Embryonic Heart Rate as a Prognostic Factor for Chromosomal Abnormalities

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Objective. The purpose of this study was to evaluate the role of a slow embryonic heart rate in embryos before 7 weeks’ gestation as a marker in screening for chromosomal abnormalities.

Methods. Fifty-seven embryos before 7 weeks’ gestation with slow heart rates were compared with 1156 embryos of the same gestational period with normal heart rates. Embryos that showed an increased risk of chromosomal abnormalities in the screening blood tests underwent invasive analysis for abnormal karyotype detection. Results. The rates of first-trimester death were 15.8% for pregnancies with slow embryonic heart rates (9 of 57) and 2.5% for those with normal heart rates (29 of 1156). Because of the increased risk of chromosomal abnormalities, amniocentesis was performed on 6 with slow embryonic heart rates and 61 with normal embryonic heart rates. After karyotype analysis, there were 2 fetuses with trisomy 21 in each group, which represented significantly higher percentage of embryos with trisomy 21 in the slow–heart rate group compared with the normal–heart rate group (P < .05).

Conclusions. When a slow embryonic heart rate is detected before 7 weeks’ gestation, there is a higher likelihood of chromosomal abnormalities. Key words: embryo; fetus; first trimester; heart rate.
uploidy and a slow embryonic heart rate has been evaluated in a previous study, and chromosomal abnormalities were reported to be more than twice as frequent in cases with a slow embryonic heart rate.9

The aim of this study was to assess the relationship between the embryonic heart rate and chromosomal abnormalities by evaluating the frequency of aneuploidy among embryos with slow versus normal heart rates.

Materials and Methods

We prospectively collected the data on all obstetric sonograms obtained between June 2007 and June 2008 that showed cardiac activity in singleton pregnancies at or before 7 weeks' gestational age. Exclusion criteria were vaginal bleeding at the time of sonographic examination and pregnancies with systemic disorders (eg, hyperthyroidism, hypothyroidism, and diabetes). If a woman had more than 1 sonogram in her pregnancy at or before 7 weeks, only the first sonogram showing cardiac activity was included in the study. Informed consent was obtained from each participant, and the Ethics Committee of the institution approved this study.

In a study done by Doubilet and Benson,4 embryos at less than 7 weeks' gestational age were divided into 2 subgroups: less than 6 weeks 3 days and 6 weeks 3 days to 7 weeks, based on crown-rump length (CRL). The gestational age was determined by transvaginal sonographic measurement of CRL in the B-mode as a single measurement from the cranial to caudal ends of the body with the embryos in a neutral position. The use of a single CRL measurement instead of averaging 3 measurements may have been a limitation of our study.

The embryonic heart rate was determined by transvaginal sonographic analysis, which was performed by watching the embryo for at least 3 minutes for embryonic heart rate patterns, and an average of 10 cardiac cycles were recorded in the M-mode. The calculation of the embryonic heart rate was made by measuring the time interval for 3 heartbeat waves in sequence, and with those data, the number of heartbeats per minute was calculated.

In the same study referred to above,4 if the embryo was less than 6 weeks 3 days, the heart rate was classified as slow if it was less than 100 bpm, whereas, if the embryo was between 6 weeks 3 days and 7 weeks, then the heart rate was classified as slow if it was less than 120 bpm. Embryonic heart rates below the lower limits that persisted throughout the 3-minute interval of observation were categorized in the slow–heart rate group, whereas temporal bradycardia that did not persist throughout the 3-minute interval was categorized in the normal–heart rate group.

Sonographic evaluations of all pregnancies were done with a LOGIQ 5 real-time scanning system with the capacity of simultaneous B- and M-mode scanning (GE Healthcare, Milwaukee, WI). Ongoing pregnancies received a subsequent sonographic follow-up at 11 to 14 weeks, and all of the embryos were evaluated in terms of CRL and nuchal translucency (NT) measurements and observation of the head, brain, chest, heart, abdominal wall, and extremities for anomalies. In addition to the sonographic evaluation and NT measurements performed in all of the patients, a combined test was advised to all. Among the patients who missed the appropriate time to give a blood sample for the combined test, a triple test in the second trimester was performed.

An NT value above the 95th percentile was considered as showing increased NT. Invasive tests (chorionic villus sampling [CVS] and amniocentesis) were suggested in patients whose combined risk or triple risk was 1 per 250 or higher at term for either Down syndrome or trisomy 18/13.

Newborn examinations of all neonates delivered in our research group at our hospital were conducted by neonatologists. Fetuses from terminated pregnancies and those with in utero death underwent fetopsy.

All statistical analyses were performed with SPSS version 13.0 software (SPSS Inc, Chicago, IL). The Student t-test and $\chi^2$ test were used for comparison of groups. Results were considered statistically significant at $P < .05$. 

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Results

The study population included 1272 singleton pregnancies of less than 7 weeks’ gestation that showed embryonic cardiac activity. Of these patients, 376 were at less than 6 weeks 3 days in gestational age, and 896 were from 6 weeks 3 days to 7 weeks of gestational age. The mean maternal age ± SD was 26.67 ± 5.11 years (range, 16–41 years), and the median gravida was 3 (range, 1–6). Pregnancies with slow embryonic heart rates were compared with those having normal embryonic heart rates with respect to chromosomal abnormalities (Table 1).

A slow embryonic heart rate was detected in 68 pregnancies. In the remaining 1204 patients, the embryonic heart rate was in the normal range for the respective gestational age. In the slow–heart rate group, 11 patients (16.1%) ceased their regular visits; therefore, their subsequent data were not available. From the remaining 57 pregnancies in the slow–heart rate group, 9 embryos (15.8%) died by the end of the first trimester.

Nuchal translucency was measured in all of the remaining 48 patients, and a combined test was performed in 12 of them. In 2 pregnancies, an elevated combined test because of an increased NT was observed. For the 36 patients who missed the combined test, a triple test was performed in the second trimester, and of these 36 patients, 4 showed an increased risk for aneuploidy even though the NT measurements were found to be within normal limits.

The overall results revealed that 6 of 48 patients (12.5%) had an increased risk for chromosomal abnormalities. The patients at risk were advised to undergo further tests (CVS or amniocentesis) for analysis according to the gestational ages of the fetuses. None of the patients preferred the CVS study, whereas all preferred amniocentesis (some had to wait a few weeks for the right time to have amniocentesis). In amniocentesis, trisomy 21 was detected in 2 fetuses (4.2%), 1 from the abnormal combined test group and the other from the abnormal triple test group. Echocardiographic findings were normal in both of these patients.

In the normal–heart rate group of 1204 patients, 48 (3.9%) were lost to follow-up, and their outcomes could not be obtained from the hospital records. Of the remaining 1156, 29 embryos (2.5%) died before the end of the first trimester. The remaining 1127 were evaluated for chromosomal abnormalities; 278 had a combined test, and 849 had a triple test. In 61 (5.4%), 13 from the combined test group and 48 from the triple test group, an increased risk for chromosomal abnormalities was observed. None of the patients showed an increased NT measurement on sonography.

Two patients volunteered for CVS. No chromosomal abnormality was found by CVS in these patients. For the remaining 59 patients, amniocentesis was performed as an advanced study for further evaluation of this increased risk group, and trisomy 21 was found in 2 patients (0.2%).

All neonates from the study group were examined by neonatologist, and no marker for aneuploidy was reported. Fetopsy found that there were no chromosomally abnormal fetuses other than the fetuses that were terminated because of diagnosed chromosomal abnormalities based on invasive tests.

The frequency of chromosomal anomalies was higher in embryos with a slow heart rate (2 of 48) than those with a normal heart rate (2 of 1127; \( P = .009 \)).

Discussion

Strategies involving biochemical studies and sonography are able to prenatally detect two-thirds of affected fetuses while selecting 5% of the chromosomally normal population for invasive testing. These are used at 15 to 18 weeks for biochemical screening or at 11 to 14 weeks when NT is assessed.10 However, new strategies are desirable to raise the detection rates and to

<table>
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<th>Parameter</th>
<th>Slow</th>
<th>Normal</th>
<th>( P )</th>
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<tr>
<td>Mean age ± SD, y</td>
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<tr>
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<td>20/48</td>
<td>356/848</td>
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<td>48/1204</td>
<td>.0002</td>
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<tr>
<td>Lost to follow-up</td>
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<tr>
<td>Miscarriage</td>
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<td>29/1156</td>
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<td>6/48</td>
<td>61/1127</td>
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<td>Chromosomal abnormality</td>
<td>2/48</td>
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Table 1. Comparison of Data for the Slow– and Normal–Heart Rate Groups
decrease unnecessary invasive tests. Most pregnant women prefer screening in the first trimester as early as possible. The data in our study imply that measurement of the embryonic heart rate before 7 weeks’ gestation may be an early marker for chromosomal abnormalities among offspring with subsequent positive combined or triple screening results.

Studies of the heart rate in chromosomally abnormal fetuses have reported conflicting results. In a previous longitudinal study involving 1 fetus with trisomy 21 at 6 to 9 weeks’ gestation, the heart rate was consistently below the third percentile of the normal range.11 In another study of 5 affected fetuses at 7 to 13 weeks, the heart rate was always within the normal range.12 On the other hand, in some previous studies, an increase in the heart rate with trisomy 21 was reported.13,14 Two different hypotheses have been proposed for tachycardia in trisomy 21. There may be a delay in the functional maturation of the parasympathetic system and a consequent delay in the physiologic decrease in the heart rate with gestation after 9 weeks.15 Alternatively, the cause of tachycardia may be a compensatory mechanism to increase cardiac output in the phase of left heart obstruction in atrioventricular or ventricular septal defects associated with relative narrowing of the aortic isthmus.16 In previous studies in which fetal tachycardia was detected in trisomy 21, the fetal cardiac rhythms were measured at 11 to 14 weeks’ gestation as part of the first-trimester screening. Data on the cardiac activity before 7 weeks’ gestation were unavailable in these studies.

In our study, we detected 4 fetuses (0.3%) with Down syndrome; 2 (4.2%) were in the slow–heart rate group, and the other 2 (0.2%) were in the normal–heart rate group. A significantly higher percentage of fetuses with trisomy 21 in the slow–heart rate group compared with the normal–heart rate group was observed, although the number of patients was relatively small in the group with slow embryonic heart rates. Another limitation of our study was that the rates of loss to follow-up and embryonic death at the end of the first trimester were substantially higher in the slow–heart rate group, such that these factors may have had a negative impact on the karyotype analysis. The early pregnancy losses were likely to have been treated at a local clinic rather than be referred to our hospital, which is a tertiary medical center; thus, the high rate of loss to follow-up in the slow–heart rate group was of concern. For comparison, the incidence of Down syndrome was 0.6% in an unselected population.17

A physiologically slower heart rate may be due to immaturity of the sinoatrial node in the early stages of pregnancy, or the atrial pacemaker may actually be slower during early gestation in the normal heart.9 However, in some cases, a slow embryonic heart rate may represent idioventricular rates of an abnormal heart.18

In a study by Russo et al,19 it was reported that 32% of congenital heart diseases diagnosed prenatally were associated with chromosomal anomalies, whereas another study showed that 36% of congenital heart disease in live births had chromosomal anomalies.20 An underlying cause of a slow embryonic heart rate may be an indication of cardiac problems with chromosomal abnormalities.

A major limitation of our study was the method of diagnosing or excluding chromosomal defects, which was based on antenatal sonographic assessment and biochemical screening tests. Ideally, all fetuses included in these kinds of studies should undergo karyotype analysis; however, this is not achievable in practice. Genetic testing of the conceptus after spontaneous abortion is not generally done, mainly because of technical difficulties in karyotyping the aborted specimen. Collection of the specimen can be difficult because many women abort at home or outside standard laboratory hours. Moreover, standard cytogenetic techniques are associated with high failure rates; thus, there are spontaneous abortions in the first trimester.21 Autosomal trisomies (in 37% of the karyotyped samples) were the most frequently detected anomalies, followed by polyploidy (9%) and monosomy X (6%).22,23 It has been the common consensus that early embryonic losses are mostly associated with chromosomal defects. Our study, on the other hand, supports the idea that embryos before 7 weeks’ gestation with slow heart rates have a greater risk of chromosomal anomalies than embryos of the same gestational age with normal heart rates.
Several studies have documented that a slow embryonic heart rate at 6 to 7 weeks' gestation is associated with a high rate of first-trimester pregnancy loss. This often occurs soon after the slow heartbeat is detected. In our study, 15.9% of cases resulted in spontaneous pregnancy loss at the end of the first trimester, and the frequency of spontaneous abortion in our study was slightly higher than that reported by some of the previous studies. As an exception, Doubilet et al reported that 60.6% of embryos with slow heart rates had died by the end of the first trimester. The higher fetal loss rate in this study may have been due to the heart rate's being classified as slow if it was less than 90 bpm before 6 weeks 3 days and less than 110 bpm at 6 weeks 3 days to 7 weeks, which were both lower than the limits used in most of the other studies. It is difficult to compare the results of different studies, mostly because of differences in the accepted cutoff values for the definition of bradycardia, and these differences lead to a divergence in the results for early fetal losses.

In conclusion, our study shows that a slow heart rate before 7 weeks' gestation may be an early marker for chromosomal abnormalities. This suggests that an early slow embryonic heart rate is a promising diagnostic factor that might be included as an additional parameter in the screening tests for detection of chromosomal abnormalities. The advantages of early embryonic heart rate detection as a screening test for chromosomal abnormalities, as opposed to combined and triple tests, are that it is a less expensive, noninvasive, convenient, and fast test that would be associated with more effective patient cooperation. However, it cannot be a substitute for the biochemical screening tests because it is more of a complementary test. Additional studies involving larger patient populations are needed before any recommendations can be made.

References


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