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Isolated echogenic foci in the fetal heart: do they increase the risk of trisomy 21 in a population previously screened by nuchal translucency?

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ABSTRACT

Objectives *To confirm the hypothesis that isolated cardiac echogenic foci at the second-trimester anomaly scan do not influence our current calculation of risk of trisomy 21 in individual pregnancies, which is based on maternal age and nuchal translucency thickness at 11–14 weeks.*

Design *Observational study in a fetal medicine unit.*

Methods *In a general pregnant population undergoing first-trimester nuchal translucency screening, data from 239 singleton pregnancies with isolated cardiac echogenic foci at the second-trimester anomaly scan were compared with those of a control group of 7449 pregnancies with normal anomaly scans. Prevalence of trisomy 21 was determined in both groups. Following the anomaly scan, the individual risks of trisomy 21 were calculated by adjusting the previous risk based on maternal age and first-trimester nuchal translucency. We assumed that echogenic foci did not alter each individual risk calculation. The expected number of cases of Down syndrome in both groups was then calculated from the sum of probabilities of each individual affected fetus. The observed number of cases was compared with the expected number in both study and control populations.*

Results *There was no statistically significant difference between the prevalence of trisomy 21 in the study group (no cases) and in the control population (three cases). From individual risk calculations, observing no cases of trisomy 21 in the study group was the most likely event if echogenic foci did not increase the risk of this chromosomal abnormality (P = 0.62).*

Conclusion *The finding of isolated echogenic foci at the time of the 20 week-scan does not significantly change the risks of trisomy 21 if background risk and previous nuchal translucency measurements are taken into account in the individual risk calculation. We suggest that no further adjustments to risk should be used.*

INTRODUCTION

Cardiac echogenic foci are small structures visualized within the fetal heart, of echogenicity similar to or greater than that of the surrounding bone. They were first reported in 1987 as a benign sonographic finding[1]. Since then their reported prevalence among different series has varied from 0.5%[2] to 20%[3] depending on the characteristics of the various populations studied. As a cardiac structure, they pose no hemodynamic disturbance, and when observed in an apparently normal four-chamber view they do not seem to be associated with structural cardiac abnormalities[4]. However, much debate exists regarding their significance as a marker for chromosomal abnormality, especially as a marker for trisomy 21.

In clinical practice, based on available information in the literature, ascertainment of risks of fetal aneuploidy for individual pregnancies following the detection of an isolated echogenic focus in the fetal heart is controversial. Several studies have indicated that if found in isolation, echogenic foci are not associated with an increased risk of aneuploidy[5–8], while others report a significantly increased risk[9–11]. A recent review supports the idea that this sonographic finding may increase the risk of chromosomal abnormality if found in high-risk groups, but not otherwise[12].

The purpose of this study was to test the hypothesis that isolated cardiac echogenic foci are not significant markers for trisomy 21 in a population previously screened by nuchal translucency (NT) in the first trimester of pregnancy. If this hypothesis is correct, the recognition of echogenic foci during a routine anomaly scan should not affect our current method

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of risk assessment for this chromosomal abnormality, which is based on maternal age, first-trimester NT measurements and ultrasound findings at the 20-week scan.

MATERIALS AND METHODS

Study group

All fetuses in pregnancies booked into and delivered at our hospital and identified from our computerized clinical database as having had both a nuchal translucency scan and a subsequent anomaly scan showing isolated cardiac echogenic foci between January 1997 and June 2000 were included in our study group. Pregnancies referred from other hospitals were excluded from the study.

All fetuses had routine first-trimester nuchal translucency scans and second-trimester anomaly scans performed by experienced sonographers or obstetricians, using standard obstetric mode ultrasound machine settings. During the study period, most fetuses also had detailed fetal echocardiography as part of our risk assessment for chromosomal abnormalities in individual pregnancies. The anatomy of the fetal heart was assessed using a sequential segmental approach[13], complemented by the use of color flow mapping and pulsed wave Doppler as indicated. All scans were carried out with either a 3.5- or a 5-MHz curvilinear probe, using various ultrasound machines (ATL, Letchworth, UK; Acuson, Uxbridge, UK; General Electrics, UK; Diasonics, UK).

Fetuses which were found to have any other recognized marker for chromosomal abnormality or a definite abnormality at the time of the 20-week scan were excluded from further analysis. Also excluded were cases of multiple gestation. Those fetuses which had been shown to have increased nuchal translucency measurements at the time of the first-trimester scan (10–14 weeks), but an otherwise normal anomaly scan were not excluded from analysis as nuchal translucency measurements were taken into account in the calculation of risk of chromosomal abnormalities for individual patients at the time of the 20-week scan.

Control group

All fetuses from pregnancies booked and delivered at our hospital who had both first- and second-trimester scans at our center during the study period, and in whom neither fetal abnormalities nor markers for chromosomal abnormalities had been detected at the time of the 20-week scan, were included in the control group. All referrals were excluded.

Follow up

Hospital records were reviewed to determine delivery outcomes for each subject. Results were also cross-matched with the registry of the Regional Genetics Service, covering genetic and cytogenetic testing for the whole area referring to our hospital.

Statistical analysis and calculation of risk of trisomy 21

The prevalence of trisomy 21 was determined in both the control and the study groups. Confidence intervals for this prevalence were calculated using the exact binomial method[14]. The prevalences in the two groups were compared using Fisher's exact test[15].

In order to test the hypothesis that the presence of isolated echogenic foci does not alter the risk of trisomy 21, we used a commercially available database (PIA-Fetal Database version 3.21, ViewPoint Bildverarbeitung GmbH, Germany) which is routinely used in our department for the calculations of risk of chromosomal abnormalities. For the risk of trisomy 21, the background risk related to maternal age is adjusted according to other known variables for the particular pregnancy being assessed. History of previously affected pregnancies, first-trimester measurement of nuchal translucency thickness and ultrasound findings at the time of the anomaly scan (abnormalities as well as soft markers) are taken into account in order to provide an estimate of the risk for the individual pregnancy. Adjustments made to the background risk (maternal age related) due to nuchal translucency thickness are based on the distribution of this measurement in the general population[16], while adjustments related to fetal anomalies or markers are based on a review of the available literature[17]. In the absence of fetal abnormalities or markers for chromosomal abnormalities, a likelihood ratio of 0.6 is used to adjust the risks at the time of the anomaly scan.

For the purpose of this study, in the calculation of risk of trisomy 21, the echogenic focus was considered as a non-marker in the study group i.e. with the assumption that the anomaly scan showed no soft markers. Therefore, for every patient in both the control and the study groups, individual risk was calculated taking into account maternal age, nuchal measurements and absence of abnormalities or soft markers. In this way, each individual risk is decreased further at 20 weeks. Thus, with this approach, and for each pregnancy, the lowest (and best) possible estimated risk of that particular fetus having trisomy 21 was obtained.

In both groups, the sum of risks of each fetus having trisomy 21 was obtained in order to ascertain the expected number of cases of this chromosomal abnormality in each group based on individual probabilities. This expected number of cases was then used to calculate the probability of observing cases of Down syndrome using the exact binomial distribution[14]. The number of abnormalities observed should follow a Poisson distribution with mean equal to the expected number. The probabilities of encountering cases of Down syndrome for such a distribution were calculated using the Poisson probability formula:

$$\exp(-m)m^r/r!,$$

where r is the number of abnormalities and m the expected number of abnormalities, the mean of the Poisson distribution[14]. The same probability was calculated in the control group, in order to verify the appropriateness of the method.

RESULTS

The prevalence of isolated cardiac echogenic foci in the population studied was 3.1% (239/7688; 95% confidence interval, 2.7–3.5%). There were no cases of trisomy 21 in this group of fetuses. During the same time period (Figure 1), 15

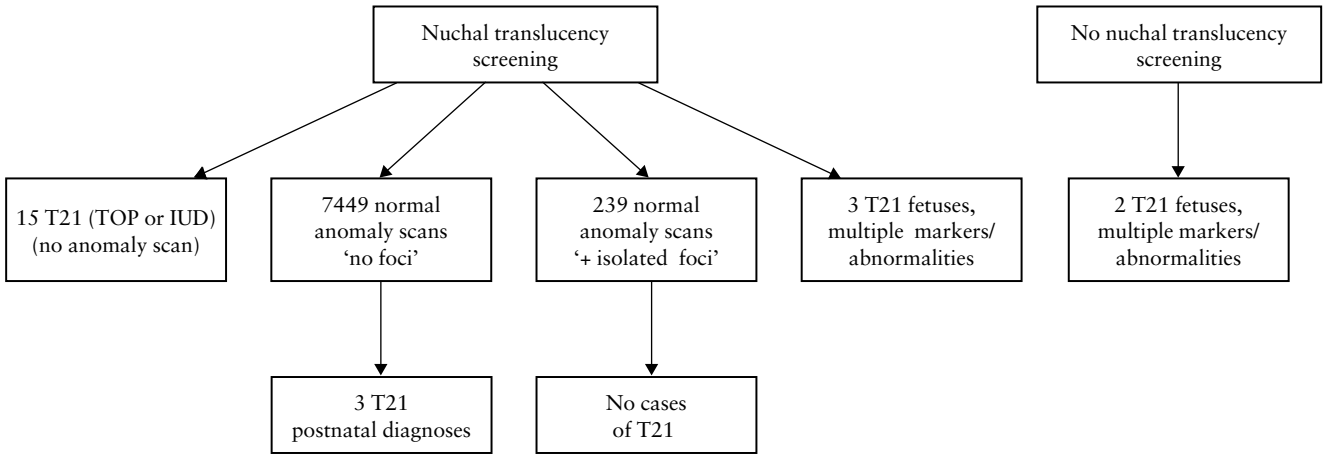

Figure 1 Summary of prenatal ultrasound findings in all cases of trisomy 21 diagnosed during the study period. T21, trisomy 21; TOP, termination of pregnancy; IUD, intrauterine death.

cases of trisomy 21 were identified and confirmed antenatally by a combination of maternal age and nuchal translucency thickness in the first trimester of pregnancy. After chorionic villus sampling, all pregnancies were either terminated or miscarried spontaneously and it was not possible to perform a complete anomaly scan; therefore, these cases were excluded from our analysis. In two other cases, the risk of trisomy 21 was 1 : 27 and 1 : 203 but the families declined invasive tests. An atrioventricular septal defect was diagnosed at 20 weeks in one case and no abnormalities or markers were detected in the other. In both, trisomy 21 was confirmed postnatally. Another two cases were considered low risk for aneuploidy following nuchal translucency screening. Both had multiple markers on the anomaly scan, one with and one without echogenic foci. Two other cases diagnosed postnatally were considered low risk for trisomy 21 at 11–14 weeks and showed no obvious abnormalities or markers at the 20 week-scan. Another two cases of Down syndrome were identified at 20 weeks in pregnancies where nuchal translucency was not assessed. These were identified by multiple markers or fetal abnormalities, one with and one without echogenic foci.

Study group

A total of 239 fetuses having had a nuchal translucency scan and showing isolated intracardiac echogenic foci at the anomaly scan were identified. Mean maternal age was 30.0 years (standard deviation, 5.4 years; range, 15–42 years; median, 30 years). Of these, 20.5% (n = 49) of the mothers were 35 years or older. For three of the fetuses, the position of the echogenic focus was not recorded. Among the remaining 236 fetuses, 82% had an echogenic focus in the left ventricle (n = 194), 6% in the right ventricle (n = 13), and 12% had bilateral foci (n = 29). There were no cases of chromosomal abnormalities in the study group.

Control group

A total of 7449 fetuses had a nuchal translucency scan and a normal anomaly scan. Mean maternal age was 30.2 years (standard deviation, 5.4 years; range, 14–51 years; median, 31 years). Of these, 21.8% (n = 1627) of the mothers were 35 years or older.

Differences in mean maternal age and in the percentage of women of 35 years or older between the study group and the control group were not significant (P = 0.44, Student's t-test and P = 0.62, χ^2 test, respectively). There were three babies with trisomy 21 in this group, all diagnosed postnatally.

Statistical analysis

The prevalence of trisomy 21 in the study group was 0 per 1000, with a 95% confidence interval of 0–15 per 1000. The prevalence of trisomy 21 in the control group was 0.39 per 1000, with a 95% confidence interval of 0.08–1.1 per 1000. The prevalence in the two groups did not show a statistically significant difference: there were no cases of trisomy 21 among 239 subjects in the study group and three cases among 7449 subjects in the control group (P = 0.91, Fisher's exact test).

Analysis of the assessment of risk of trisomy 21

Study group The expected number of cases of trisomy 21 in the study group (sum of all individual probabilities) was 0.48. Applying the exact binomial distribution, the probability of finding no abnormalities in the study group was 0.62, the probability of finding one case of trisomy 21 was 0.30, and the probability of encountering two or more abnormalities was 0.08. Hence, our finding of no cases of Down syndrome in the study group did not differ significantly from the expected distribution in the population we studied and was the most likely probability (n = 0, P = 0.62).

Control group Utilizing a similar analysis, the expected number of cases of trisomy 21 in the control group was 5.6. The probability of finding three abnormalities was 0.11, the probability of observing between four and six abnormalities was 0.48 and that of seven or more was 0.33. Consequently, the observed number of anomalies (three cases) was not significantly different from the expected distribution (P = 0.11). This was, however, the less likely probability.

DISCUSSION

This study confirmed the hypothesis that when isolated echogenic foci are not considered 'soft markers' for trisomy 21 in a population previously screened by nuchal translucency, the risks of this chromosomal abnormality have not been underestimated. We showed no statistical difference between the prevalence of trisomy 21 in the study and control groups. Furthermore, we demonstrated that the frequency of observed cases of Down syndrome in the study group (no cases) fell within the calculated probability of observing no cases in the population we studied and that this was the most likely event to occur ($P = 0.62$). The implications are that such an assumption can be made when calculating the risks of a particular fetus having this specific chromosomal abnormality.

The prevalence of echogenic foci in prospective studies in the general low-risk population is variable[5–8]. Its rate of detection seems, however, to be increasing. The reason for this is likely to be multifactorial, including, for example, the use of modern ultrasound equipment, the wider use of multiple views to assess the fetal heart and the move towards earlier scans. It is generally accepted that echogenic foci 'disappear' towards late gestation and early infancy[2,5,6] and that their prevalence is higher in the first trimester[7]. In our experience, the absolute size of the foci does not seem to change significantly during pregnancy, but their relative size is considerably less later in gestation. We therefore feel that as their size remains relatively stable, they are progressively and relatively smaller as the fetus and the surrounding cardiac structures grow, until they are no longer easily visible.

The majority of fetuses with this finding are karyotypically normal. However, data from pathological studies have suggested an association with trisomies 13 and 21[18]. Such an association has been confirmed in studies of high-risk pregnancies[19–23] but not in studies of low-risk populations[5–8]; one of which[5] specifically addressed fetuses with cardiac echogenic foci with no associated anomalies. Risks of chromosomal abnormality associated with an isolated echogenic focus have been calculated. Simpson and colleagues[9] analyzed a series of 228 fetuses with this isolated finding from a low-risk maternal population (aged < 35 years) and found two cases of chromosomal abnormalities diagnosed postnatally: one case each of trisomy 21 and unbalanced translocation. The authors concluded that isolated cardiac echogenic foci are associated with an overall prevalence of 1% of chromosomal abnormality and suggested that fetal karyotype should be considered in every case found to have an isolated focus. Nyberg and colleagues[24] adjusted maternal age-related risk according to sonographic findings by assigning a likelihood ratio of 2 for echogenic foci and 0.4 for a normal ultrasound. Thilaganathan and colleagues[8] did not find any significant association between isolated cardiac echogenic foci and Down syndrome in a general population which had been screened by either nuchal translucency or maternal serum biochemistry. Thus far, however, measurements of first-trimester nuchal translucency have not been systematically taken into account in conjunction with ultrasound findings and maternal age in the analysis of risk of trisomy 21 in fetuses presenting with isolated echogenic foci in the heart.

The group of patients we studied originated from a hospital-based population which represents a general population and constitutes a mixture of low- and high-risk pregnancies. The population was of approximately 50% Caucasian ethnic origin and 50% Afro-Caribbean so no overestimation of the prevalence of echogenic foci due to their higher frequency in Asian populations should have occurred[25]. The fetuses which formed the study group were selected from this general population by a single criterion: the finding of cardiac echogenic foci and no other markers or abnormalities on the ultrasound scan. All anomaly scans were carried out in our fetal medicine department, which is a tertiary center. This is an important consideration as we feel confident that all cases included in our study group had had a thorough examination to exclude fetal abnormalities as well as other 'soft markers'.

It is of major importance to consider that, among the 21 cases of Down syndrome observed during the study period which had first-trimester risk assessment based on maternal age and NT, 15 affected pregnancies were diagnosed in early gestation following fetal karyotyping. None of these pregnancies were ongoing and therefore the prevalence of trisomy 21 at the time of the anomaly scan was decreased. Consequently, the specificity and positive predictive value of any ultrasound marker for Down syndrome was lower compared to a population not undergoing an effective program of screening. This may account for the lower observed number of cases of trisomy 21 in the control group ($n = 3$) compared to the calculated expected number ($n = 5.6$).

In previous studies addressing the significance of cardiac echogenic foci, the populations studied were often not homogeneous in respect to the type of Down syndrome screening received, if any at all. Since screening programs affect the prevalence of trisomy 21 later in gestation, it is not straightforward to extrapolate the significance of ultrasound markers from selected populations or from populations whose characteristics have not been properly described. We feel it is inappropriate to generalize the risks of chromosomal abnormality and to act upon this generalization as there are risks of fetal loss associated with invasive karyotyping procedure. We suggest that assessing individual risks taking into account all data available for the specific pregnancy, as demonstrated in this study, offers a more logical approach for individual patients.

We were only able to calculate the risk for trisomy 21, not the risk for all possible chromosomal abnormalities. Since NT screening has been proved to be effective for screening trisomies 18 and 13 and sex chromosomal abnormalities[26–28], we think that the considerations expressed above should also apply to these aneuploidies. However, larger populations are required to confirm this.

All our patients had detailed scans by experienced personnel. This must also be taken into account before the examination is considered not to have shown any soft markers or definite abnormalities as these findings could change individual risks considerably. We are in agreement with Sepulveda and Romero[12] that as the echogenic focus is usually easily seen during routine anomaly scan, this should prompt a detailed fetal examination. If this examination, to include a detailed assessment of the four-chamber view, is to be performed

locally at district hospitals or at tertiary referral centers, there should be a policy for each individual unit to reach a decision based on the level of expertise available locally. Whether cardiac assessment should also include the great vessels is a matter of debate, as thus far there have been little data to suggest that the presence of an echogenic focus in an otherwise normal four-chamber view is associated with higher prevalence of congenital heart disease than that expected in the general population[4]. In addition, if about 3% of the population presents an echogenic focus, there might not, as yet, be enough resources to provide detailed fetal echocardiography for every case shown to have a normal four-chamber view with an echogenic focus.

Based on all of the above, and facing a patient in whom there are no other findings on the anomaly scan, our current risk assessment for trisomy 21 consists of taking into account only maternal age and NT. Until larger studies can confirm our analysis, we suggest that in clinical practice no further adjustment is made to the risk (assuming a likelihood ratio of 1), i.e. the risk should be neither decreased because the anomaly scan is normal, nor increased.

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