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Fetal heart rate in trisomy 21 and other chromosomal abnormalities at 10–14 weeks of gestation

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ABSTRACT

Fetal heart rate was measured routinely as part of a prospective study examining the efficacy of screening for trisomy 21 by fetal nuchal translucency thickness and maternal age. In 6903 normal singleton pregnancies the fetal heart rate decreased from a mean of 171 bpm at 10 weeks of gestation to 156 bpm at 14 weeks ($r = 0.413$, $p < 0.0001$). *In 85 trisomy 21 pregnancies, the mean heart rate was significantly higher than in the normal group (mean difference 0.67 SD, 95% confidence interval 0.42–0.92,* $t = 5.3$, $p < 0.001$). *The fetal heart rate in trisomy 18 and triploid fetuses was significantly lower and in trisomy 13 and Turner syndrome was higher than normal. There was no significant association between delta fetal heart rate and delta nuchal translucency thickness in either the normal* ($r = -0.018$) *or the trisomy 21* ($r = -0.031$) *pregnancies. Consequently, the risk for chromosomal defects can be derived by combining data from maternal age, fetal nuchal translucency and fetal heart rate. The effectiveness of screening by this method was examined in a self-selected population with completed pregnancies that had undergone first-trimester scanning. This population contained 6903 normal and 29 trisomy 21 fetuses. For a false-positive rate of about 5%, the sensitivity for trisomy 21 was 48% by maternal age, 26% by fetal heart rate, 72% by nuchal translucency thickness, 59% by maternal age and fetal heart rate, 76% by maternal age and nuchal translucency thickness and 83% by a combination of maternal age, nuchal translucency thickness and fetal heart rate.*

INTRODUCTION

Chromosomal abnormalities are associated with increased nuchal translucency thickness at 10–14 weeks of gestation[1]. Screening by this sonographic marker and maternal age can identify about 80% of trisomic fetuses for a false-positive rate of 5%[2].

Pathological studies of chromosomally abnormal fetuses have demonstrated a high association with relative narrowing of the aortic isthmus and a wide range of intracardiac defects. In trisomy 21 the commonest abnormalities were atrioventricular or ventricular septal defects and narrowing of the aortic isthmus[3,4]. Trisomy 18 was associated with ventricular septal defects and/or polyvalvular abnormalities[5], whilst in trisomy 13, there were atrioventricular or ventricular septal defects, valvular abnormalities and either narrowing of the isthmus or truncus arteriosus, and Turner syndrome was associated with severe narrowing of the whole aortic arch.

The aim of the present study was to examine whether the heart rate of chromosomally abnormal fetuses differs from normal and the extent to which this measurement can improve the sensitivity of screening for trisomy 21 by maternal age and fetal nuchal translucency thickness.

PATIENTS AND METHODS

Total population

Fetal heart rate was measured at 10–14 weeks of gestation in 13 675 singleton pregnancies. These patients were either self-referred to our center to participate in an ongoing study examining the effectiveness of screening for trisomies by maternal age and fetal nuchal translucency thickness ($n = 13\,317$) or they were referred for fetal karyotyping because increased nuchal translucency thickness had been detected at their local hospital ($n = 358$). In this group of 13 675 pregnancies, there were at least (not all pregnancies are yet completed) 182 chromosomal abnormalities, including 85 with trisomy 21.

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Screened population

In the total group of 13 675 cases, there were 7146 that fulfilled the following criteria: (1) they participated in the screening study at our center (cases referred from other hospitals were excluded); and (2) they had an estimated date of delivery before 1 October 1995. In this group there were 58 chromosomally abnormal fetuses and 6903 pregnancies that resulted in phenotypically normal live births. Excluded were 31 pregnancies where parents opted for termination because of fetal structural abnormalities diagnosed at the 20-week scan, 35 pregnancies that resulted in perinatal death and 119 pregnancies where no follow up was obtained.

Methodology

Transabdominal ultrasound examination (curvilinear 5-MHz transducer, Toshiba SSA 250A, Toshiba Medical Systems Limited, Tokyo, Japan) was carried out to obtain a sagittal section of the fetus for measurement of the crown–rump length and nuchal translucency thickness[1,2]. Gestational age was calculated from the crown–rump length. Simultaneous M-mode and real-time B-mode imaging were used to obtain recordings of 6–10 cardiac cycles, the interval was measured with electronic callipers and the heart rate was calculated using the software of the ultrasound machine.

Parents were given the estimated risks of chromosomal abnormality, calculated on the basis of maternal age and fetal nuchal translucency thickness, and they were asked to decide in favor of or against invasive testing[2]. Details of fetal karyotype were obtained from the cytogenetic laboratories and details on pregnancy outcome were obtained from the referring doctors or the patients who were given a questionnaire at the time of the initial scan. Our policy was to contact patients by phone if we had not received outcome details within 2 months of the expected date of delivery.

Statistical analysis

In the normal group from the screened population (n = 6903), regression analysis was used to determine the significance of the association between fetal heart rate and gestational age and a reference range (5th, 50th and 95th centiles) was established. All fetal heart rate measurements were then expressed as the number of standard deviations by which the value differed from the appropriate normal mean (delta value). Student's t-test was used to examine the significance of the difference in delta values between the normal group and each subgroup with chromosomal abnormalities.

Likelihood ratios were derived from the proportions of normal (n = 6903) and trisomy 21 (n = 85) fetuses with a given delta value. The background risk, based on maternal age and gestational age[5], was expressed as an odds ratio and was then multiplied by the appropriate likelihood ratio to derive adjusted risks. Regression analysis demonstrated no significant association between delta nuchal translucency and delta fetal heart rate (see results) and a combined likelihood ratio was calculated by multiplying the likelihood ratio for fetal heart rate from this study by the likelihood ratio of nuchal translucency thickness[6].

The screened population was then examined to determine the sensitivity of the model combining maternal age, fetal nuchal translucency thickness and fetal heart rate.

RESULTS

The median maternal age was 33 years (range 16–46) and the median gestation from crown–rump length was 12 weeks (range 10–14). In the normal group (n = 6903), the mean fetal heart rate decreased from 171 bpm at 10 weeks to 156 bpm at 14 weeks of gestation (Figure 1; fetal heart rate = 208.8 − 3.78 × gestation, SD = 6.93 bpm, r = −0.413, $p < 0.0001$).

In the total trisomy 21 group (n = 85), the fetal heart rate was significantly higher than in the normal group and the values were above the 95th centile in 18 (21%) of the cases (Table 1, Figure 2; mean difference 0.67 SD, 95% confidence interval 0.42–0.92, t = 5.3, $p < 0.001$). The fetal heart rate in trisomy 18 and triploid fetuses was significantly lower and in trisomy 13 and Turner syndrome was higher than normal (Table 1, Figure 2). There was no

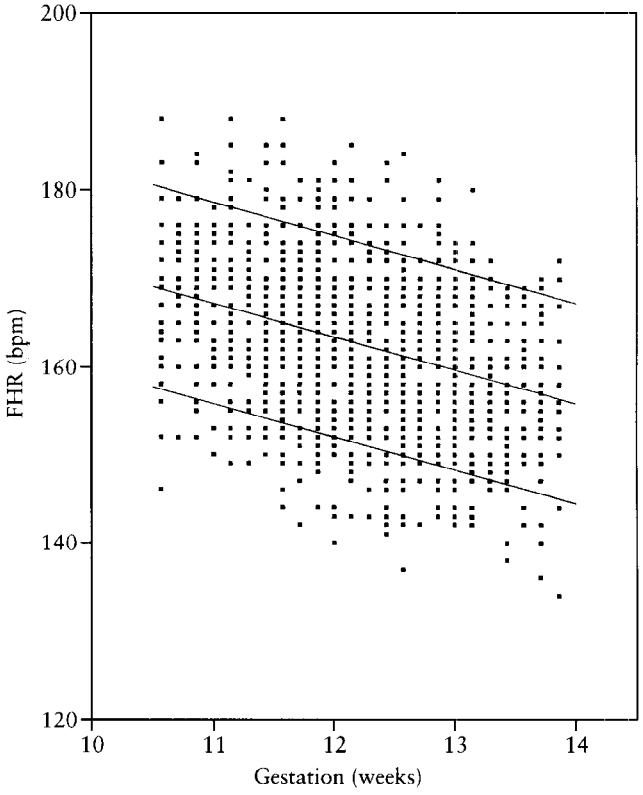

Figure 1 Fetal heart rate (FHR) in 6903 normal fetuses plotted against gestation by crown–rump length. The lines indicate the mean, 5th and 95th centiles

Table 1 Difference in mean fetal heart rate from the normal mean for crown–rump length in trisomy 21 and other chromosomal abnormalities in the total population of 13 675 pregnancies

Karyotype	*n*	*Mean difference* (SD)	*95% CI*	*t*	*p*
Trisomy 21	85	0.67	0.42 to 0.92	5.3	< 0.001
Trisomy 18	34	−0.33	−0.01 to −0.67	2.0	< 0.05
Trisomy 13	16	1.56	0.89 to 2.23	5.0	< 0.001
Turner	19	1.71	0.31 to 1.37	5.5	< 0.001
Triploidy	8	−0.84	−0.00 to −1.68	2.4	< 0.05
Other	20	−0.10	−0.31 to 0.51	0.5	ns

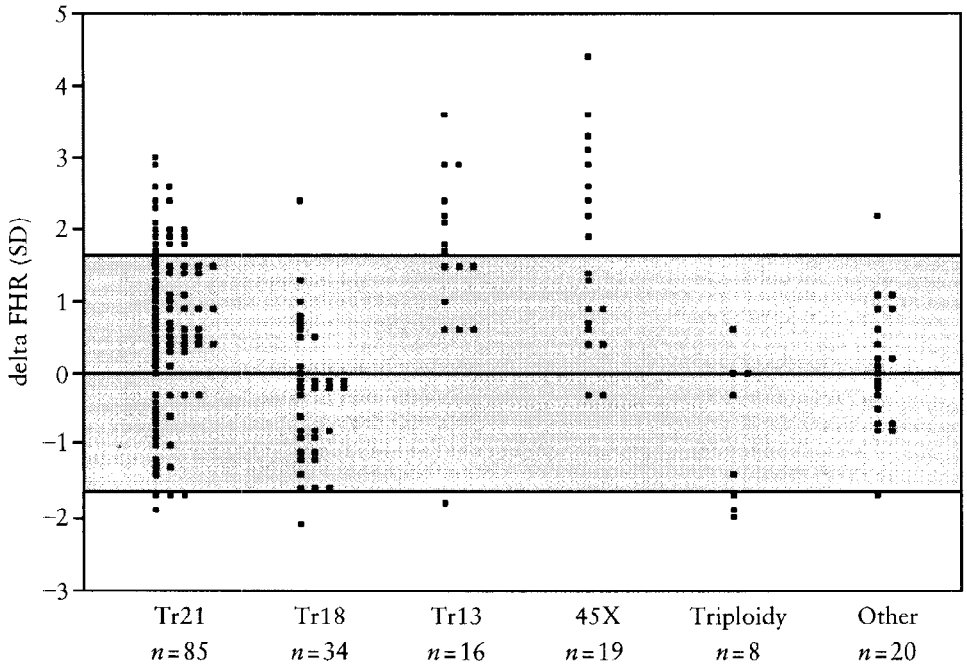

Figure 2 Individual delta values for fetal heart rate (FHR) in fetuses with trisomy 21 (Tr21), trisomy 18 (Tr18), trisomy 13 (Tr13), Turner syndrome (45X), triploidy and other chromosomal abnormalities. The horizontal lines represent the mean, 5th and 95th centiles

significant difference from normal in the 20 fetuses with other chromosome abnormalities (47,XXY, $n = 7$; 47,XXX, $n = 1$; 92,XXYY, $n = 1$; marker chromosome, $n = 3$; deletion 4p, $n = 1$; deletion 8p, $n = 1$; trisomy 22, $n = 1$; unbalanced translocations, $n = 5$).

The frequency distributions of delta fetal heart rate in the normal group and in the trisomy 21 group were used to derive likelihood ratios, as shown in Figure 3. There was no significant association between delta nuchal translucency and delta fetal heart rate in either the normal group or in the trisomy 21 group (Figure 4; $r = -0.018$ and $r = -0.031$, respectively) and therefore, a combined likelihood ratio was calculated by multiplying the individual ones. The result was applied to the background risk to derive an estimate of the risk based on both parameters. For example, in a pregnancy where the delta fetal nuchal translucency was 1.0 mm (likelihood ratio = 2.2) and the fetal heart rate was 1.7 standard deviations above the mean (likelihood ratio = 2.9), the derived likelihood ratio based on both parameters was 6.38; the background risk for trisomy 21 in a woman aged 30 years at 12 weeks of gestation (1 : 525) was adjusted to 6.38 : 525 or 1 : 83.

The effectiveness of screening by the model combining maternal age, fetal nuchal translucency thickness and fetal heart in the screened population is shown in Table 2. This population contained 6903 normal and 58 chromosomally abnormal cases. Screening by maternal age alone (about 5% of the women were at least 40 years old) identified 48% of the trisomy 21 fetuses and 36% of all chromosomal abnormalities. Screening by fetal heart rate alone (cut-off 95th centile) identified 26% of the trisomy 21 fetuses and 21% of all chromosomal abnormalities. Screening by nuchal translucency thickness alone (cut-off 95th centile) identified 72% of the trisomy 21 fetuses and 76% of all chromosomal abnormalities. For each of the models using various combinations of maternal age, fetal nuchal translucency thickness and fetal heart rate a combined estimated risk was calculated for each patient and a cut-off risk was selected to correspond with a false-positive rate of about 5%. Screening by maternal age and fetal heart rate (cut off risk 1 in 65) identified 59% of the trisomy 21 fetuses and 36% of all chromosomal abnormalities. Screening by maternal age and fetal nuchal translucency thickness (cut-off risk 1 in 100) identified 76% of the trisomy 21

fetuses and 76% of all chromosomal abnormalities. Screening by a combination of maternal age, fetal nuchal translucency thickness and fetal heart rate (cut-off risk 1 in 100) identified 83% of the trisomy 21 fetuses and 81% of all chromosomal abnormalities.

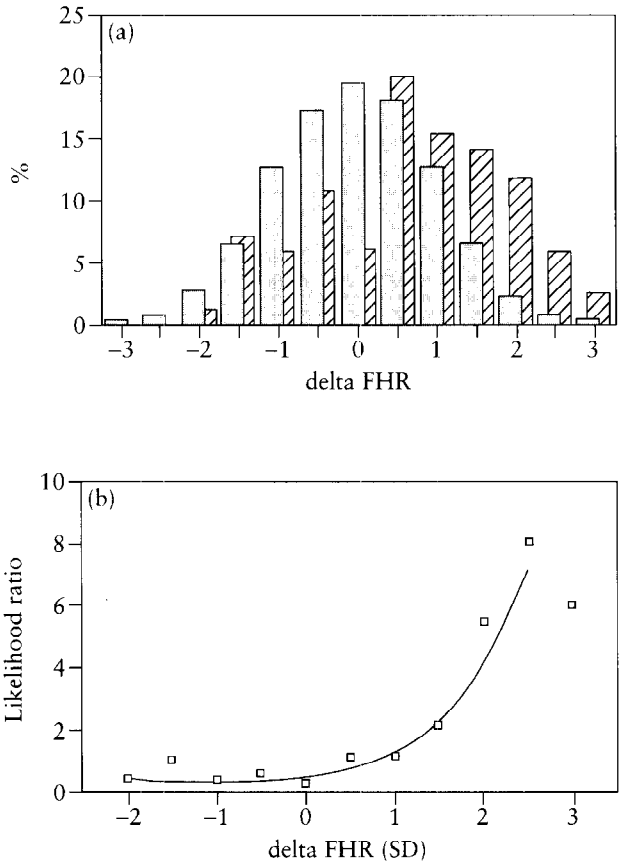

Figure 3 Distributions of fetal heart rate (FHR) measurements expressed as number of standard deviations from the normal mean (a) in 6903 normal fetuses (stippled bars) and in 85 fetuses with trisomy 21 (hatched bars). Likelihood ratios for trisomy 21 (b) were derived by dividing the percentage of trisomic fetuses with a given delta FHR by the percentage of normal fetuses with the same delta FHR

DISCUSSION

In normal pregnancy there is a decrease in fetal heart rate between 10 and 14 weeks of gestation. These findings are compatible with those of previous studies, which have demonstrated that the heart rate increases from about 110 bpm at 5 weeks of gestation, to 170 bpm at 9 weeks, and then gradually decreases to 150 bpm by 13 weeks[7–9]. The early increase in heart rate coincides with the morphological development of the heart and the subsequent decrease may be the result of functional maturation of the parasympathetic system[7,9,10].

The mean heart rate in our 85 trisomy 21 fetuses at 10–14 weeks of gestation was significantly increased and in 21% of the cases the rate was above the 95th centile of the normal range. In a previous longitudinal study of one trisomy 21 fetus at 6–9 weeks of gestation the heart rate was consistently below the 3rd centile of the normal range[11]. In another cross-sectional study of five affected fetuses at 7–13 weeks, the heart rate was always within the normal range[12].

In trisomy 21 there may be a delay in the functional maturation of the parasympathetic system and consequent delay in the physiological decrease in heart rate with gestation after 9 weeks. A hypothesis of developmental delay has also been proposed as the possible mechanism for the alterations in maternal serum biochemistry of trisomic pregnancies[13]. Alternatively, the higher heart rate of trisomy 21 fetuses represents a compensatory response to the heart failure that may be responsible for the increased nuchal translucency[14]. In fetal life the heart normally performs near the peak of the Frank–Starling curve of ventricular function[15] and therefore, compensatory increase in cardiac output can only be achieved by relative tachycardia[16]. Maximum tachycardia may be reached with early heart failure, offering an explanation for the lack of a significant association between the extent of increase in nuchal translucency thickness and fetal heart rate. The same hypotheses may also be advanced for the observed tachycardia of fetuses with Turner syndrome or trisomy 13.

Table 2 Detection rates of trisomy 21 and other chromosomal abnormalities for a false-positive rate (FPR) of about 5% in the screened population. The cut-off for maternal age was 40 years and for fetal heart rate (FHR) and nuchal translucency thickness (NT) was the 95th centile of the appropriate normal range for crown–rump length. For each of the models using various combinations of age, FHR and NT a combined estimated risk was calculated for each patient and a cut-off risk was selected to correspond with a false-positive rate of about 5%. The cut-off of 1 in 65 was used for age and FHR, and 1 in 100 for age and NT, and age, NT and FHR

		Age ≥ 40 years		*FHR > 95th centile*		*NT > 95th centile*		*Age + FHR risk > 1/65*		*Age + NT risk > 1/100*		*Age + NT + FHR risk > 1/100*	
Karyotype	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Trisomy 21	29	14	48	8	26	21	72	17	59	22	76	24	83
Trisomy 18	15	4	27	1	7	14	93	2	13	14	93	14	93
Trisomy 13	3	1	33	2	67	2	67	1	33	2	67	2	67
Turner	3	0	0	0	0	2	67	1	33	2	67	2	67
Triploidy	3	0	0	0	0	2	67	0	0	2	67	2	67
Other	5	2	40	1	20	3	60	0	0	2	40	3	60
Total	58	21	36	12	21	44	76	21	36	44	76	47	81
FPR			5.8		5.0		5.0		5.3		6.0		5.6

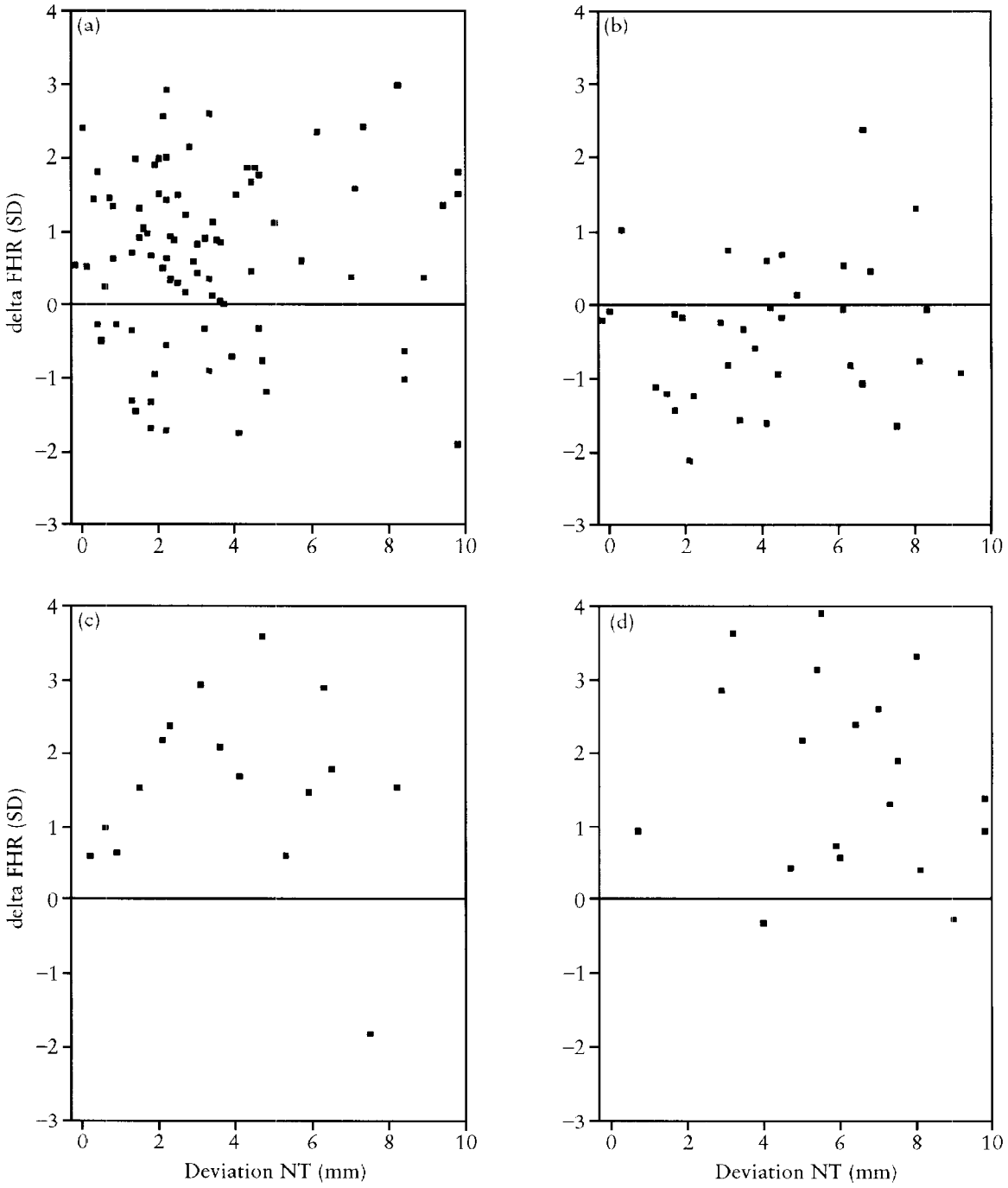

Figure 4 Association between fetal nuchal translucency thickness (NT) and fetal heart rate (FHR) in chromosomally abnormal fetuses expressed as deviations from the appropriate normal mean. (a) Trisomy 21; (b) trisomy 18; (c) trisomy 13; (d) Turner syndrome

The relative bradycardia of trisomy 18 fetuses may be related to the fact that in this chromosomal abnormality there is early onset growth retardation and the developmental delay is more severe than in trisomies 21 and 13; in such fetuses the maturation in heart rate would be equivalent to about 8 weeks of gestation. Triploidy is associated with a high rate of early intrauterine lethality and the observed bradycardia in some of these fetuses may represent a preterminal event.

The findings of the screening study suggest that incorporation of fetal heart rate in the model for prediction of risk for chromosomal abnormalities improves the sensitivity of screening by maternal age and fetal nuchal translucency thickness. The extent of improvement remains to be established in an ongoing multicenter study.

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