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Non-invasive prenatal detection of haemoglobin Bart's disease by cardiothoracic ratio during the first trimester

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ABSTRACT

Objective: To evaluate the efficacy of the sonographic cardiothoracic ratio (CTR) in early pregnancy for the prediction of fetal haemoglobin (Hb) Bart's disease.
Study design: Over a 1.5-year period at a Chinese tertiary obstetric centre, women at risk of Hb Bart's disease were given the option of a non-invasive approach to exclude an affected pregnancy between 11 weeks and 13 weeks and 6 days of gestation, with a routine rescan after a 2-week interval. The fetal CTR, a sonographic marker, was assessed, and invasive testing followed in cases of fetal cardiomegaly. The diagnosis of fetal Hb Bart's disease was based on DNA analysis from chorionic villus sampling.
Results: Of 154 at-risk cases studied, five cases (four at 11 weeks of gestation) were subjected to direct invasive testing because of an unsatisfactory scan. Of the remaining 149 cases, non-invasive ultrasound examinations were performed successfully. Thirty-four (22.8%) affected pregnancies were revealed, including one picked up on rescan. The sensitivity and specificity of the non-invasive approach were 97.1% and 100%, respectively. The need for an invasive test was reduced by 74.7%, and all affected pregnancies except one were diagnosed before 14 weeks of gestation.
Conclusion: CTR can differentiate reliably between pregnancies with and without Hb Bart's disease. This non-invasive approach for the exclusion of Hb Bart's disease can be used in early pregnancy.

Introduction

Alpha-thalassaemia is inherited as an autosomal-recessive disorder. It is probably the most common monogenic gene disorder in the world, and is particularly common in South-East Asia, including southern China [1]. Haemoglobin (Hb) Bart's disease (homozygous α^0-thalassemia) is the most severe form of α-thalassaemia in which no α-globin is produced. Death almost always occurs towards term or shortly after birth, although a very small number of patients survive following intra-uterine and postnatal repeated transfusions [2–4]. Treatment is controversial as survivors show abnormal subsequent development. In addition, maternal complications during pregnancy include pre-eclampsia and postpartum haemorrhage [5].

When both partners of a couple carry an α^0-thalassaemia, the risk of having a fetus with Hb Bart's disease is 25%. Prenatal diagnosis should be offered because of the risks for the fetus and the mother. Traditionally, a direct invasive method involving chorionic villus sampling (CVS) or amniocentesis is used for prenatal detection of an affected fetus. However, due to the severe anaemia that can present in the first trimester, ultrasound examination can readily detect the many anaemic signs found in fetuses with Hb Bart's disease. Indeed, sonographic screening for hydropic fetuses, followed by selective invasive testing, has been adopted as the standard procedure for second-trimester at-risk pregnancies referred to the study centre [6,7]. This study evaluated the efficacy of the sonographic cardiothoracic ratio (CTR) in early pregnancy for prediction of fetal Hb Bart's disease in mainland China.

Materials and methods

Subjects

This study was conducted with the approval of the Ethics Committee of Guangzhou Maternal and Neonatal Hospital, where the programme of prenatal control for severe thalassaemia syndrome is well established [8]. Between January 2013 and June

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2014, consecutive pregnant women at risk of fetal Hb Bart's disease and attending the prenatal diagnostic unit were recruited into the study with written informed consent. The women were offered the option of: (a) a direct invasive CVS test; or (b) the non-invasive approach, with two serial ultrasound scans to detect fetal CTR. The option of an invasive test was also offered to establish the diagnosis if cardiomegaly was detected.

The screening marker for α-thalassaemia is a low mean corpuscular volume (MCV) with a cut-off value <80 femtoliter, ruling out the possibility of iron deficiency. Hb pattern and Hb H inclusion bodies are also checked when a low MCV is found. Gap-polymerase chain reaction (gap-PCR) assay is used to confirm the common α-thalassaemia deletions. The inclusion criteria were as follows: (1) singleton pregnancies at a gestational age of 11 weeks to 13 weeks and 6 days, determined by fetal sonographic crown–rump length measurement; (2) couples at risk of having fetuses with Hb Bart's disease because both partners were found to be α^0-thalassemia-positive in the prenatal screening programme, or their previous pregnancies had been affected by the disease; and (3) couples who opted for the non-invasive approach, with serial ultrasound examinations at the first referral and at the second appointment 2 weeks later. CVS was only offered to patients with abnormal sonographic findings at any time. The diagnosis of Hb Bart's disease was confirmed by DNA analysis using a gap-PCR assay [7]. Pregnancy outcome was further ascertained by follow-up until the termination of pregnancy for affected cases. Patients who were not subjected to invasive prenatal testing were followed by routine prenatal care, including a structural scan at 18–20 weeks of gestation, and cord blood was collected at birth for haematological analysis.

Ultrasonographic measurement

A transabdominal sonographic examination was performed for fetal biometric measurements, and nuchal translucency, ductus venosus and tricuspid flow were evaluated. A Voluson E8 (GE Healthcare, Fairfield, CT, USA) ultrasound machine was used, equipped with a 4- or 7-MHz curvilinear transabdominal transducer. Fetal CTR was chosen as the parameter to predict which fetuses were affected by Hb Bart's disease in this study. In the measurement of CTR, the probe was oriented to obtain a cross-sectional view of the fetal thorax at the level of the four-cardiac-chamber view. The cardiac diameter was taken at the level of the atrioventricular valves during end diastole between the epicardial surfaces, the transverse thoracic diameter was measured between the outer edge of the ribs in the same image with demonstration of symmetrical bilateral ribs, and the ratio was calculated (Fig. 1). CTR was measured two or three times until the difference was less than 0.02. Cardiomegaly was defined as CTR ≥0.49 at 11–12 weeks of gestation, and ≥0.5 at 13 weeks of gestation based on a previous study [9] and the authors' experience. LZ and MP performed ultrasound examinations on subjects in this study; both had been trained intensively in this technique. When two measurements of the same fetus in a subgroup of 30 subjects were compared, the intra- and interobserver variability reproducibility of CTR was <0.02 on 95% of occasions. The mean measurements of normal and affected pregnancies were compared using two-tailed Student's *t*-test.

Results

During the study period, 154 singleton pregnancies at risk of fetal Hb Bart's disease were recruited. Satisfactory abdominal sonographic imaging was obtained in 149 (96.1%) cases. Cardiac measurement was not possible in five pregnancies (four at 11 weeks of gestation and one at 12 weeks of gestation) because a good four-chamber view was not obtained. These five women could not wait for a repeated scan, and opted for an immediate CVS. Abnormal fetal CTR was found in 33 of the 149 pregnant women at their first referral. Invasive testing was performed immediately on the same day, and fetal Hb Bart's disease was confirmed in all 33 women on the day after sampling. In one case, the initial scan at 12 weeks showed a normal fetal CTR (0.48), but a subsequent scan at 14 weeks showed an increased CTR (0.52). CVS followed in this case, and confirmed the diagnosis of Hb Bart's disease. Invasive testing was not performed in the remaining 115 pregnancies, in which a normal fetal CTR was found by the initial and subsequent scans. All but one of these women continued their pregnancies to term, and the neonates were confirmed as healthy by haemoglobin analysis of cord blood at birth. In one woman, the fetal CTR measurement was normal at 11 weeks and 13 weeks of gestation, but classic hydropic changes with normal CTR were detected at the 18–20-week structural assessment. Cordocentesis was performed and revealed a normal genotype and karyotype. The causes of hydrops in this case remain undefined.

The mean CTR values in affected and unaffected pregnancies are shown in Table 1. The sensitivity and specificity of CTR as a marker of Hb Bart's disease at 11–13 weeks of gestation were 97.1% and 100%, respectively. Fig. 2 illustrates the number of invasive procedures avoided with this diagnostic strategy in this study. In this series, the need for an invasive test was reduced by 74.7% (115/154), and all but one of the affected pregnancies were diagnosed before 14 weeks of gestation and were terminated in a timely manner. Retesting to confirm the prenatal findings was conducted by cord blood analysis at birth in the 114 unaffected pregnancies. All results were in concordance with the prenatal sonographic results.

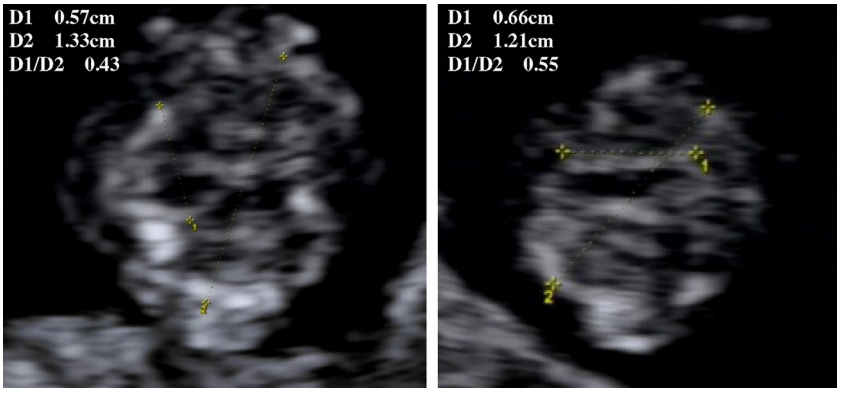

Fig. 1. Examples of normal and increased fetal cardiothoracic ratio at 11 weeks of gestation.