Original Article

Accuracy of Subjective Ultrasonographic Prediction of Fetal Cardiomegaly in Hemoglobin Bart's Disease by Non-Expert Sonologists

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Objective: To determine the accuracy of subjective ultrasonographic assessment of fetal cardiomegaly in predicting fetal hemoglobin (Hb) Bart's disease by non-expert sonologists.

Materials and Methods: Ninety video clips of fetal chest ultrasounds performed on fetuses at risk of Hb Bart's disease at 18 to 22 weeks of gestation were retrieved from medical records. One expert and four non-expert obstetric sonologists, all blinded to patient information and initial assessment data, subjectively assessed the clips for fetal cardiomegaly. The sensitivity and specificity of subjective ultrasonographic assessment by the non-expert sonologists were compared to those based on cardiothoracic ratio (CTR), middle cerebral artery peak systolic velocity (MCA-PSV), and placental thickness measured by specialists.

Results: The sensitivity of subjective ultrasonographic assessment by the non-expert sonologists and the expert was not significantly different (82.4% versus 91.9%, p=0.061). The sensitivity of CTR (100%) measured by the expert was significantly higher than that by subjective ultrasonographic assessment by the non-expert sonologists (p<0.001). However, the sensitivities of MCA-PSV (89.2%) and placental thickness (70.3%) measured by the specialist were comparable with the sensitivity of subjective ultrasonographic assessment by the non-expert sonologists (p=0.195 and 0.059, respectively).

Conclusion: A subjective ultrasonographic assessment of fetal cardiomegaly by non-expert sonologists is acceptable in identifying Hb Bart's disease in fetuses. Its sensitivity was comparable with MCA-PSV, but less than CTR, as measured by experts.

Keywords: Alpha thalassemia, Anemia, Cardiomegaly, Fetal heart, Fetal hemoglobin, Fetal ultrasonography

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Hemoglobin (Hb) Bart's or homozygous α-thalassemia-1 disease is the most common cause of fetal anemia leading to hydrops fetalis and stillbirth in Southeast Asia[1-3]. In pregnancies at risk, the affected fetuses are definitively diagnosed by invasive techniques, such as chorionic villous sampling or cordocentesis that can be complicated and lead to fetal loss[4]. Alternatively, sonographic techniques offer a non-invasive screening tool for signs of fetal anemia and hydrops that have been shown to be effective in selected cases to perform or avoid the invasive procedures[5-7]. Fetal cardiomegaly, defined as an increase in cardiac diameter or thoracic diameter ratio (cardiothoracic ratio, CTR) of more than 0.5, is one of the early sonographic markers that has been proven to be an effective predictor for Hb Bart's disease[8]. However, CTR measurements require a good quality fetal chest image in cross-sectional plane, the correct fetal cardiac four-chamber view and precise placement of cursors at the greatest dimensions during end-diastole, these need expertise and training[9]. Unfortunately, trained sonologists are not available in most parts of Thailand, especially in rural areas where

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Hb Bart's disease is highly prevalent. In the present experience, the authors have observed that a subjective ultrasonographic assessment of fetal cardiac size is good enough to differentiate fetuses affected by Hb Bart's disease from unaffected ones. However, no scientific evidence of the effectiveness of subjective ultrasonographic assessment of fetal cardiac size in predicting fetal anemia or Hb Bart's disease has been published. Therefore, the present study was conducted to determine the accuracy of subjective ultrasonographic assessment of fetal cardiomegaly in predicting fetal Hb Bart's disease, specifically by general obstetricians with limited experience in fetal ultrasound, compared to diagnosis using CTR, middle cerebral artery peak systolic velocity (MCA-PSV), or placental thickness as measured by experts.

Materials and Methods

A diagnostic study with cross-sectional comparisons was conducted with ethical approval by the Institute Review Board. The patient data and video clips of pregnant women underwent fetal ultrasound and prenatal diagnosis procedures between April 2014 and August 2016 were consecutively selected from the Maternal and Fetal Medicine (MFM) medical records. The inclusion criteria were 1) pregnant women at risk of fetal Hb Bart's disease who were diagnosed when both of the couples were α-thalassemia-1 carriers, based on polymerase chain reaction (PCR; SEA-type) technique, 2) gestational age of 18 to 22 weeks, based on a known last menstrual period and early fetal biometry, either by crown-rump length in the first trimester or biparietal diameter in the second trimester, 3) known final diagnosis of fetal thalassemia status by cordocentesis for Hb typing using high-performance liquid chromatography and DNA analysis (if needed), and 4) available video clips of real-time 2D ultrasound with complete cross-sectional plane of the fetal chest. Exclusion criteria included 1) multi-fetal pregnancies, 2) fetal structural or chromosomal abnormalities, 3) fetal anemia due to any causes other than Hb Bart's disease, and 4) fetuses with visualized hydropic signs, i.e., pleural effusion, pericardial effusion, or ascites.

The relevant video clips of the fetuses were retrieved, stored on external hard drives and distributed to each investigator by Tongsong T with blindness to patient identity and fetal status of Hb Bart's disease. All of the fetal ultrasound video clips were originally carried out using a real-time machine with 2- to 5-MHz curvilinear transabdominal transducers (Voluson E8; GE Healthcare, Milwaukee, WI, USA). The data of other sonographic markers of fetal anemia, such as CTR, MCA-PSV, and placental thickness, originally measured by the MFM specialists using techniques as described elsewhere, were also retrieved from the database, but blinded to the investigators. The data of fetal Hb and hematocrit (Hct), analyzed by an automated complete blood count (CBC) machine (Coulter STKS analyzer; Beckman, USA), were also available for analysis. Hb level was then transformed into multiple of median (MoM) values. Fetal anemia was categorized as mild (0.84 to 0.65 MoM), moderate (0.64 to 0.55 MoM), or severe (<0.55 MoM)[10].

Based on the sensitivity of CTR in predicting Hb Bart's fetuses in a previous study[11], at least 84 video clips were required to determine accuracy with a power of 90% at a confidence interval of 95%. All of the identification-blinded video clips were given to four investigators (Jirapatsakul C, Rueangdetnarong H, Wudtisan J, and Thapsamuthdechakorn A) in their second year of a residency training program in obstetrics and gynecology. They represented 'non-expert sonologists' or general obstetricians. In each video clip, a subjective estimation of fetal heart size (whether normal or with cardiomegaly as in Figure 1) was firstly assessed and recorded, and CTR measurement was subsequently performed. The four non-expert sonologists were instructed and standardized in CTR measurements by the expert (Tongprasert F). A cross-sectional view of the fetal thorax at the level of the four-chamber view was used for the CTR measurements. The cardiac diameter (outer-to-outer) was measured at the level of the atrioventricular valves during end diastole and the transverse thoracic diameter was measured in the same image. CTR was then calculated by dividing the cardiac diameter by the thoracic diameter. An expert (Tongprasert F), a maternal fetal medicine specialist with 12 years of experience in fetal ultrasound, also made a subjective assessement of fetal cardiomegaly.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Released 2012, Armonk, NY, USA). The demographic characteristics, sonographic markers, Hb and Hct were described and compared between the affected group (Hb Bart's disease) and the unaffected group (normal Hb typing or α-thalassemia-1 carrier fetuses) by the independent samples t-test or Mann-Whitney U test, as appropriate. The sensitivity and specificity of subjective ultrasonographic assessment of cardiomegaly by the non-expert sonologists in identifying affected fetuses was calculated and

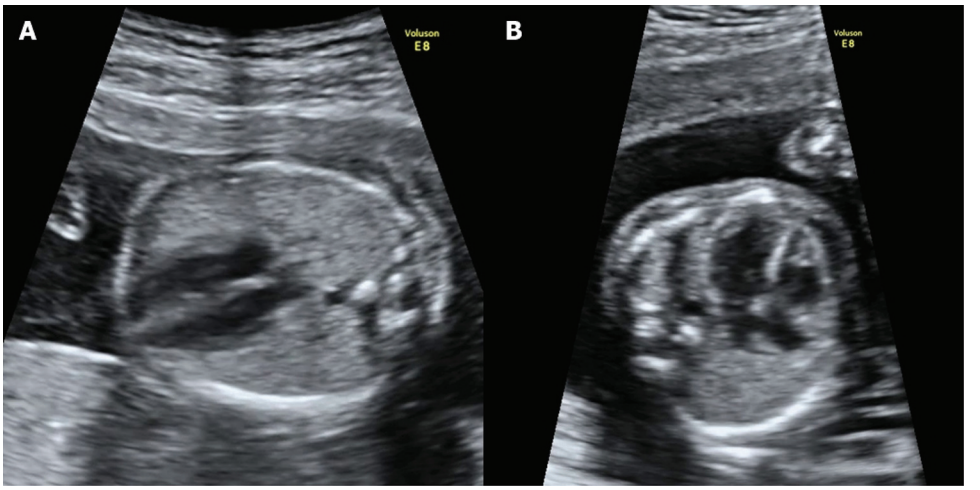

Figure 1. Normal heart size (A) and cardiomegaly (B).

Table 1. Characteristics of the fetuses affected and unaffected by homozygous alpha thalassemia-1 disease

Characteristics	Unaffected group (n=53) Median±IQR	Affected group (n=37) Median±IQR	p-value
GA at cordocentesis (week)	19.0±1.0	19.0±1.0	0.058
CTR (%)	47.0±6.0	60.0±5.0	<0.001
MCA-PSV (cm/second)	24.6±5.4	40.5±6.6	<0.001
MCA-PSV (MoM)	1.12±0.32	1.97±0.35	<0.001
Placental thickness (cm)	2.45±0.79	3.34±0.67	<0.001
Hb (g/dl)	10.90±1.00	6.90±1.00	<0.001
Hct (%)	33.70±2.75	27.70±3.30	<0.001

IQR=interquartile range; GA=gestational age; CTR=cardiothoracic ratio; MCA-PSV=middle cerebral artery peak systolic velocity; Hb=hemoglobin; Hct=hematocrit; MoM=multiple of median

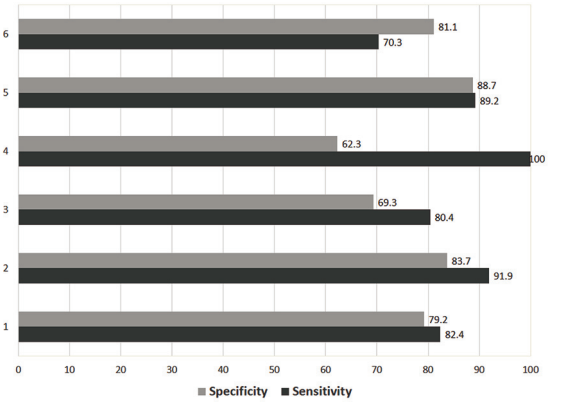

Figure 2. Sensitivity and specificity of a subjective ultrasonographic assessment of fetal cardiomegaly, cardiothoracic ratio (CTR) and other sonographic markers by non-expert sonologists and maternal fetal medicine specialists for predicting fetal Hb Bart's disease.

1) Subjective ultrasonographic assessment by non-expert sonologists; 2) Subjective ultrasonographic assessment by a specialist; 3) CTR by non-expert sonologists; 4) CTR by specialists; 5) MCA-PSV by specialists; 6) Placental thickness by specialists

compared with those derived from CTR, MCV-PSV, placental thickness, and subjective ultrasonographic assessment by the experts, using chi-square test. The inter-observer reliability of the four non-expert sonologists was calculated by Fleiss's kappa analysis using the Microsoft Excel software.

Results

Ninety video clips meeting the inclusion criteria were retrieved from the database, including 37 video clips (41.1%) of affected fetuses and 53 video clips (58.9%) of unaffected fetuses. The sonographic markers and hematologic characteristics are shown in Table 1. Of the 37 clips of affected fetuses, all had cardiomegaly, defined as a CTR of 50% or more as originally measured by specialists, 89.2% had high MCA-PSV of 1.5 MoM or more, and 70.3% had placentomegaly, defined as placental thickness of 3.0 cm or more. Hb and Hct data were available for 84 of the 90 fetuses. The fetuses with Hb Bart's disease were categorized with mild (42.9%), moderate (45.7%), or severe (11.4%) anemia. Of the fetuses diagnosed as α-thalassemia-1 carriers or normal Hb typing, all had normal Hb levels.

Sensitivity and specificity of subjective ultrasonographic assessment of fetal cardiomegaly, CTR, and other sonographic markers for predicting fetal Hb Bart's disease are presented in Figure 2. The sensitivity of the subjective ultrasonographic assessment of fetal

Table 2. Sensitivity for predicting anemic fetuses and specificity for predicting non-anemic fetuses of a subjective ultrasonographic assessment of fetal cardiomegaly, CTR, MCA-PSV and placental thickness

Variables	Specificity for predicting non-anemic fetuses (%) (n=49) (95% CI)	Sensitivity for predicting anemic fetuses (%) (95% CI)		
		Mild anemia (n=15)	Moderate anemia (n=16)	Severe anemia (n=4)
Subjective ultrasonographic assessment by non-expert sonologists	80.1 (68.0 to 91.2)	85.0 (59.5 to 98.3)	86.0 (54.4 to 96.0)	75.0 (39.8 to 100.0)
Subjective ultrasonographic assessment by a specialist	83.7 (70.3 to 92.7)	93.3 (68.1 to 99.8)	87.5 (61.7 to 98.5)	100.0 (39.8 to 100.0)
CTR by non-expert sonologists	70.4 (61.1 to 86.7)	83.4 (59.5 to 98.3)	82.8 (54.4 to 96.0)	75.0 (19.4 to 99.4)
CTR by specialists	67.3 (52.5 to 80.1)	100.0 (78.2 to 100.0)	100.0 (79.4 to 100.0)	100.0 (39.8 to 100.0)
MCA-PSV by specialists	95.9 (86.0 to 99.5)	80.0 (51.9 to 95.7)	93.8 (69.8 to 99.8)	100.0 (39.8 to 100.0)
Placental thickness by specialists	79.6 (65.7 to 89.8)	60.0 (32.3 to 83.7)	87.5 (61.7 to 98.5)	75.0 (19.4 to 99.4)

CI=confidence interval; CTR=cardiothoracic ratio; MCA-PSV=middle cerebral artery peak systolic velocity

cardiomegaly by the non-expert sonologists and the expert was not significantly different, though it tended to be higher when assessed by the expert (82.45% versus 91.90%, p=0.061). Using Fleiss's kappa, the inter-observer agreement among the non-expert sonologists was perfect (κ=1.00). The sensitivity of CTR measured by the non-expert sonologists was significantly lower than that by the expert (80.43% versus 100.0%, p<0.001). Sensitivity for predicting anemic fetuses and specificity for predicting non-anemic fetuses of each variable are presented in Table 2.

Discussion

In Southeast Asia, Hb Bart's disease is the most common cause of hydrops fetalis, accounting for nearly 90% of the cases[12]. In addition to the disease being almosty uniformly lethal to the affected fetuses, the mothers often suffer from serious complications, such as preeclampsia, dystocia, and postpartum hemorrhage[13]. Although prenatal diagnosis by invasive techniques can provide a definitive diagnosis in all pregnancies at risk of fetal Hb Bart's disease, these techniques carry a risk of fetal loss for unaffected pregnancies[14,15]. Alternatively, a non-invasive prenatal screening by serial ultrasonography to identify signs of fetal anemia is an option that benefits pregnant women to avoid unnecessary fetal loss related to the procedures.

The sonographic signs of fetal anemia include an increase in peak systolic velocity of the middle cerebral artery (MCA-PSV), cardiomegaly, and placentomegaly. These are proven early signs of fetal anemia in Hb Bart's disease, and can be seen as early as the late first trimester, although it is impractical to scan for these signs in very small fetuses[9,16]. During the second trimester, these three sonographic signs have been proven effective in early detection of fetal Hb Bart's disease. Among the early sonographic signs, cardiomegaly is the earliest, most effective and most practical sign to look for in general antenatal care clinics[5,8]. The objective measurement of cardiac circumference or the ratio of cardiac diameter and transverse thoracic diameter (CTR) have been shown to be accurate methods for evaluating fetal heart size[11,17]. However, these quantitative measurements need expertise and special training, as mentioned above. Although CTR is well accepted to use as a sonographic marker of fetal Hb Bart's disease, some question whether general obstetricians can do this accurately and efficiently[9,18]. Therefore, the present study focused on the effectiveness of subjective ultrasonographic assessment of fetal cardiac size in predicting fetal Hb Bart's disease, which could offer a more practical approach for general obstetricians.

In the present study, a subjective ultrasonographic assessment of fetal cardiomegaly by general obstetricians was effective in predicting fetal Hb Bart's disease at between 18 and 22 weeks of gestation with a sensitivity of 82.4% and a specificity of 80.1% and was not significantly different from the ultrasonographic assessment by the expert. CTR measurement by non-expert sonologists was much less effective than that performed by the expert. Notably, the sensitivity of subjective ultrasonographic assessment by the non-expert sonologists was much better than that of CTR measurement. Thus, CTR measurement by inexperienced practitioners in the present study did not improve detection of fetal Hb Bart's disease. In contrast, the sensitivity of subjective ultrasonographic assessment by the expert was less than that of CTR measurement. These

findings suggest that accurate CTR measurement requires more expertise, systematic training, and more experience. Additionally, the measurement is time consuming, and probably not practical for busy antenatal care clinics. However, the measurement of CTR has been proven by many researchers to be the most efficient method of prenatal Hb Bart's screening in the second trimester[5,8], as also seen in the present study. When it is performed by a specialist, the sensitivity was 100%. Of note, the sensitivity of subjective ultrasonographic assessment was surprisingly comparable to MCA-PSV, and better than measuring placental thickness. It is reasonable to conclude that in areas of high prevalence of fetal Hb Bart's disease, screening using subjective ultrasonographic assessment of cardiomegaly is preferred for non-expert sonologists and CTR measurement is preferred for experts. Integrating CTR measurement into basic obstetric ultrasound training may be valuable and proper in high prevalence areas. However, a subjective ultrasonographic assessment of fetal heart size is acceptable for general obstetricians in high workload settings.

Importantly, the present study strongly encourages sonologists practicing in areas of high prevalence of fetal Hb Bart's disease, such as Southeast Asia, to pay more attention to fetal cardiac size, even if only using subjective ultrasonographic assessment. This may be helpful in early detection of the disease before the hydropic changes develop, obviating serious morbidity. Additionally, subjective ultrasonographic assessment may guide general obstetricians in recommending further evaluation by MFM specialists. The present study underlines that subjective ultrasonographic assessment of fetal cardiac size by non-expert sonologists or general obstetricians is as effective as MCA-PSV measurement performed by MFM specialists. However, the present results should be interpreted with some caution, as our obstetric residents were frequently exposed to sonographic findings of fetal cardiomegaly at mid-pregnancy in their routine work because of the high prevalence of the disease in the authors' center, thus, they might be more familiar with such images. However, the authors believe that the efficacy of subjective ultrasonographic assessment is likely to be reproducible by general obstetricians, since they certainly have more experience than the investigators (non-expert sonologists) in the present study, who were in a residency training program, and not yet qualified obstetricians.

A strength of the present study was that all of the sonologists were blinded to fetal diagnosis and other sonographic markers of fetal anemia, such as placental thickness, MCA-PSV values or fluid collection in other organs that might be clues to a correct diagnosis. A limitation of the present study was that the ultrasonographic assessments were confined to pregnancies at a gestational age of 18 to 22 weeks, thus, the results might be not applicable to other gestational ages.

In conclusion, a subjective ultrasonographic assessment of fetal cardiomegaly by non-expert sonologists is acceptable in identifying fetal Hb Bart's disease. Its sensitivity was comparable with MCA-PSV, but less than CTR as measured by experts. As subjective ultrasonographic assessment of fetal cardiomegaly at mid-pregnancy is simpler and less time consuming than CTR measurement, non-expert sonologists or general obstetricians should be encouraged to use this screening tool, especially in the areas of high prevalence of Hb Bart's disease. However, CTR measurement by experts in pregnancies at risk remains a more accurate screening tool, although requiring systematic training and practice.

What is already known on this topic?

Sonographic markers such as fetal cardiomegaly, high MCA-PSV, and placentomegaly are effective screening methods for fetal Hb Bart's disease.

Fetal cardiomegaly ultrasonographic assessment, measured by CTR technique, requires expertise and training.

What this study adds?

A subjective ultrasonographic assessment of fetal cardiomegaly by non-expert sonologists or general obstetricians is acceptable in identifying fetal Hb Bart's disease.

CTR measurement by experts or maternal fetal medicine specialists is the most accurate method in fetal Hb Bart's disease screening.

Conflicts of interest

The authors declare no conflict of interest.

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