Reference Ranges of Placental Volume Measured by Virtual Organ Computer-Aided Analysis Between 10 And 14 Weeks of Gestation

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ABSTRACT: *Objective.* To establish the reference ranges of the placental volume between 10 and 14 weeks of gestation of Thai fetuses.

Methods. The placental volumes were acquired in normal pregnancies between 10 and 14 weeks of gestation using transabdominal three-dimensional ultrasound. The placental volume was then analyzed using VOCAL (virtual organ computer-aided analysis) technique with a rotation angle of 30°. The measured values were regressed to identify the best-fit model.

Results. A total of 236 volume datasets met the inclusion criteria and were used for offline analysis. Placental volume significantly increased with increasing crown-rump length (CRL). The best-fit regression models for predicted mean and SD as a function of CRL, available for z score calculation and construction of the percentile chart, are as follows:

$$\ln(\text{placental volume}) = \ln(0.187) + 1.375\times \ln(\text{CRL in mm}) \quad (r = 0.824; p < 0.001),$$

$$\text{Predicted SD} = -0.895 + (0.266\times\text{CRL in mm}) \quad (r = 0.190; p < 0.001).$$

Conclusion. Reference ranges of placental volume have been constructed. This normative data may be a useful tool in the evaluation of various conditions affecting placental size, eg, fetal hemoglobin Bart's disease. © 2017 Wiley Periodicals, Inc. *J Clin Ultrasound* **45**:185–191, 2017; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22441

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INTRODUCTION

Evaluation of the placenta size is helpful in the detection of placental abnormalities that can significantly affect the pregnancy's management and outcome. Several disorders are associated with abnormal placental size, eg, small placenta caused by fetal growth restriction and aneuploidy[1–4] or enlarged placenta in cases of hydrops fetalis caused by anemia. In our experience, placental thickness representing placental size, measured by two-dimensional ultrasound (2D US), can be used as a sonomarker in predicting hemoglobin (Hb) Bart's disease among fetuses at risk.[5] In the past, the measurement of placental thickness, rather than total volume, was used to estimate the placental size, whereas measurement of total placental volume, which is theoretically most accurate in estimation of placental size, is too complicated for routine use. Recently, three-dimensional ultrasound (3D US) with virtual organ computer-aided analysis (VOCAL) technique has enabled us to measure placental volume with higher precision and reproducibility than the estimated volume based on mathematical formulas using placental diameters.[6]

Prior to clinical use, reference ranges must first be determined for a given population.

Although such reference ranges have been published several times, especially in Western populations, few studies used the VOCAL method and presented the volume distribution according to the crown-rump length (CRL). In addition, most previous studies did not perform regression analysis of the residuals to evaluate the dispersion (SD) according to gestational age, leading to limitation in clinical use and z score. In Thailand, Titapant and Cherdchoogieat[7] have published a nomogram of placental volume between 12 and 20 weeks of gestation, but they did not present the placental volume as a function of CRL and did not give the SDs, limiting its use in clinical practice. Therefore, we conducted this study to establish the US reference ranges of the placenta volume among Thai fetuses.

MATERIALS AND METHODS

A prospective study was conducted between February 2015 and May 2016 with the approval of our Institution Review Board at a single tertiary center. The pregnant women attending our antenatal care clinic were invited to participate in the study, for which a written informed consent was obtained. The pregnant women met the following inclusion criteria: (1) singleton pregnancies with a live fetus; (2) accurate gestational age based on US dating in the first trimester and reliable last menstrual periods; (3) gestational age between 10 and 14 weeks at the time of placental volume acquisition; and (4) low-risk pregnancies without known obstetric or medical complications, such as pregestational diabetes mellitus, heart disease, chronic hypertension, etc. The exclusion criteria were the following: (1) fetal chromosomal or structural abnormalities; (2) fetal growth restriction (less than 10th percentile) or macrosomia (more than 90th percentile); (3) obstetrical complications such as placenta previa or preeclampsia; (4) poor quality of the acquired volume dataset; and (5) unavailable final pregnancy outcome. The baseline characteristics of the pregnant women included maternal age, parity, body mass index, smoking habit, gestational age at delivery, and birth weight.

The US examination of the placenta was performed using a Voluson E8 machine (GE Healthcare, Milwaukee, WI) equipped with a 3D convex abdominal 3.5-MHz transducer. The placental volume was acquired with a full bladder and the transducer placed perpendicular to the placenta to visualize the entire placenta. The scan settings were adjusted to cover the largest region of interest, including the full placental surface. The placental boundaries were defined by the basal plate and the chorionic plate, excluding the myometrium. Optimal focal and harmonic settings were adjusted to get the best resolution to define the contours of the placenta. The volume datasets were acquired, stored in the hard disk of the machine, and then transferred to an external hard disk for offline analysis. The measurement of the placental volume was performed using 4D View (version 10.5) processing software (GE Healthcare) by a single author (D.M.). The placenta volume was calculated using VOCAL technique with an angle of rotation of 30°. Each volume was analyzed twice. In each measurement, the axial plane was used as a reference, and the calipers were placed on either side of the placenta. With six planes, reconstruction of the volume was performed and measured in cubic centimeters, as shown in Figure 1. The pregnancies were followed up until delivery, and the pregnancy outcomes were also assessed and recorded.

Statistical Analysis

To construct the reference ranges with type I error at 0.05 and maximum error of 0.1, the study needed a sample size of $\geq$45 cases per week. The data were analyzed using SPSS software, version 21.0 (IBM SPSS Statistics for Windows, 2012 release, Armonk, NY). Regression analysis of the placental volume as a function of CRL was used to determine the best-fit equation model, and the nomogram of placenta volume was constructed following the statistical technique suggested by Royston and Wright.[8] Regression analysis for the SD was also performed to identify the best-fit model for SD for z-score calculation. Normality and goodness of fit regression models were assessed by checking the scatter patterns of points relative to fit means and SDs, expressed as z scores. Intraobserver variability was evaluated using Bland-Altman plots.

RESULTS

A total of 236 volume datasets were successfully acquired between 10 and 14 weeks of gestation with satisfactory quality and were available for offline analysis. The baseline demographic data of the women were as follows: All were healthy

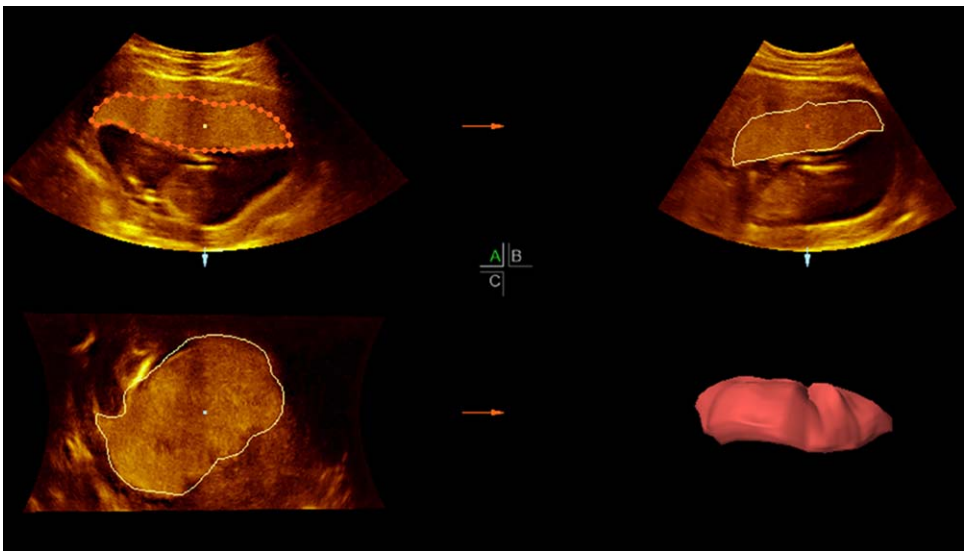

FIGURE 1. Placental volume measurement with the VOCAL technique: The volume dataset is traced along the placental contour in plane A. The rendered image of the volume is shown in the bottom right panel.

Thai women. Approximately half of them (124; 52.5%) were nulliparous. The mean (± SD) maternal age was 29.4 ± 4.7 years (range 18–42 years). Mean maternal BMI (± SD) was 22.6 ± 3.9. The mean (± SD) gestational age at the time of acquisition was 86.9 ± 9.5 days (range 70–104 days). The mean (± SD) gestational age at delivery was 38.6 ± 1.0 weeks (range 37–41 week). The mean (± SD) birth weight was 3050 ± 355 grams. Bland-Altman plot for intraobserver variability (Figure 2) showed good agreement with a mean difference of 0.669 cm^3 with limits of agreement of −4.247–5.585. The frequencies of placental volume measurements for each gestational week are presented in Table 1. Distribution of the placental volumes per each gestational week of acquisition from 10 weeks to 14 weeks is shown in Figure 3. The mean placental volume increased from 20 cm^3 at CRL of 31 mm to 92 cm^3 at CRL of 91 mm. Predicted mean and SD of placental volume, as a function of CRL, were described by the best-fit regression models (Figure 4), as follows:

$$\text{Predicted mean of placental volume (PV)} = 0.187 \times (\text{CRL in mm})^{1.375}$$

or

$$\ln(\text{PV}) = \ln(0.187) + 1.375 \times \ln(\text{CRL in mm}) \quad (r = 0.824; p < 0.001)$$

Placental volume significantly increased with gestational age. Likewise, the SD also increased significantly with CRL. Therefore, regression analysis for SD as a function of CRL was also performed. The best-fit model for predicting SD is

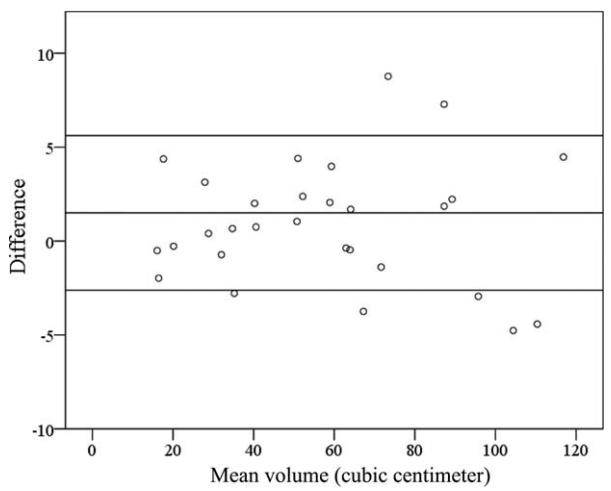

FIGURE 2. Bland-Altman plot for intraobserver variability shows good agreement (the horizontal lines represent the mean difference and the limits of agreement).

TABLE 1
Number of Placental Volume Measurements for Each Gestational Age

Gestational age (weeks)	Frequency	Percent
10	48	20.3
11	47	19.9
12	47	19.9
13	50	21.2
14	44	18.6
Total	236	100.0

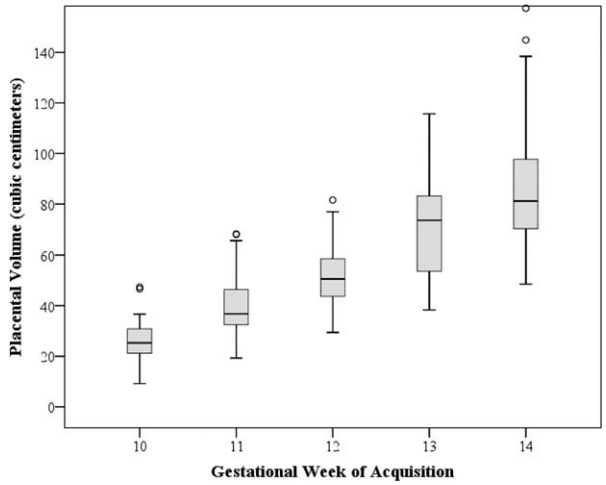

FIGURE 3. Distribution of the placental volumes at each gestational week from 10 weeks to 14 weeks.

$$\text{Predicted SD of PV} = -0.895 + (0.266 \times \text{CRL in mm}) \quad (r = 0.190; p < 0.001)$$

The model was validated by calculated z score. The normalcy of the z scores was shown in a QQ plot in SPSS output. Furthermore, the z scores were equally distributed above and below zero across the entire range of CRLs as well as following a standard normal distribution. The number of z scores distributing outside of the range ± 2 SD was as expected, approximately 5% of the values as seen in Figure 5. The percentile chart of reference ranges was constructed and is presented in Table 2.

z Scores for each measured value of placental volume could readily be calculated as follows: z score = (measured PV value – predicted value)/ predicted SD (predicted value for mean and SD of placental volume are available from the equations listed above).

DISCUSSION

This study demonstrated that mean placental volume as well as its SD in late first trimester increased with CRL or gestational age. The models for predicting mean and SD of placental volume as functions of CRL are provided. These can be used to calculate z score for any measurement value in quantitative assessment of placental size. In addition, the percentile chart of placental volumes at various points of CRL has also been provided. Our reference ranges may be the basis for future studies to evaluate the effectiveness of placental volume measurement among pregnancies at higher risk of placental disorders.

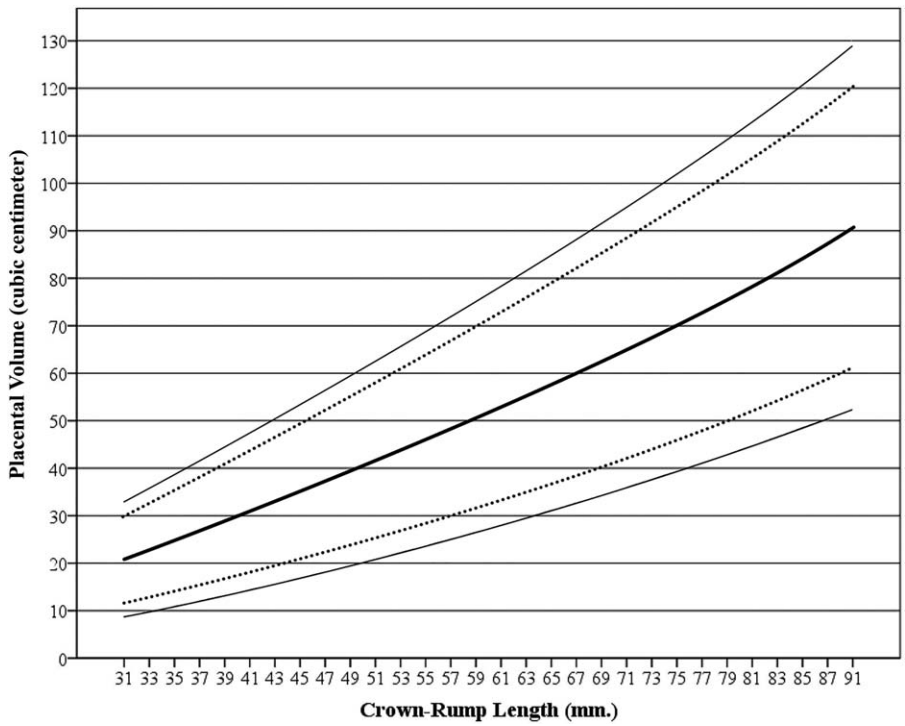

FIGURE 4. Power function relationship between CRL in millimeters and placental volume in cubic centimeter (the lines represent fifth, 10th, 50th, 90th, and 95th percentiles).

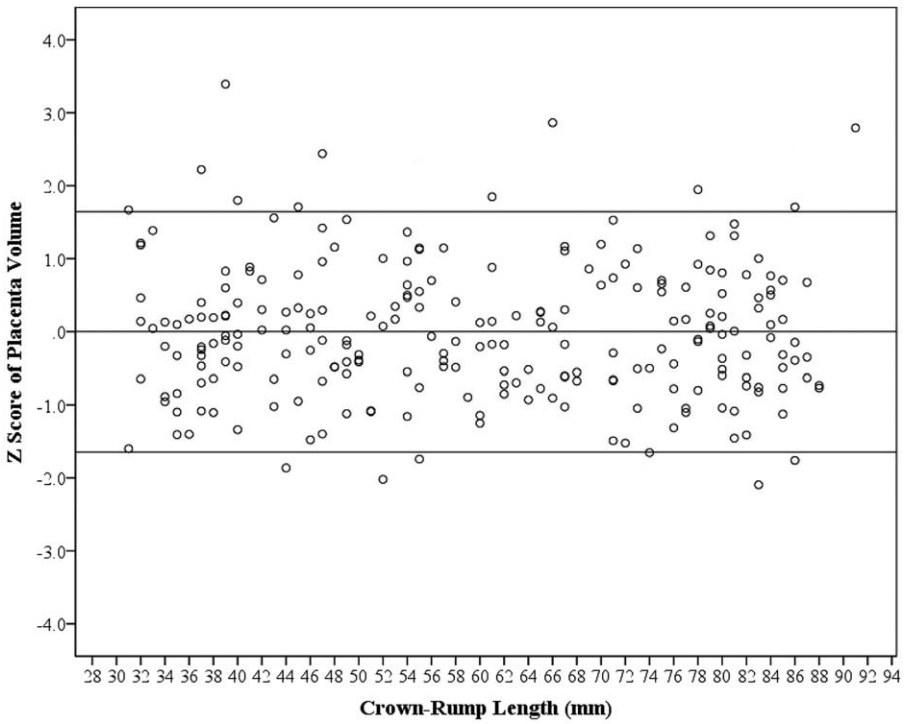

FIGURE 5. Distribution of calculated z scores of placental volume (cm^3) against CRL, indicating adequate level of fit.

TABLE 2
Placental Volume (in cm^3) as a Function of Crown-Rump Length (in mm)

CRL	5th	10th	50th	90th	95th	CRL	5th	10th	50th	90th	95th
31	8.9	11.6	21.0	30.4	33.1	61	28.0	33.6	53.2	72.9	78.5
32	9.4	12.2	21.9	31.7	34.5	62	28.7	34.4	54.4	74.4	80.1
33	9.9	12.8	22.9	33.0	35.9	63	29.5	35.3	55.6	76.0	81.8
34	10.4	13.4	23.8	34.3	37.3	64	30.3	36.2	56.9	77.5	83.4
35	10.9	14.0	24.8	35.6	38.7	65	31.1	37.1	58.1	79.1	85.1
36	11.5	14.7	25.8	36.9	40.1	66	31.9	38.0	59.3	80.7	86.8
37	12.0	15.3	26.8	38.2	41.5	67	32.7	38.9	60.6	82.2	88.4
38	12.6	16.0	27.8	39.6	42.9	68	33.5	39.8	61.8	83.8	90.1
39	13.2	16.6	28.8	40.9	44.4	69	34.3	40.7	63.1	85.4	91.8
40	13.7	17.3	29.8	42.3	45.8	70	35.1	41.6	64.3	87.0	93.5
41	14.3	18.0	30.8	43.7	47.3	71	35.9	42.5	65.6	88.6	95.2
42	14.9	18.7	31.9	45.0	48.8	72	36.8	43.5	66.9	90.3	96.9
43	15.5	19.4	32.9	46.4	50.3	73	37.6	44.4	68.1	91.9	98.6
44	16.2	20.1	34.0	47.8	51.8	74	38.5	45.3	69.4	93.5	100.4
45	16.8	20.8	35.0	49.2	53.3	75	39.3	46.3	70.7	95.1	102.1
46	17.4	21.6	36.1	50.6	54.8	76	40.2	47.2	72.0	96.8	103.8
47	18.1	22.3	37.2	52.1	56.3	77	41.1	48.2	73.3	98.4	105.6
48	18.7	23.1	38.3	53.5	57.8	78	41.9	49.2	74.6	100.1	107.3
49	19.4	23.8	39.4	54.9	59.4	79	42.8	50.2	75.9	101.7	109.1
50	20.1	24.6	40.5	56.4	60.9	80	43.7	51.1	77.3	103.4	110.8
51	20.7	25.4	41.6	57.9	62.5	81	44.6	52.1	78.6	105.1	112.6
52	21.4	26.2	42.7	59.3	64.0	82	45.5	53.1	79.9	106.7	114.4
53	22.1	26.9	43.9	60.8	65.6	83	46.4	54.1	81.3	108.4	116.2
54	22.8	27.8	45.0	62.3	67.2	84	47.3	55.1	82.6	110.1	118.0
55	23.5	28.6	46.2	63.8	68.8	85	48.2	56.2	84.0	111.8	119.8
56	24.3	29.4	47.3	65.3	70.4	86	49.1	57.2	85.3	113.5	121.6
57	25.0	30.2	48.5	66.8	72.0	87	50.1	58.2	86.7	115.2	123.4
58	25.7	31.0	49.7	68.3	73.6	88	51.0	59.2	88.1	116.9	125.2
59	26.5	31.9	50.8	69.8	75.2	91	53.8	62.4	92.2	122.1	130.6
60	27.2	32.7	52.0	71.3	76.8						

Abbreviations: PV, placental volume; CRL, crown-rump length.
The values are generated from the prediction equations as follows:
$\ln(PV) = \ln(0.187) + 1.375 \times \ln(\text{CRL in mm})$ and predicted SD of $PV = -0.895 + (0.266 \times \text{CRL in mm})$.

Most previous studies did not perform residual regression analysis to create a model for SD prediction as a function of CRL or gestational age but they used an assumed constant SD for any gestational week to construct the nomogram. Importantly, this could lead to less accurate prediction if the residual (SD) distribution according to the CRL was not taken into account.[8] We found that the SD also increased significantly with CRL and was not constant as assumed in most studies. This is important because the correct z score and the percentile chart are reliable only when the SD values are reliable.

The measurement of placental volume in early gestation can improve the prediction of small- or large-for-date fetuses based on maternal characteristics alone, especially when combined with serum markers like PAPP-A.[2] In addition, assessment of placental volume is useful in first-trimester risk estimation for aneuploidy.[1,3] We have found that placental enlargement in fetal Hb Bart's disease can occur as early as in the late first trimester, and assessment of placental size is therefore clinically useful. For example, placental thickness assessed by 2D US at 11–14 weeks of gestation can differentiate fetuses with Hb Bart's disease from unaffected fetuses with a sensitivity of 70.0% and a specificity of 63.5%.[5] However, a more reliable measurement technique of placenta size like 3D US and VOCAL, which is theoretically better than placental thickness, should improve the accuracy of such a diagnosis. With new 3D US technology, we prefer to use the VOCAL mode in measurement placental volume because it is simpler, faster, and more reproducible when compared with the multiplanar mode, although the measured values are not significantly different.[9] In addition, the VOCAL method also permits us to modify the contours of the placenta in the volume dataset. Although the measurement with VOCAL is more complicated than the mere measurement of placental thickness using 2D US, it is easily performed and provides more reliable values. Thus, placental volume measured with VOCAL is expected to improve the prediction of fetal Hb Bart's disease, especially when combined with other sonomarkers such as cardiac size.

We focused on placental volume in the first trimester because our primary use of the placental volume was to assess the risk of fetal Hb Bart's disease, the most common serious fetal disorder in our population. Placental size measurement in the detection of fetal Hb Bart's disease is usually less necessary in late gestation, because several signs of hydropic changes have usually already developed. Moreover, the difficulty in measurement of placental volume increases with gestational age, while its reliability decreases.[10] More difficult technique with advanced gestational age is due to the limitation of capturing the whole placenta within the transducer field of view and necessity of adjusting the location of measurement or degree of probe movements across the placenta.[11]

The strengths of this study include the adequate sample size for each gestational week and the fact that a CRL-specific SD model was identified. This can be used for a more reliable calculation of z score and construction of the percentile charts. The weaknesses of this study include the fact that the reference ranges are limited to the late first trimester, the fact that the resolution of 3D US volume datasets can be somewhat compromised when compared with 2D US, resulting in the exclusion of some cases from analysis, and finally, the fact that we did not correlate the placental volume with placental thickness.

In conclusion, we constructed the reference ranges of the placental volume in late first trimester as a function of CRL among Thai fetuses. These reference ranges may help in the evaluation of conditions affecting placenta size, especially fetal Hb Bart's disease. Nevertheless, the real usefulness of these reference ranges in clinical practice must be tested in future studies.

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REFERENCES

1. Wegrzyn P, Faro C, Falcon O, et al. Placental volume measured by three-dimensional ultrasound at 11 to 13 + 6 weeks of gestation: relation to chromosomal defects. Ultrasound Obstet Gynecol 2005;26: 28.
2. Plasencia W, Akolekar R, Dagklis T, et al. Placental volume at 11–13 weeks' gestation in the prediction of birth weight percentile. Fetal Diag Ther 2011;30:23.
3. Metzenbauer M, Hafner E, Schuchter K, et al. First-trimester placental volume as a marker for chromosomal anomalies: preliminary results from an unselected population. Ultrasound Obstet Gynecol 2002;19:240.

4. Collins SL, Stevenson GN, Noble JA, et al. Rapid calculation of standardized placental volume at 11 to 13 weeks and the prediction of small for gestational age babies. Ultrasound Med Biol 2013;39: 253.
5. Sirichotiyakul S, Luewan S, Srisupundit K, et al. Prenatal ultrasound evaluation of fetal Hb Bart's disease among pregnancies at risk at 11 to 14 weeks of gestation. Prenat Diagn 2014;34:230.
6. Aye CY, Stevenson GN, Impey L, et al. Comparison of 2-D and 3-D estimates of placental volume in early pregnancy. Ultrasound Med Biol 2015;41: 734.
7. Titapant V, Cherdchoogieat P. Nomogram of placental thickness, placental volume and placental vascular indices in healthy pregnant women between 12 and 20 weeks of gestation. J Med Assoc Thai 2014;97:267.
8. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound Obstet Gynecol 1998;11:30.
9. Nowak PM, Nardozza LM, Araujo Junior E, et al. Comparison of placental volume in early pregnancy using multiplanar and VOCAL methods. Placenta 2008;29:241.
10. Jones NW, Raine-Fenning NJ, Mousa HA, et al. Evaluating the intra- and interobserver reliability of three-dimensional ultrasound and power Doppler angiography (3D-PDA) for assessment of placental volume and vascularity in the second trimester of pregnancy. Ultrasound Med Biol 2011;37:376.
11. de Paula CF, Ruano R, Campos JA, et al. Quantitative analysis of placental vasculature by three-dimensional power Doppler ultrasonography in normal pregnancies from 12 to 40 weeks of gestation. Placenta 2009;30:142.