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The mitral gap at 11 + 0 to 13 + 6 weeks: marker of trisomy 21 or artifact?

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ABSTRACT

Objectives *To investigate the possible association between a particular pulsed Doppler waveform pattern, mitral gap, and trisomy 21 at 11 + 0 to 13 + 6 weeks.*

Methods *We performed two studies. The first was a retrospective analysis of pulsed Doppler velocity waveforms of the mitral valve inflow, recorded during specialist fetal echocardiography in 291 chromosomally normal and 144 trisomy 21 fetuses with a nuchal translucency (NT) thickness of 3.5 mm or more. We examined each waveform in each trace to determine whether there was a gap between the E-wave (early diastolic filling) and A-wave (atrial contraction) in the waveform across the mitral valve. We also examined each trace that contained at least one waveform with a mitral gap and, first, noted the order of waveforms with a mitral gap relative to those without and, second, measured the A-wave peak velocity in a representative waveform with a mitral gap and in one without. The second study was a prospective investigation in which Doppler velocity waveforms of the mitral valve inflow were assessed in 227 singleton pregnancies immediately before chorionic villus sampling.*

Results *A mitral gap was observed in 16 (5.5%) of the chromosomally normal and in 25 (17.4%) of the trisomy 21 fetuses. The incidence of mitral gap was significantly associated with the presence of cardiac defects but not with thickness of NT. The median number of waveforms per recorded image was 6 (range, 3–7) and in 32 (78%) of the 41 traces with a mitral gap only one or two of the waveforms was abnormal. The abnormal waveforms were in the middle or at the end of the trace in 95% of cases and had a lower mean A-wave peak velocity than did the normal waveforms (mean difference 3.7 cm/s; 95% CI, 0.3–7.0 cm/s;* $P = 0.03$*). In a prospective study of 10 normal fetuses we could produce a mitral gap deliberately by moving the sample volume out of the center of flow in the atrioventricular valve. In the prospective study of 227 pregnancies undergoing chorionic villus sampling a mitral gap was observed in 26/197 (13.2%) in which the fetal karyotype was subsequently found to be normal, 4/20 (20%) with trisomy 21 and 1/10 with other chromosomal defects.*

Conclusions *At 11 + 0 to 13 + 6 weeks, a mitral gap may be more common in fetuses with trisomy 21 than in fetuses with a normal karyotype. However, it is possible that a mitral gap does not reflect an underlying hemodynamic abnormality, but is rather the result of suboptimal positioning of the Doppler sample volume as the fetus moves during acquisition.*

INTRODUCTION

Increased nuchal translucency (NT) thickness at 11 + 0 to 13 + 6 weeks' gestation identifies fetuses at high risk for trisomy 21 and other chromosomal abnormalities, congenital cardiac defects and a wide range of malformations and genetic syndromes[1–4].

In trisomy 21, in addition to the increased NT there is Doppler ultrasound evidence of tricuspid regurgitation and increased impedance to flow in the ductus venosus[5–9]. Another recently described finding detected by Doppler ultrasound imaging is the presence of a gap between the E-wave (early diastolic filling) and A-wave (atrial contraction) in the waveform across the mitral valve[10]. A mitral gap was observed in at least one of 8–10 waveforms in 35/47 (74.5%) fetuses with trisomy 21 and in 12/212 (5.7%) chromosomally normal fetuses presenting at 11–14 weeks with NT above the 95th centile of the normal range[10].

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The aim of our study was to investigate further the possible association between abnormal mitral waveforms and trisomy 21 at 11 + 0 to 13 + 6 weeks.

METHODS

Retrospective study

In our center screening for trisomy 21 is based on the measurement of fetal NT thickness at 11 + 0 to 13 + 6 weeks[1]. When the fetal NT is 3.5 mm or more, which corresponds to the 99th centile of the normal range, fetal echocardiography by a specialist pediatric cardiologists is carried out. Transabdominal sonography using a 7-MHz curvilinear transducer (Acuson Aspen system, Mountain View, CA, USA) is used, and the four-chamber view of the heart, outflow tracts, arterial duct and aortic arch are assessed on cross-sectional imaging. In addition, Doppler ultrasound imaging is used to assess cardiac function, and pulsed-wave Doppler traces of both atrioventricular valves are recorded and stored digitally. The sample volume is positioned across the mitral and tricuspid valves in an apical four-chamber view with an insonation angle of less than 30° to the interventricular septum (Figure 1). The ultrasound machine is set to visualize on screen a sweep velocity of the Doppler image for a duration of about 3 s. The cardiologists are unaware of the fetal karyotype at the time of the scan but obviously aware of other features on the scan, including NT thickness and the presence of tricuspid regurgitation and fetal cardiac abnormalities.

Crown–rump length (CRL), NT thickness and the presence of cardiac defects are recorded in a fetal database at the time of the examination. In continuing pregnancies, detailed follow-up ultrasound examination is performed at approximately 20 weeks' gestation.

We searched the database to identify fetuses with an NT of 3.5 mm or more, known fetal karyotype from chorionic villus sampling (either trisomy 21 or normal), successful fetal echocardiography and recording of pulsed Doppler traces of the mitral valve. In each case the recorded waveforms across the mitral valve were assessed by two examiners who were not aware of the fetal karyotype. The flow pattern was regarded as abnormal if there was a gap between the E-wave and A-wave at the baseline in at least one of the profiles (mitral gap), as described previously (Figure 1)[10].

In all cases, assessment of the presence of mitral gap was performed by two independent operators to examine the degree of interobserver agreement. During this assessment we realized that only a few of the waveforms were affected in traces with mitral gap, and they tended to be the last ones and to have a lower peak velocity in the A and E waves.

On the basis of these observations we re-examined each trace that contained at least one waveform with a mitral

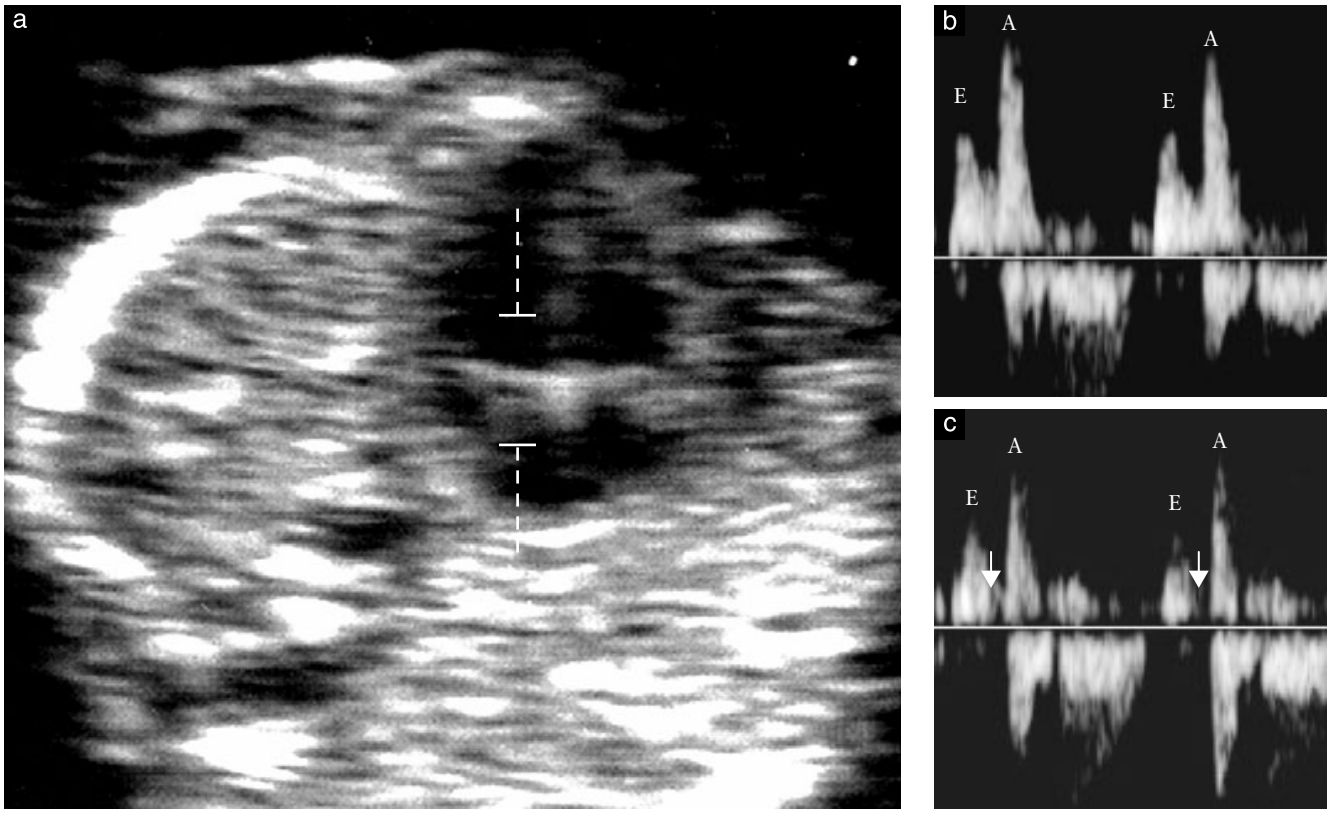

Figure 1 (a) Ultrasound image showing a typical four-chamber view of the fetal heart at 12 weeks. The Doppler sample volume is positioned in the mitral valve orifice, including the left atrium and ventricle. The alignment of the atrioventricular valve flow is parallel to the ultrasound beam. The waveforms in (b) are normal and those in (c) demonstrate a mitral gap (arrows). A, peak velocity at atrial contraction; E, peak velocity at early diastolic filling.

gap and, first, noted the position in the trace of such abnormal waveforms and, second, measured the A-wave peak velocity in a representative waveform with a mitral gap and in one without.

Prospective studies

On the basis of the results of the retrospective study we suspected that the mitral gap may be an artifact produced by fetal movement that would alter the position of the pulsed sample volume, displacing it out of the mitral valve orifice. We therefore prospectively examined 10 fetuses with normal waveforms to determine whether a mitral gap could be reproduced by moving the sample volume away from the center of flow across the valve.

In addition, we carried out a prospective study in which Doppler velocity waveforms of the mitral valve inflow were assessed in 227 singleton pregnancies immediately before chorionic villus sampling. In these cases the parents decided to have fetal karyotyping following first-trimester combined screening for trisomy 21.

Statistical analysis

In the retrospective study the degree of interobserver agreement for mitral gap was examined using the kappa coefficient. This statistic is essentially based on a cross-tabulation of the diagnoses obtained by different methods or observers and is arbitrarily characterized as poor (if $< 20\%$), fair (21–40%), good (41–60%), very good (61–80%) or excellent ($> 80\%$). The *t*-test, Mann–Whitney *U*-test, Chi-square test and Fisher's exact test were used for comparisons between the trisomy 21 and the chromosomally normal groups. Regression analysis was used to determine the significance of the association between the incidence of mitral gap and maternal age, CRL, NT thickness and presence of cardiac defects in each group.

In the prospective study the Chi-square test was used to determine the significance of differences in the prevalence of mitral gap between the normal and trisomy 21 pregnancies. The data were analyzed using the statistical software SPSS version 12 (Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

Retrospective study

The database search identified 291 chromosomally normal and 144 trisomy 21 fetuses with available Doppler flow traces across the mitral valve. The median number of waveforms per recorded image was 6 (range, 3–7). A mitral gap was observed in 41 cases. In 26 (63.4%) images only one of the waveforms had a mitral gap (Figure 2). In only one of the 41 traces were all waveforms abnormal. In the 40 traces with a mixture of normal and abnormal waveforms (Figure 2) the abnormal ones were at the beginning of the trace in two (5%) cases, in the middle in 15 (37.5%) and at the end in 23 (57.5%). Furthermore, the mean A-wave peak velocity of the normal waveforms (mean 35.9 (range, 20–55) cm/s) was higher than that of the waveforms with a mitral gap (mean 32.2 (range, 20–50) cm/s), with a mean difference of 3.7 cm/s (95% CI, 0.3–7.0 cm/s; $P = 0.03$) (Figure 3).

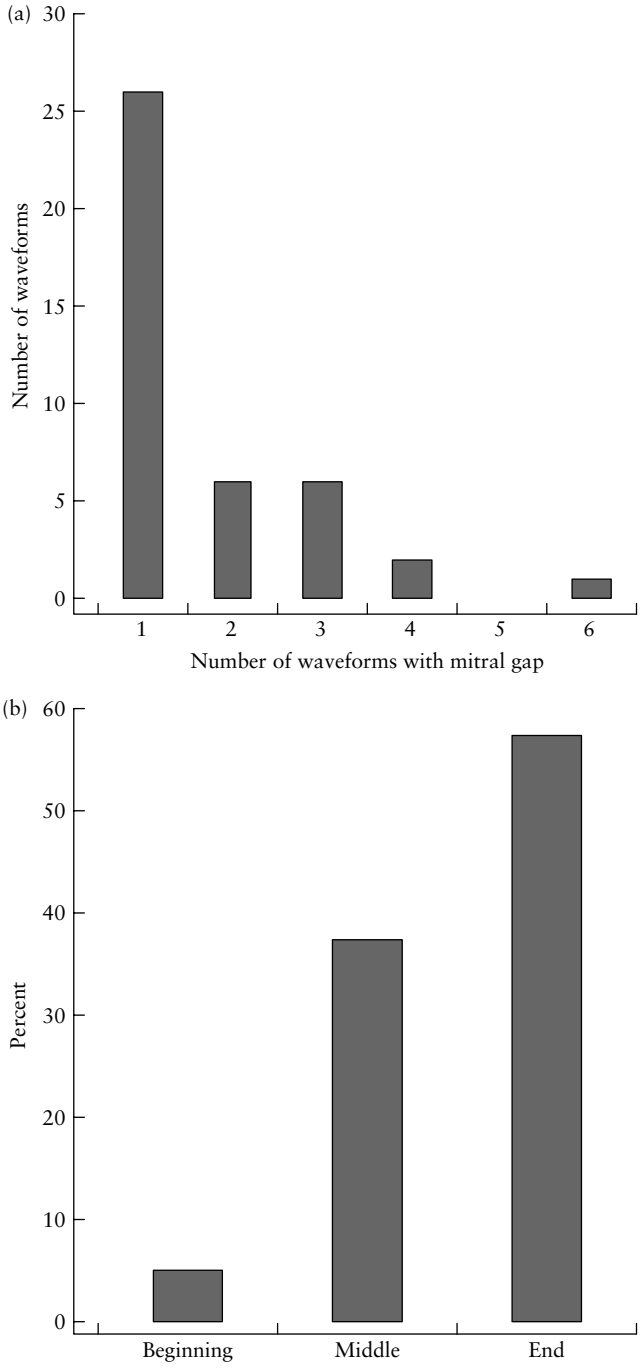

Figure 2 (a) Number of waveforms with a mitral gap per trace with an average of six waveforms. (b) Relative position of waveforms with mitral gap in the traces that had a mixture of normal and abnormal waveforms.

A mitral gap was diagnosed in 16 (5.5%) of the chromosomally normal and 25 (17.4%) of the trisomy 21 fetuses. The agreement between the two observers on the diagnosis of mitral gap was excellent (kappa 0.85; 95% CI, 0.76–0.94). There was concordance for the presence

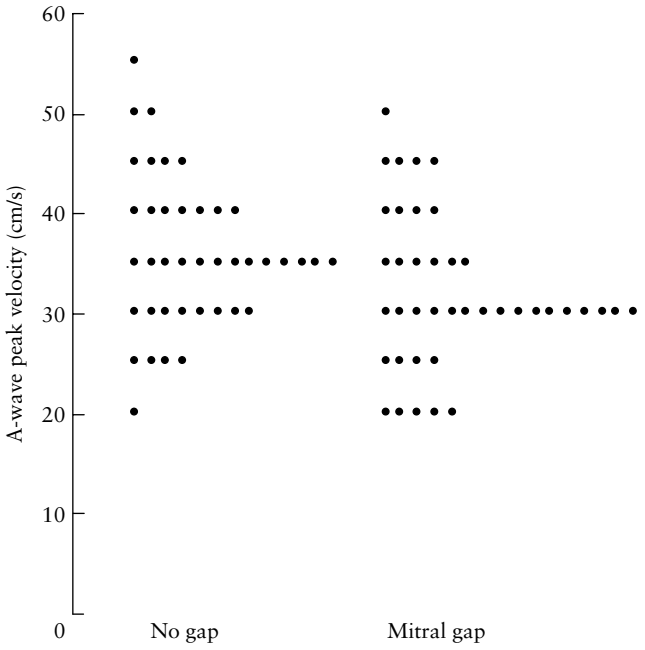

Figure 3 A-wave peak velocity in normal (no gap) and abnormal (mitral gap) waveforms in the traces with a mixture of normal and abnormal waveforms.

of mitral gap in 35 cases and for absence in 389 cases. In the 11 cases in which there was discordance the two operators examined the tracings together and reached an agreement that there was a mitral gap in six cases.

The incidence of cardiac defects and mitral gap was significantly higher in the pregnancies with trisomy 21 fetuses than in the chromosomally normal group (Table 1). Fetal echocardiography in the first and/or second trimester identified cardiac defects in 42 (29.2%) of the trisomy 21 fetuses and in 21 (7.2%) of the chromosomally normal fetuses. In the cases where fetal echocardiography was performed both at $11+0$ to $13+6$ weeks and at 18–22 weeks there was very good agreement between the findings (kappa 0.68; 95% CI, 0.46–0.90).

Logistic regression analysis demonstrated that in the trisomy 21 fetuses the incidence of mitral gap was significantly associated with the presence of cardiac defects ($P = 0.046$) but not maternal age ($P = 0.981$), CRL ($P = 0.580$) and NT thickness ($P = 0.459$). The commonest cardiac abnormality in trisomic fetuses was an atrioventricular septal defect; this was found in 32 cases and a mitral gap was observed in nine (28.1%) of these (Table 2). In the chromosomally normal group there was no significant association between the incidence of mitral gap and any of the other findings (cardiac defects, $P = 0.938$; maternal age, $P = 0.577$; CRL, $P = 0.361$; NT, $P = 0.232$).

Prospective studies

In all 10 fetuses examined appearance of a mitral gap could be generated in a fetal Doppler tracing by moving

Table 1 Comparison of the trisomy 21 and normal karyotype groups

	Trisomy 21 (n = *144*)	*Normal karyotype* (n = *291*)	P
Maternal age (years, median (range))	36 (21–44)	32 (18–49)	< 0.001*
Crown–rump length (mm, median (range))	67.3 (46.2–83.4)	63.9 (45.0–84.0)	< 0.05*
Nuchal translucency (mm, median (range))	5.4 (3.5–11.7)	4.3 (3.5–22.5)	< 0.001†
Cardiac defects (*n* (%))	42 (29.2)	21 (7.2)	< 0.001‡
Mitral gap (*n* (%))	25 (17.4)	16 (5.5)	< 0.001‡

**t*-test. †Mann–Whitney *U*-test. ‡Chi-square test.

Table 2 Relationship between cardiac defects and incidence of mitral gap

	Trisomy 21 (n = *144*)		*Normal karyotype* (n = *291*)	
Cardiac defect	n	*Mitral gap*	n	*Mitral gap*
None (*n* (%))	102	13 (12.7)	270	15 (5.6)
Any defect (*n* (%))	42	12 (28.6)	21	1 (4.8)
Atrioventricular septal defect	32	9 (28.1)	1	0
Ventricular septal defect	1	0	3	0
Coarctation of the aorta	5	3 (60.0)	5	1 (20.0)
Aortic atresia	0	0	1	0
Pulmonary atresia/stenosis	1	0	4	0
Tetralogy of Fallot	2	0	1	0
Tricuspid atresia/dysplasia	1	0	2	0
Double-outlet right ventricle	0	0	1	0
Transposition of the great arteries	0	0	2	0
Right aortic arch	0	0	1	0

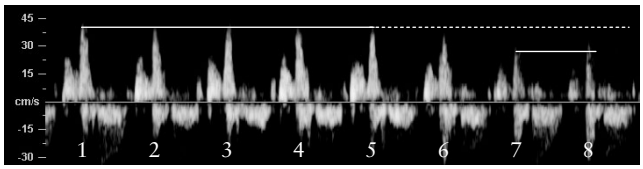

Figure 4 Pulsed Doppler trace of the flow across the mitral valve, in which the first six waveforms are normal with no mitral gap and an A-wave peak velocity of about 40 cm/s. The last two waveforms, with a mitral gap and an A-wave peak velocity of 25 cm/s, were obtained by moving the sample volume to the edge of the flow profile within the valve.

the sample volume out of the center of flow in the atrioventricular valve (Figure 4).

In the prospective study of 227 pregnancies undergoing chorionic villus sampling the median maternal age was 35 (range, 17–49) years, the median fetal CRL was 68 (range, 45–84) mm and the median fetal NT was 2.5 (range, 1.1–13.5) mm. The median number of Doppler waveforms from the mitral valve per fetus was 7 (range, 4–9). A mitral gap was observed in 26/197 (13.2%) cases in which the fetal karyotype was subsequently found to be normal, 4/20 (20%) with trisomy 21, 1/4 with trisomy 18, 0/4 with Turner syndrome and 0/2 with triploidy. The prevalence of mitral gap in the trisomy 21 fetuses was not significantly higher than that in the normal group ($P = 0.492$, Fisher's exact test). In the 31 cases with a mitral gap this abnormality was observed in only one of the waveforms in 25 (80.6%) cases and in 2–4 of the waveforms in six cases. Logistic regression analysis demonstrated that there was no significant association between the incidence of mitral gap and maternal age, CRL or NT in either the trisomy 21 or the chromosomally normal fetuses ($P = 0.236$ and $P = 0.681$, $P = 0.916$ and $P = 0.366$, and $P = 0.480$ and $P = 0.804$, respectively).

DISCUSSION

Our studies have confirmed that the incidence of a gap between the E- and A-wave in the waveform across the mitral valve at 11 + 0 to 13 + 6 weeks' gestation may be higher in fetuses with trisomy 21 than in chromosomally normal fetuses. In both our retrospective study and the study by Zoppi *et al.*[10], the incidence of mitral gap in the normal group was about 5%. However, the incidence of mitral gap in trisomy 21 in our study of 144 cases was 17%, whereas in the report by Zoppi *et al.*[10] it was 75% in 47 cases. Although there was a difference in the inclusion criteria in terms of minimum fetal NT thickness being the 99th centile (3.5 mm) in our study and the 95th centile in the previous report, this is unlikely to explain the major discrepancy in results because in both studies there was no significant association between the incidence of mitral gap and NT thickness. In our prospective study, which included fetuses with low NT, the incidence of mitral gap was not significantly different between the trisomy 21 and the chromosomally normal fetuses.

A more likely explanation for the discordant results between our studies and that of Zoppi *et al.*[10] is the difference in study design and methodology for Doppler investigations. We examined recorded images that on average contained six waveforms, which corresponds to an assessment for about 3 s, whereas Zoppi and colleagues assessed the waveforms over a period of 10 s. As the definition of mitral gap was based on the demonstration of even one abnormal waveform it is likely that Zoppi and coworkers would have diagnosed more cases with a mitral gap by examining three times as many waveforms. Supportive evidence for this suggestion is provided by our finding that in most cases only one or two waveforms demonstrated the gap and such abnormal waveforms tended to be the last ones in each recording (Figure 2). Another difference between the studies is that Zoppi *et al.* placed the pulsed Doppler sample volume immediately distal to the mitral valve, whereas in our study the sample volume was placed across the valve. However, this difference would not alter the waveform produced from the blood flow between the left atrium and ventricle across the mitral valve.

The mechanism underlying the mitral gap is uncertain. It has been suggested that this waveform reflects impaired diastolic function of the fetal heart with greater filling pressure or altered relaxation of the left ventricle[10]. However, the inconsistency of mitral gap within a particular trace implies that the diastolic function was varying on a beat-to-beat basis, which seems unlikely in the setting of a regular rhythm. In addition, previous studies have found no evidence of impaired cardiac function in association with increased NT in either chromosomally normal or abnormal fetuses[11,12]. A significant association between cardiac defects and tricuspid regurgitation has been observed, and the incidence of both increases with NT thickness[2,6]. Surprisingly, although there was a relationship between the incidence of cardiac defects and both NT thickness and mitral gap in this study, there was no significant association between mitral gap and NT.

It is possible that a mitral gap does not reflect an underlying hemodynamic abnormality, but is rather the result of suboptimal positioning of the Doppler sample volume as the fetus moves during acquisition. It should be noted that, in order to obtain the highest resolution of the Doppler trace, the cross-sectional component of the duplex image is not updated during the sweep and confirms the position of the sample volume only at the beginning of the sweep. The tendency of waveforms with mitral gap to occur towards the end of a sweep and for them to have lower A-wave peak velocities is consistent with fetal movement causing a loss of optimum alignment and signal strength. Even with the low-frequency filter set at minimum level, poor signal strength may lead to apparent separation of E and A waves.

As demonstrated in our prospective study in 10 normal fetuses we could produce a mitral gap deliberately by moving the sample volume out of the center of flow in the atrioventricular valve. One explanation for the possible increase in the incidence of mitral gap in trisomy 21 compared with chromosomally normal fetuses that merits

further investigation is that fetuses with trisomy 21 are more active than normal fetuses and therefore more likely to displace the sample volume from its initial chosen position and produce a mitral gap.

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