *Obstet. Gynecol.*, **81**, 679–82
15. Schwanitz, G., Zerres, K., Gembruch, U., Bald, R., Gamerdinger, F. and Hansmann, M. (1990). Prenatal detection of heart defects as an indication for chromosome analysis. *Ann. Génét.*, **33**, 79–83
16. Smythe, J. F., Copel, J. A. and Kleinman, C. S. (1992). Outcome of prenatally detected cardiac malformations. *Am. J. Cardiol.*, **19**, 1471–4
17. Nicolaides, K. H., Azar, G., Byrne, D., Mansur, C. and Marks, K. (1992). Fetal nuchal translucency: ultrasound screening for chromosomal defects in the first trimester of pregnancy. *Br. Med. J.*, **304**, 867–9
18. Nicolaides, K. H., Brizot, M. L. and Snijders, R. J. M. (1994). Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy. *Br. J. Obstet. Gynaecol.*, **101**, 782–6
19. Cullen, M. T., Green, J., Whetham, J., Salafia, C., Gabrielli, S. and Hobbins, J. C. (1990). Transvaginal ultrasonographic detection of congenital anomalies in the first trimester. *Am. J. Obstet. Gynecol.*, **163**, 466–76
20. Rottem, S. and Bronshtein, M. (1990). Transvaginal sonographic diagnosis of congenital anomalies between 9 weeks and 16 weeks, menstrual age. *J. Clin. Ultrasound*, **18**, 307–14
21. Nora, J. J. and Nora, A. H. (1978). The evolution of specific and environmental counseling in congenital heart diseases. *Circulation*, **57**, 205–13
22. Hyett, J. A., Moscoso, G. and Nicolaides, K. H. (1995). First trimester nuchal translucency and cardiac septal defects in fetuses with trisomy 21. *Am. J. Obstet. Gynecol.*, **172**, 1411–13
23. Gembruch, U., Knöpfle, G., Chatterjee, M., Bald, R., Redel, D. A., Födisch, H. J. and Hansmann, M. (1991). Prenatal diagnosis of atrioventricular canal malformations with up-to-date echocardiographic technology: report of 14 cases. *Am. Heart J.*, **121**, 1489–97
24. Achiron, R., Glasner, J., Gelernter, I., Hegesh, J. and Yagel, S. (1992). Extended fetal echocardiographic examination for detecting cardiac malformations in low risk pregnancies. *Br. Med. J.*, **304**, 671–4
25. Sharland, G. K. and Allan, L. D. (1992). Screening for congenital heart disease prenatally. Results of a 2½-year study in the South East Thames Region. *Br. J. Obstet. Gynaecol.*, **99**, 220–5
26. Allan, L. D., Chita, S. K., Anderson, R. H., Fagg, N., Crawford, D. C. and Tynan, M. J. (1988). Coarctation of the aorta in prenatal life: an echocardiographic, anatomical, and functional study. *Br. Heart J.*, **59**, 356–60
27. Allan, L. D., Sharland, G. K. and Tynan, M. J. (1989). The natural history of the hypoplastic left heart syndrome. *Int. J. Cardiol.*, **25**, 341–3
28. Marasini, M., De Caro, E., Pongiglione, G., Ribaldone, D. and Caponnetto, S. (1993). Left heart obstructive disease with ventricular hypoplasia: changes in the echocardiographic appearance during pregnancy. *J. Clin. Ultrasound*, **21**, 65–8
29. Todros, T., Presbitero, P., Gaglioti, P. and Demarie, D. (1988). Pulmonary stenosis with intact ventricular septum: documentation of development of the lesion echocardiographically during fetal life. *Int. J. Cardiol.*, **19**, 355–60
30. Lacro, R. V., Jones, K. L. and Benirschke, K. (1988). Coarctation of the aorta in Turner syndrome: a pathologic study of fetuses with nuchal cystic hygromas, hydrops fetalis and female genitalia. *Pediatrics*, **81**, 445–51
31. Van Egmond, H., Orye, E., Praett, M., Coppens, M. and Devloo-Blacquaert, A. (1988). Hypoplastic left heart syndrome and 45X karyotype. *Br. Heart J.*, **669**, 69–71
32. Clark, E. B. (1984). Neck web and congenital heart defects: a pathogenic association in 45 XO Turner syndrome? *Teratology*, **29**, 355–61
33. Hyett, J. A., Moscoso, G. and Nicolaides, K. H. (1995). Morphometric analysis of the great vessels in early fetal life. *Hum. Reprod.*, **10**, 3045–8
34. Gembruch, U., Hansmann, M., Bald, R., Zerres, K., Schwanitz, G. and Födisch, H. J. (1988). Prenatal diagnosis and management in fetuses with cystic hygromata colli. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **29**, 241–55
35. Rustico, M. A., Benettoni, A., Bussani, R., Maieron, A. and Mandruzzato, G. (1995). Early fetal endocardial fibroelastosis and critical aortic stenosis: a case report. *Ultrasound Obstet. Gynecol.*, **5**, 202–5
36. Rastelli, G. C., Kirklin, J. W. and Titus, J. L. (1966). Anatomical observations on complete form of persistent common atrioventricular canal with special references to atrioventricular valve. *Mayo Clinic Proc.*, **44**, 296–308