Ultrasound Obstet Gynecol 2003; **21**: 354–358
Published online 19 March 2003 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.89

Relationship of isolated fetal intracardiac echogenic focus to trisomy 21 at the mid-trimester sonogram in women younger than 35 years

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KEYWORDS: Down syndrome; echogenic intracardiac focus; fetus; maternal age; ultrasound

ABSTRACT

Objective *To determine whether an isolated echogenic intracardiac focus in the fetal heart in the mid-trimester (16–24 weeks) in women aged 18–34 years of age is associated with trisomy 21.*

Method *This was a prospective population-based observational study. A search of all obstetric sonograms performed in our region from January 1997 to December 1999 was carried out. From 12 373 pregnancies we identified 267 cases of echogenic foci in the fetal heart. Trisomy 21 was detected in 38 deliveries (0.31%). An echogenic focus was seen in 193 of the 9167 women < 35 years of age who had an obstetric sonogram at 16–24 weeks' gestation, and an echogenic focus was seen in 67 of the 1968 women > 35 years. The study group comprised the 149 women aged 18–34 years who had an echogenic focus in the fetal heart as the only abnormality at an obstetric sonogram performed at 16–24 weeks' gestation.*

Results *There were no abnormal outcomes or cases of trisomy 21 among the 149 pregnancies with an echogenic focus as an isolated finding in women aged 18–34 years (0% (95% confidence interval, 0.00–2.43)). The prevalence of isolated echogenic focus was 1.6% for women < 35 and 1.8% for women ≥ 35 years old. Of the 25 fetuses with trisomy 21 undergoing an obstetric sonogram at any gestational age, five (20%) had an echogenic focus. An isolated echogenic focus was present in one fetus with trisomy 21 seen at 26 weeks' gestation in a 17-year-old mother. Echogenic foci were single and in the left ventricle in 84.7% of cases.*

Conclusion *An isolated echogenic focus in the fetal heart at mid-trimester ultrasound in women aged 18–34 years is not associated with increased risk for trisomy 21.*

INTRODUCTION

Trisomy 21 is the most common karyotype abnormality in liveborn infants. The prevalence of trisomy 21 is 1–2 per thousand births. The prevalence of major congenital anomalies is approximately 28 per 1000 births[1]. Much effort is expended in attempting to detect trisomy 21 prenatally, including second-trimester ultrasound. There is controversy as to whether an isolated echogenic focus in the fetal heart is a marker for trisomy 21 in the low-risk population. An echogenic focus is seen in 1.1–9.6% of obstetric sonograms[2–12] and an echogenic focus is seen in about 11% of Down syndrome fetuses[13]. Is the intracardiac echogenic focus a useful marker for trisomy 21? Some studies in low-risk populations have concluded that the echogenic focus is not a useful marker[2,3]; other authors have criticized the methodology of these papers, and have determined that the echogenic focus is a marker for Down syndrome in the high-risk population[4,6,8,10]. Some authors have determined that the echogenic focus, even as an isolated finding, is likely to be statistically significantly associated with Down syndrome in low-risk populations[8,10] by extrapolating data obtained in high-risk populations. From a meta-analysis, Smith-Bindman *et al.*[13] concluded that an echogenic focus identified at the second-trimester sonogram should not be considered a marker for trisomy 21.

The purpose of our study was to establish whether an isolated echogenic focus in the fetal heart at second-trimester ultrasound in women aged 18–34 years of age was associated with trisomy 21. This is the group of

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Accepted: 22 November 2002

women in which the finding of an echogenic focus may make the most difference to management.

METHODS

We performed a word search for echogenic focus or echogenic foci for all obstetric sonograms performed during the study period January 1997 to December 1999 at all public and private radiology sites in the region. These sites use the same computerized radiology information system.

During the study period, there were 12 373 deliveries of which 10 186 births (83%) were to women < 35 years of age (Statistics New Zealand).

The reports were scrutinized and those which included echogenic foci in the fetal heart were selected for further consideration. We extracted information on maternal age, gestation, number and site of intracardiac echogenic foci, and other ultrasound findings including structural fetal abnormalities, nuchal fold thickness > 6 mm, ventriculomegaly, fetal renal dilatation, small or absent fetal stomach, pericardial effusion, echogenic bowel, and choroid plexus cyst. All sonographers in the region participate in the same continuing professional development program, and sonographers and radiologists get regular feedback from a weekly regional fetal advice group, which reviews suspected fetal anomalies. If an intracardiac echogenic focus is seen on obstetric ultrasound examination, an advice sheet on this topic is sent with the radiologist's report to the referrer. The advice sheet concludes that an echogenic focus should be considered a 'soft sign' of aneuploidy; karyotyping should be considered if more than one 'soft sign' is present.

The population in our study was unselected. Neither maternal serum nor nuchal translucency screening programs were in place although maternal serum evaluation was performed in 75 women, and nuchal translucency thickness measured in fewer than 20. The women who had these tests were not excluded from the population.

Obstetric sonograms are performed routinely at 18–20 weeks' gestation in this region, by sonographers supervised by radiologists. The detection rate of fetal anomalies at second-trimester ultrasound in this region is 11.6 per thousand[14].

Pregnancy outcome was determined from maternal medical notes including birthing record, and infant notes. If there was any ambiguity in these, the carers were contacted for clarification. Outcome was defined as normal if the infant was described as normal in the birthing records and no antenatal abnormality was seen at obstetric sonograms or amniocentesis if performed. Outcome was considered abnormal if clinical abnormality was identified at the complete clinical examination recorded in the birthing records and/or at karyotype analysis.

From the 267 cases of echogenic focus in the total population, we excluded 118. In 67 maternal age was < 18 or > 34 years. Of those echogenic foci seen in women aged 18–34 years, a further 45 were excluded as the echogenic focus was not the only sonographic finding, and a further six were excluded as the initial obstetric sonogram in the pregnancy was after 24 weeks' gestation.

Of the 118 excluded, maternal age was < 18 in two women (both 17) one of whom had a first sonogram at 26 weeks' gestation with an echogenic focus as the only abnormal finding, and whose liveborn infant had trisomy 21. A further 65 women were aged ≥ 35 years.

Of the 118 cases excluded, 53 were isolated echogenic focus, and 65 were non-isolated. Of these 65, 45 were in women aged 18–34 years and 10 of these had an abnormal outcome (one trisomy 13, one trisomy 21 and the remainder with structural abnormalities, karyotyping not performed). Of the 65 non-isolated echogenic foci, 20 were in women aged > 34 years. Of these 20, seven were abnormal, two with trisomy 21 and the remainder with structural abnormalities, either with karyotyping not performed or the culture did not grow.

During the study period, trisomy 21 was detected in 38 deliveries either pre- or postnatally. Of these 38, maternal age was < 18 in one, 18–34 years in 13, > 34 years in 21, and unknown in three. An obstetric sonogram was performed at 16–24 weeks' gestation in 22 of the 38, and three others had the first obstetric sonogram after 24 weeks' gestation: the 17-year-old with echogenic focus seen at the 26-week scan, a 22-year-old with growth restriction diagnosed at 31 weeks whose infant died with an undiagnosed ventriculoseptal defect, and a 37-year-old with fetal atrioventricular canal defect diagnosed at 35 weeks' gestation.

The number of liveborn infants with Down syndrome delivered during the study period is likely to be an accurate figure. However, karyotyping of fetuses following termination of pregnancy for fetal abnormality was incomplete during the study period and karyotyping was technically unsuccessful for many aborted fetuses.

The incidence of trisomy 21 in the total population was 0.31%, 0.12% in women < 35 years, and 0.91% in women ≥ 35 years.

We designed the study to estimate the probability of an abnormal outcome in fetuses found to have an echogenic focus in the fetal heart at obstetric ultrasound. We anticipated a study population of approximately 150–200. We determined the precision possible with sample sizes of 150 and 200: for a population of 150, if 0% were abnormal, then the 95% confidence interval (CI) would be 0.00–2.43 and if 4% were abnormal then the 95% CI would be 1.46–8.56; for a population of 200, if 0% were abnormal, then the 95% CI would be 0.00–1.83 and if 2% were abnormal, then the 95% CI would be 0.55–5.04. We anticipated that if we found 2% to be abnormal among the group with an isolated echogenic focus, we would have established that isolated echogenic focus was a 'hard sign' of aneuploidy. If we found that 0% were abnormal, we would need a control group to determine if echogenic focus was a 'soft sign'.

Neither national nor local data include the number of pregnant women having a sonogram. However, there are

reliable data on the number of obstetric sonograms, the indication for sonograms and the number of deliveries, from which it can be inferred that there are an average of 2.3 obstetric scans per birth in the region (Ultrasound Utilisation Committee, Health Funding Authority, New Zealand, pers. comm.). We estimate that an obstetric sonogram at 16–24 weeks' gestation was performed in 9167 of the 10 186 (approximately 90%) women < 35 years old. An echogenic focus was seen in 202 of these. Of the 202, two women were < 18 years old. Of the 2187 deliveries to women ≥ 35 years, we estimate that 1968 had an obstetric sonogram at 16–24 weeks' gestation. This number could be an over-estimate, as there is a trend for older women to avoid prenatal testing if they do not intend to act on the result. An echogenic focus was seen in 65 of these.

The study group comprised the 149 pregnant women who were aged 18–34 years who had an echogenic focus in the fetal heart as the only abnormality at an obstetric sonogram performed at 16–24 weeks' gestation.

RESULTS

There were no abnormal outcomes among the 149 pregnancies with echogenic focus as an isolated finding in women aged 18–34 years (0%; 95% CI, 0.00–2.43).

In the population of women < 35 years old who had a 16–24-week obstetric sonogram, the prevalence of all echogenic foci was 193/9167 (2.1%) compared with 3.1% for fetuses of mothers ≥ 35 years old. There was no significant difference in the prevalence of isolated echogenic foci among women < 35 years (2.1%) compared with women ≥ 35 years old (2.2%, $P = 0.8$).

The prevalence of isolated echogenic foci among fetuses with trisomy 21, regardless of maternal age or gestational age was: for all echogenic foci, 4/25 (16%); for isolated echogenic focus, 1/25 (4.0%). For the 38 with trisomy 21 in the population, the pregnancy outcome was termination of pregnancy in eight (all had karyotyping because of the abnormal sonogram), neonatal death in one, and 29 were liveborn. Of those 13 infants with trisomy 21 born to mothers aged 18–34 years, karyotyping was performed in four because of the abnormal sonogram, and the outcome was termination of pregnancy in three and neonatal death in one. The other nine were born alive. A second-trimester sonogram was performed in 10 of the 13. In these 10, sonographic findings were: normal in five, cardiac abnormality in three, choroid plexus cyst as an isolated finding in one, and one with choroid plexus cyst, echogenic focus, and small fetal stomach. An echogenic focus (as a non-isolated finding) was seen in only one of these 10.

Of the 21 cases of trisomy 21 born to women > 34 years of age or < 18 years of age, 11 had an obstetric sonogram at 16–24 weeks' gestation. In these 11 fetuses the sonogram was normal for three, abnormal for seven (five elected termination of pregnancy after karyotyping), and in one a further sonogram was recommended because of 'heart not well seen'; no further sonogram took place, however.

Of the 38 with trisomy 21 in the population, 12 had abnormal sonograms in the second trimester (11 had karyotyping performed) and two more had an abnormal sonogram in the third trimester but karyotyping was delayed until after delivery. Of the 21 cases of trisomy 21 born to women > 34 years of age or < 18 years of age an echogenic focus was seen as an isolated finding in one 17-year-old, and as a non-isolated finding in two cases (maternal ages, 38 and 44 years).

Echogenic foci were single and left ventricular in 84.7% of cases, single and right-sided in 3.6% of cases and multiple in 11.9% of cases.

DISCUSSION

The prevalence of echogenic foci in our total population was 2.4%. This is at the lower end of the range of previously reported prevalences of 2.3–9.6%[2,4–10] but is very similar to the prevalence reported in low-risk populations. There is a trend for the reported prevalence of echogenic foci to be higher in populations at higher risk for aneuploidy (Table 1). The prevalence of isolated echogenic focus in our population was lower, at 1.8%. We confirm the findings of others that the prevalence of isolated echogenic focus is similar across different maternal age bands[8,10]. If isolated echogenic focus were associated with trisomy 21, one would expect the prevalence of isolated echogenic focus to increase with increasing maternal age.

In our study, echogenic foci were predominantly found in the left ventricle (85%) similar to the 61–88% reported by others[2,4,10].

Smith-Bindman *et al.*[13] estimated the sensitivity of an isolated echogenic focus for detecting trisomy 21 to be 11% (95% CI, 6–18) based on a meta-analysis of three publications[4,6,7]. Winter *et al.*[8] found an isolated echogenic focus to be 8% sensitive in detecting trisomy 21 in women < 35 years of age. If we include the 17-year-old mother first scanned at 26 weeks' gestation, then our sensitivity of isolated echogenic focus in detecting trisomy 21 was 4%. Recent publications have addressed the likelihood of a fetus with an isolated echogenic focus having trisomy 21. In their meta-analysis, Smith-Bindman *et al.*[13] estimated the likelihood ratio to be 2.8 (95% CI, 1.5–55) based on three publications. Those that argue isolated echogenic focus is associated with trisomy 21 base their conclusions on likelihood ratios. The likelihood ratio is directly related to sensitivity and inversely related to specificity. For any population the higher the sensitivity, the higher the likelihood ratio if specificity remains the same. It is unclear why the sensitivity of echogenic focus for trisomy 21 is lower in low-risk populations than in high-risk populations (Table 1). Therefore direct translation of likelihood ratios from a high-risk population to a low-risk population should be done with caution. Our study has insufficient power to determine whether the likelihood ratio in our

Table 1 Association of isolated echogenic foci to trisomy 21 correlated with maternal and gestational ages

Study	*EF* prevalence (%)	*T21* prevalence (%)	*All EF* (n)		*Isolated EF* (n)		*Isolated EF* (n) MA = *18–34 years*		*Isolated EF* (n) *MA < 35 years* GA = *16–24 weeks*	
			EF	*T21 + EF*	*EF*	*T21 + EF*	*EF*	*T21 + EF*	*EF*	*T21 + EF*
Present study	2.4	0.34	267	4	202	1	155	1	149	0
Bromley 1995[4]	4.9	1.6	66	4	66	3	NS	0	NS	0
Nyberg 1998[5]	5.3	Case control	57	24	19	8	NS	NS	NS	NS
Manning 1998[6]	2.7	1.9	24	3	23	2	NS	NS	NS	NS
Vibhakar 1999[7]	4.8	3.5	204	11	164	7	NS	NS	NS	NS
Winter 2000[8]	13.3	1.7	163	16	145	6	51	1	51	1
Wax 2000[9]	3.2	0.7	26	2	21	0	NS	NS	NS	NS
Huggon 2001[10]	9.6	1.2	853	28	548	5	NS	3	NS	NS
Achiron 1997[2]	3.0	0.000	66	0	66	0	66	0	66	0
Bromley 1998[15]	NS	NS	290	14	NS	1	NS	0	NS	0
Sepulveda 1995[20]	NS	NS	NS	3	NS	0	NS	0	NS	0
Dildy 1996[11]	4.9	0	25	0	?25	0	NS	0	NS	0
Merati 1996[12]	3.3	0	37	0	35	0	NS	0	NS	0
Totals			2078	109	1314	33	272	5	266	1

EF, echogenic focus; T21, trisomy 21; All, all echogenic foci whether isolated or in combination with other sonographic abnormalities; Isolated, echogenic focus was only abnormal finding at sonography; MA, maternal age; GA, gestational age; NS, not stated.

low-risk population differs from figures derived from higher risk populations. More recently Winter *et al.*[8] have determined the relative risk to be 1.6 (95% CI, 0.2–12.4), which is statistically non-significant. Bromley *et al.*[15] have estimated the relative risk to be 1.

Isolated echogenic focus has been associated with trisomy 21 in 33 published cases (Table 1). Of these 33, 10 were in women > 34 years and in 18 maternal age was not stated, but all were from high-risk populations[4,6,7]. Only five were in women < 35 years. Of these five, three were from a high-risk population referred for fetal echocardiography[10] and gestational age was not stated. One was in a woman aged 34.7 years, but the triple test had assessed her risk as 1:140[8]. The other was our 17-year-old first scanned at 26 weeks' gestation. Our interpretation from the previous studies and our own is that there is no convincing evidence for elevated risk if an isolated echogenic focus is seen in a fetus whose mother is aged < 35 years.

Does the absence of an echogenic focus reduce the risk for trisomy 21? The studies of Smith-Bindman *et al.*[13] and the estimation from Bromley *et al.*[15] indicate that the risk for trisomy 21 is not lowered; however, others argue that the risk is lowered (likelihood ratio, 0.4–0.6)[5,10,16].

If only considered are studies in which the population is clearly defined as < 35 years of age, and the echogenic focus is an isolated finding at an obstetric sonogram at 16–24 weeks' gestation, then only one case of trisomy 21 has been reported. This highlights the inadequacy of the literature to date in addressing the important clinical question of the association between a sonographically isolated echogenic intracardiac focus and trisomy 21 in a low-risk population. We believe that our study has specifically addressed this question and our conclusion is that, because no association has been demonstrated, until more studies on low-risk populations are reported, an echogenic focus seen at second-trimester ultrasound examination in a women aged 18–34 years should be considered as neither increasing nor decreasing the risk of aneuploidy. We accept that a finding of zero does not confer increased confidence in the result[17].

Our study has a number of strengths. We have performed a comprehensive community-based study in a non-selected population that had not undergone pre-screening by triple testing or nuchal translucency thickness assessment. We excluded women < 18 years of age because of the increased risk for poor perinatal outcome[18]. Amniocentesis is unlikely to be offered to women < 18 years old unless a structural fetal abnormality is seen. We also excluded women aged ≥ 35 years because of their increased risk of trisomy 21 and other poor obstetric outcomes. Our maternal age selection criteria are similar to those in other studies[9,15,19]. We excluded echogenic foci seen when the initial sonogram was after 24 weeks' gestation, because the options for pregnancy management are very different in such cases. Others have used the same exclusion criterion[7–9,11,12]. We addressed the significance of the presence of an isolated echogenic focus seen in the second trimester in women aged 18–34 years, which is representative of the time and age group of routine fetal morphology scans in most institutions in the world. We specifically addressed the association of echogenic focus with trisomy 21, excluding other aneuploidies, and we identified what we believe to be all infants or fetuses with trisomy 21 during the study period.

A weakness of our study was that karyotyping was performed in only a few cases; we assumed that clinically normal infants did not have trisomy 21. However, we have a single referral center for all trisomy 21 infants and one pathology laboratory, so we are unlikely to be underestimating the number of liveborn trisomy 21 infants. Furthermore, we did not establish specific criteria

for the diagnosis of an echogenic focus. However, as the community of sonographers in the region attend the same continuing professional development activities, the criteria are likely to be similar, although we accept that individual sonographers as well as individual radiologists are subject to personal bias in either under- or over-reporting echogenic foci. We only reviewed the verified reports of the obstetric sonograms and did not review the images. This could actually be regarded as a strength rather than a weakness. Prenatal sonograms were performed in only 25 of the 38 trisomy 21 infants. The remaining 13 infants were born to older mothers. There appears to be a trend in our community for some mothers at increased risk of Down syndrome pregnancies to avoid prenatal testing, perhaps because they do not intend acting on the result. We are not able to indicate how many trisomy 21 infants had abnormalities detectable on retrospective review of the obstetric sonogram, even though it is our standard practice to review all such sonograms, because record keeping is not adequate for retrospective review.

In conclusion, no cases of trisomy 21 were detected at second-trimester ultrasound examination among fetuses with an intracardiac echogenic focus in our low-risk population, indicating the absence of an association.

ACKNOWLEDGMENTS

We thank the following: Dr Elisabeth Wells, Biostatistician, for help with planning the size of the study population required, and for statistical analysis of the results; Statistics New Zealand for providing regional population data; Dr Richard Chisholm for help with obtaining access to all cases in the region; Tedi McDonald for helping with the layout and typing of the paper.

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