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RESEARCH ARTICLE

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Effectiveness of placental volume measured by virtual organ computer-aided analysis in prediction of fetal hemoglobin Bart's disease in late first trimester

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Abstract

Objective: To evaluate the effectiveness of placental volume measured by virtual organ computer-aided analysis (VOCAL) at 12 to 14 weeks of gestation in predicting fetal hemoglobin (Hb) Bart's disease among pregnancies at risk.

Methods: This study involves 3-dimensional ultrasound (3D-US) volume datasets derived from pregnancies at risk of fetal Hb Bart's disease at 12 to 14 weeks of pregnancy. VOCAL technique was used to measure and calculate placental volume by the authors, who did not know the fetal diagnosis. Placental thickness was also measured. The diagnostic values of placental volume and placental thickness in prediction of fetal Hb Bart's disease were calculated.

Results: Sixty-five volume datasets, including 22 datasets of the affected fetuses and 43 unaffected fetuses, were included. The mean placental volume (±SD) of the affected cases was significantly higher than that of the unaffected ones, 85.35 ± 20.84 cm^3 vs 52.24 ± 19.01 cm^3 (Student's *t* test, $P < .001$). In predicting Hb Bart's disease, placental volume and placental thickness had sensitivities of 77.3% and 72.7% respectively as well as specificities of 88.37% and 76.7% respectively.

Conclusion: Of fetuses at risk of Hb Bart's disease, 3D-US VOCAL placental volume may be useful in early detection of affected fetuses. Its effectiveness is superior to that of conventional placental thickness measurement.

KEYWORDS
hemoglobin Bart's disease, homozygous alpha-thalassemia-1 disease, placental thickness, placental volume, virtual organ computer-aided analysis (VOCAL)

1 | INTRODUCTION

Hemoglobin (Hb) Bart's disease or homozygous alpha-thalassemia-1 is an autosomal recessive disorder characterized by no alpha-globin chain production because of the absence of all four alpha genes. Hb Bart's disease is the most common cause of hydrops fetalis in South East Asia,[1,2] and this disease is increasing in other parts of the world due to population migrations. The affected fetuses are inevitably either dead in utero or die shortly after birth. Moreover, in cases where early termination was not done, serious obstetric complications frequently occur, including preeclampsia, usually more severe with early-onset; obstructed labor; and postpartum hemorrhage due to a huge placenta.[2] Therefore, the ability to achieve early detection before the development of hydropic changes is essential. The fetuses with the disease suffer from deficient α-globin chain production and cannot form hemoglobin F ($\alpha 2\gamma 2$), resulting in severe fetal anemia in as early as the first trimester. In response to fetal anemic hypoxia, the fetuses increase blood volume and cardiac output to preserve tissue

oxygen perfusion, leading to fluid accumulation in various organs, including the placenta. Accordingly, placentomegaly, or increased placental thickness, is one of the sonographic signs that can be used for prenatal diagnosis of Hb Bart's disease.[3-6] Placental size evaluation, especially when combined with cardiac size assessment, can increase diagnostic performance in predicting the affected fetuses,[4,7] even in the late first trimester.[8] In the evaluation of placental size, placental thickness, measured at the greatest dimension, is the most commonly used technique because of its ease and simplicity. However, placental volume is theoretically more appropriate than placental thickness in representing placental size. Nevertheless, studies focusing on the accuracy of using placental volume in predicting Hb Bart' disease are rarely published. Chen et al.[9] firstly reported the use of placental volume assessed by three dimensional (3D)-US in diagnosis of Hb Bart's disease. They concluded that 3D-US placental volume was not superior to that of 2D-US. However, their study included pregnancies at gestational ages of 9 to 12 weeks, when fetal anemia is very subtle or when it is too early for the development of fetal anemia and increased placental size. We hypothesize that with the new modern virtual organ computer-aided analysis (VOCAL) technology and high ultrasound resolution, placental volume measurement may yield more accurate measurements and greater effectiveness in the diagnosis of Hb Bart's disease between 11 and 14 weeks of gestation. Accordingly, we conducted this study to assess the effectiveness of placental volume measured by VOCAL at 12 to 14 weeks of gestation in predicting fetuses with Hb Bart's disease among pregnancies at risk.

2 | METHODS

This study involves diagnostic testing conducted on pregnancies at risk of fetal Hb Bart's disease. The study was carried out at a tertiary care and teaching center. The study was ethically approved by IRB (the local institutional review board); Study Code: OBG-2563-07230 / Research ID: 7230. The patients were prospectively recruited, with written informed consents. The population of the study was pregnancies at risk of fetal Hb Bart's disease, and participants were enrolled from our established program of screening and prevention of severe thalassemia (Chiang Mai protocol for prenatal control of severe thalassemia[10]). The inclusion criteria are as follows: (1) singleton pregnancy; (2) gestational age between 12 and 14 weeks; (3) at risk of having fetuses with Hb Bart's disease, defined by both parents being carriers of alpha-thalassemia-1; and (4) known final diagnosis of fetal status for Hb Bart's disease, based on chorionic villous sampling (DNA analysis), cordocentesis (fetal hemoglobin typing, using high performance liquid chromatography) or neonatal blood analysis. The exclusion criteria are as follows: (1) fetal anomaly or chromosomal disorders; (2) fetal anemia due to any causes apart from Hb Bart's disease, for examples parvovirus B19 infection or alloimmunization; (3) poor quality of volume datasets; and (4) unknown final diagnosis. All pregnancies underwent ultrasound examination before the invasive diagnostic procedure (either chorionic villous samplings or subsequent cordocentesis). All ultrasound examinations were done by the maternal-fetal medicine (MFM) fellows or MFM staff members (between 2015

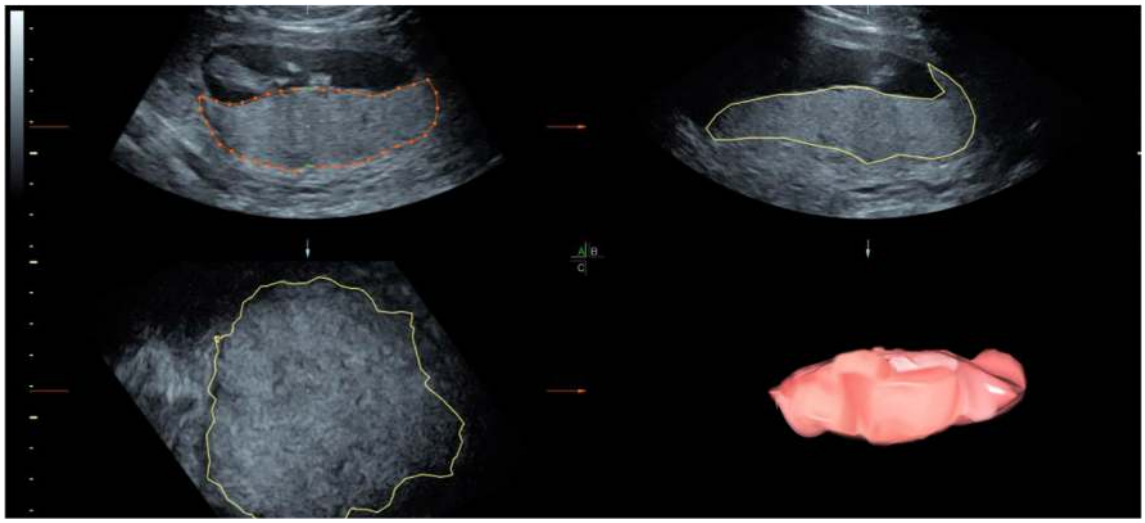

FIGURE 1 An example of placental volume measurement using 3D-US VOCAL technique: The volume dataset is traced along the placental boundary in panel-A (left upper). The rendered image of the volume is shown in the right lower panel

Final diagnosis	Normal (n = 43)	Hb Bart's disease (n = 22)	*P* value
Gestational age (days)	87.7 ± 4.91	87.6 ± 5.15	.963
Crown rump length (mm)	63.5 ± 10.03	67.0 ± 10.08	.190
Placental volume (cm^3)	52.2 ± 19.01	85.3 ± 20.84	<.001
Placental thickness (mm)	15.7 ± 2.98	19.7 ± 2.87	<.001

TABLE 1 Comparisons gestational age, Crown rump length, placental volume and placental thickness between affected and unaffected pregnancies

and 2019) using Voluson E10 machine (GE Healthcare Ultrasound, Milwaukee, WI), equipped with transabdominal 2- to 4-MHz curvilinear transducers as well as a 3D convex transabdominal 3.5-MHz transducer. In addition to the standard ultrasound scan for first trimester screening, the volume including entire placenta was also acquired during a maternal full bladder and the 3D-US probe was placed perpendicular to the placenta to demonstrate the whole placenta. The acquisition settings were optimized to include the volume of interest, including the entire placental surface area. Proper focal and harmonic settings were optimized to visualize the highest quality images for delineation of the placental contours. The boundaries of the placenta were determined by the outlines of the chorionic surface and the basal plate, excluding the myometrium. After volume acquisition, the volume datasets were saved in the hard disk of the ultrasound machine and later copied to an external storage hard drive for subsequent off-line measurements. The baseline characteristics and the details of ultrasound examinations (identification data, images, cine loops, all biometry values) were prospectively recorded in research record forms and subsequently entered into the computerized database. The fetal diagnoses were subsequently added to the relevant records, once the results were available.

On placental volume measurements, the volume datasets were assigned by author "TT" to author "PB", who was not aware of any clinical information and the fetal diagnosis, for anonymous measurements. The volume datasets were analyzed offline using the 4D-view version 14 ext.42015 software (GE Healthcare, Austria, GmbH) by the first author (PB). The measurements were based on VOCAL procedure with a rotation angle of 6°. In each volume calculation, the cross-sectional plane was used as a reference, and the electronic markers were placed on both sides of the placenta. Based on the 30 planes of measurements, the placental volume was reconstructed and automatically calculated in cubic centimeters, as presented in Figure 1.

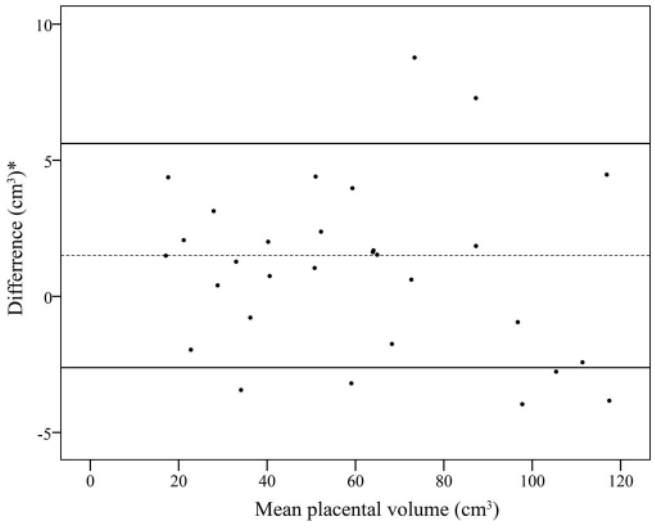

FIGURE 2 Bland - Altman plot for inter-observer variability shows good agreement (The horizontal lines represent the mean difference and the limits of agreement) (* measured placental volume difference between the two observers)

2.1 | Statistical analysis

The statistical analysis was done using the statistical software SPSS version 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York). The gold standard for the diagnostic test is fetal Hb Bart's disease. The performances of placental volume and placental thickness in diagnosis of the affected fetuses were assessed by sensitivity, specificity, negative and positive predictive values, using the cut-off point of 95th percentile of each gestational week for placental volume[11] and the cut-off value of 18 mm for placental thickness in late first trimester.[8] $P < .05$ was considered statistically significant. In line with the sample size calculation, which is based on a previous study[8] in which the sensitivity of placental thickness was approximately 70%, this study needed a sample size of at least 21 affected fetuses to gain a power of 80% at 95% confidence interval, when allowable error was given at 0.20.

3 | RESULTS

A total of 65 volume datasets of pregnancies at risk were analyzed, including 22 volume datasets of affected pregnancies (Hb Bart's disease) and 43 volume datasets of unaffected pregnancies. The mean gestational age on the day of ultrasound examination was 87.68 ± 4.95 days, with no significant difference between both groups, as shown in Table 1. Likewise, the mean crown-rump length was 64.74 mm, with no significant difference between both groups. The mean placental volume and placental thickness were significantly greater in the affected pregnancies, as presented in Table 1. Bland - Altman plot for inter-observer variability (SL vs PB) revealed good agreement with mean difference of 0.769 cm^3 with limits of agreement of −5.242 to 6.524, as presented in Figure 2.

TABLE 2 Diagnostic indices of placental volume in identifying Hb Bart's disease (using a cut-off value of 95th percentile)

	Hb Bart's disease fetuses (cases)	Normal fetuses (cases)	Total
Abnormal placental volume	17	5	22
Normal placental volume	5	38	43
Total	22	43	65

Note: Sensitivity: 77.3% (17/22) 95% CI: 59.8-94.8%. Specificity: 88.4% (38/43) 95% CI: 78.8-98.0%. Positive predictive value: 77.3% (17/22) 95% CI: 59.8-94.8%. Negative predictive value: 88.4% (38/43) 95% CI: 75.0-100.0%.

	Affected fetuses	Normal fetuses	Total
Abnormal placental thickness	16	10	26
Normal placental thickness	6	33	39
Total	22	43	65

TABLE 3 Diagnostic indices of placental thickness in identifying Hb Bart's disease (using a cut-off value of 18 mm)

Note: Sensitivity: 72.7% (16/22) 95% CI: 54.1-91.3%. Specificity: 76.7% (33/43) 95% CI: 64.1-89.4%. Positive predictive value: 61.5% (16/26) 95% CI: 42.8-80.2%. Negative predictive value: 84.6% (33/39) 95% CI: 70.7-98.5%.

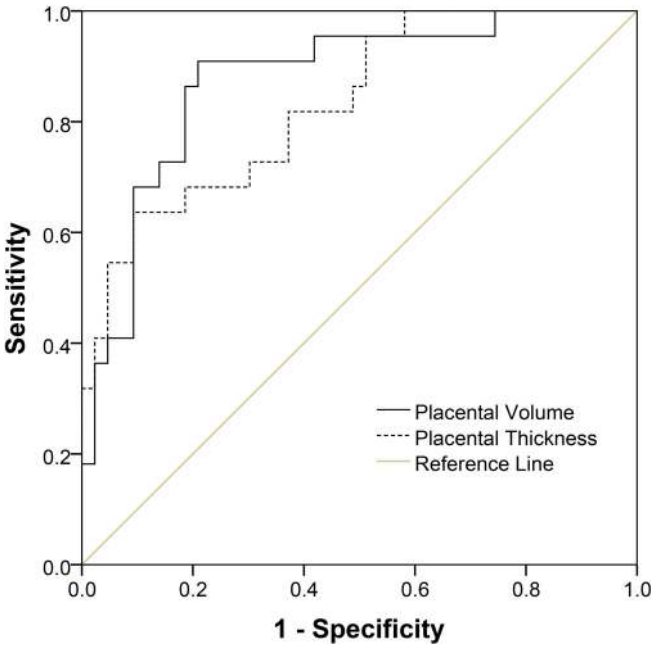

FIGURE 3 Receiver-operated characteristic (ROC) curve of placental volume and placental thickness in predicting fetuses affected by Hb Bart's disease (area under curve for placental volume and placental thickness: 0.874 (95%CI: 0.783-0.965) and 0.832 (95% CI: 0.729-0.934), respectively

The sensitivities of placental volume and placental thickness are 77.3% and 72.7% respectively, while the specificities of placental volume and placental thickness are 88.4% and 76.7% respectively, as presented in Table 2 and Table 3 respectively. The effectiveness of placental volume in predicting fetal Hb Bart's disease is significantly better than that of placental thickness (McNemar Chi square test; *P*-value <.001). The area under curves (AUCs) of placental volume and placental thickness in predicting fetal Hb Bart's disease are 0.874 (95% CI: 0.783-0.965) and 0.832 (95% CI: 0.729-0.934) respectively, as presented in Figure 3. The two AUCs are significantly different (Z-test; *P* value <.001).

4 | DISCUSSION

The insights gained from this study are as follows. Placental volume determined by VOCAL technique is superior to placental thickness measured by conventional 2D-US in diagnosis of Hb Bart's disease among fetuses at risk. As expected, this might be explained by the fact that placental volume theoretically represents the placental size better than placental thickness does. This is consistent with the fact that placental thickness represents only one dimension of the placenta whereas placental volume including all placental dimensions certainly represents better placental size. Our result supports that an increase in placental size secondary to hypervolemia as well as increased cardiac output due to fetal anemia caused by Hb Bart's disease develops in late first trimester. Accordingly, placental size assessment may be useful in early detection of affected fetuses. Though the diagnostic performance of placental size assessment is not as good as cardiac size, which gives a sensitivity of more than 90% in late first trimester,[4,8,12] it is certainly useful when used as an adjunct to other sonographic markers to increase the specificity,[4,8] or in cases where cardiac size evaluation is unreliable.

To date, there is only one study, published by Chen et al.,[9] that focused on placental volume as a predictor of fetal anemia or Hb Bart's disease. They measured placental volume with 3D-US by a multiplanar technique, and found that placental volume determined by 3D-US does not seem to be superior to that of 2D-US in the first trimester diagnosis of Hb Bart's disease. However, their study included only pregnancies at 9-12 weeks of gestation, which is too early for the affected fetuses to show an increase in placental size. Fetuses with Hb Bart's disease tend to have persistent embryonic hemoglobin in compensation for lack of alpha-globin chain. Thus, the development of fetal anemia might not be obvious yet at 9 to 12 weeks of gestation. Furthermore, the sample size, which included only 11 affected cases, was too small to evaluate the effectiveness of placental volume. In contrast, our study involved pregnancies at 12 to 14 weeks of gestation, the period at which placental size usually increase.[4,8]

The strengths of this study are as follows: (1) The placental volume cut-off used in this study was based on reference ranges that were created from our population.[11] (2) The technique used for measurements was based on VOCAL method with a rotation of 6°, producing 30 planes per datasets to reconstruct the placental volume, increasing reliability in representation of the actual placental volume. (3) The author who performed the dataset analysis was blinded to the diagnosis and did not see other parts of the sonographic images, such as fetal structures. Only the volume datasets of the placenta were anonymously provided to the author. Accordingly, no or minimal bias in measurements could be expected. The weaknesses of this study include the following: (1) The sample size is still relatively small. (2) Ultrasound machines with VOCAL function for placental volume measurement are not widely available, leading to a limitation in actual

clinical practice. (3) Compared to placental thickness measurement, placental volume measurement is more time-consuming, labor-intensive and less practical in daily use. However, the volume datasets can be simply acquired and digitally sent for analysis by the experts, available anywhere, without patient referral.

In conclusion, our results suggest that placental volume measured by VOCAL technique in late first trimester, using the cut-off value of 95th percentile of the gestational week, gives a sensitivity of 77% and specificity of 88%, which are significantly higher than those of placental thickness measurement in differentiating fetuses affected by Hb Bart's disease from the unaffected ones.

CONFLICT OF INTEREST

No conflict of interest.

AUTHORS' CONTRIBUTIONS

Phenphan Bootchaingam: conceptualization, acquisition of data, volume dataset analysis, manuscript writing.

Cholaros Charoenratana: database development, acquisition of data.

Suchaya Luewan: database development, acquisition of data, data analysis manuscript editing.

Theera Tongsong: data validation and data analysis manuscript editing.

All authors contributed to interpretation and writing of the paper and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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