Utilizing Two-Dimensional Ultrasound to Develop Normative Curves for Estimated Placental Volume

Elizabeth Kagan Arleo, MD[1] Robert N. Troiano, MD[1] Raphaella da Silva, MD[1]
Daniella Greenbaum, HSDG[1] Harvey J. Kliman, MD, PhD[2]

[1] Department of Radiology, New York-Presbyterian/Weill Cornell, New York, New York
[2] Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

Address for correspondence Elizabeth Kagan Arleo, MD, New York-Presbyterian/Weill Cornell, 425 East 61st Street, 9th Floor, New York, NY 10065 (e-mail: ela9033@med.cornell.edu).

Am J Perinatol

Abstract

Objective The objective of this study was to use two-dimensional (2D) ultrasound (US) during routine prenatal surveillance to develop normative estimated placental volume (EPV) growth curves.

Study Design Patients $\geq$ 18 years old with singleton pregnancies were prospectively followed from 11 weeks gestational age (GA) until delivery. At routine US visits, placental width, height, and thickness were measured and EPV calculated using a validated mathematical model.

Results In this study, 423 patients were scanned between 9.7 and 39.3 weeks GA to generate a total of 627 EPV calculations. Readings were clustered at 12 and 20 weeks, times of routine scanning. The mean EPV was 73 $\pm$ 47 cc at 12.5 $\pm$ 1.5 weeks ($n = 444$) and 276 $\pm$ 106 cc at 20 $\pm$ 2 weeks ($n = 151$). The data best fit a parabolic function as follows: $EPV = (0.384GA - 0.00366GA^2)^3$. Tenth and 90th percentile lines were generated with $\pm$ 1.28 SE offset. EPV readings below the 10th or above the 90th percentiles tended to be associated with either small or large newborns, respectively.

Conclusion Routine 2D US created EPV growth curves, which may be useful for stratifying patients into prenatal risk groups.

Keywords
- placenta
- EPV
- prenatal care

Prenatal obstetrical ultrasound (US) is routinely ordered for screening purposes at 11 to 14 weeks for nuchal translucency in the assessment of Down syndrome, at 18 to 20 weeks for an anatomic survey, and sometimes at 32 to 36 weeks to evaluate fetal size and placental location. However, currently, placental volume is not assessed on such USs, despite the fact that it is directly responsible for the growth and well-being of the developing fetus. Although assessment of gestational size is performed as soon as a tiny embryo can be visualized in the early first trimester, with measurement of crown-rump length, placental size has remained largely ignored. A major reason for this is that in the past, determining placental volume prenatally has often been time-consuming and/or required expensive technology and expertise. However in 2010, Azpurua et al demonstrated that placental weight can be accurately predicted using routine two-dimensional (2D) US to obtain placental width, height, and thickness, which, in conjunction with a validated mathematical equation, can be used to calculate the convex–concave shell volume of the placenta.[1]

Abnormally decreased placental weight has been associated with intrauterine fetal demise (IUFD) and intrauterine growth restriction (IUGR)[2–8]; therefore, knowledge about placenta volume prenatally has important implications for

received
June 25, 2013
accepted after revision
August 19, 2013

DOI http://dx.doi.org/10.1055/s-0033-1357265.
ISSN 0735-1631.

patient care. However, just as pediatric growth charts consist of a series of percentile curves, placental growth charts would be necessary to place an individual prenatal placenta volume estimate into context. Thus, the objective of this original clinical research was to use 2D US during routine prenatal surveillance to develop normative estimated placental volume (EPV) growth curves using a validated mathematical model.[1]

Materials and Methods

This prospective observational human study was approved by the Institutional Review Board at the Weill Cornell Medical College, Office of Research Integrity and Assurance and the Human Investigation Committee of the Yale University School of Medicine (protocol number 0905005157). Informed consent was obtained from each patient.

Patients were accrued from pregnant patients presenting to the imaging division of the Department of Obstetrics and Gynecology, New York-Presbyterian/Weill Cornell Medical Center between May 2010 and February 2011. Inclusion criteria included all pregnant patients $\geq$ 18 years old with singleton pregnancies presenting for routine screening prenatal US. Exclusion criteria included patients younger than 18 years, patients with more than a single gestation, and patients with known uterine, fetal, or placental abnormalities (including placenta previa). In total, the patient population consisted of 423 consecutively consenting patients, each of which had one to four EPV measurements performed during one or more prenatal visits.

EPV was calculated using the following validated convex–concave shell formula (►**Fig. 1**): $V = (\pi T/6) \times [4H(W - T) + W(W - 4T) + 4T^2]$, where V is the volume; W, the maximal width; H, the height at maximal height; and T, the thickness at maximal height.[1] Once the maximal placental width was established, a cross-sectional image perpendicular to the plane of the placenta was taken on the US machine. Reference points were placed at the two tips of the placenta to establish the width measurement. Another reference point was placed at the apex of the placental curve at the interface of the placenta and decidua, which was connected to a point along the width to establish a perpendicular height line. The thickness was measured along the height line to the point where the placenta edge was crossed at the interface between the placenta and the amniotic fluid. For flat placentas, which were seen most often at 10 to 12 weeks of gestation, the width was established as described above, but the height and thickness lines were the same distance since there was no curvature to the placenta.

EPV readings were then graphed against gestational age (GA) to generate normative growth curves with EPV percentiles using R version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria), which also generated an R^2 correlation coefficient and p value for the best fit curves. Patients with more than one EPV reading also had individual pair graphs, generated to demonstrate EPV trends. Pregnancy outcome information was obtained from electronic medical records, with special attention to those patients with outlying

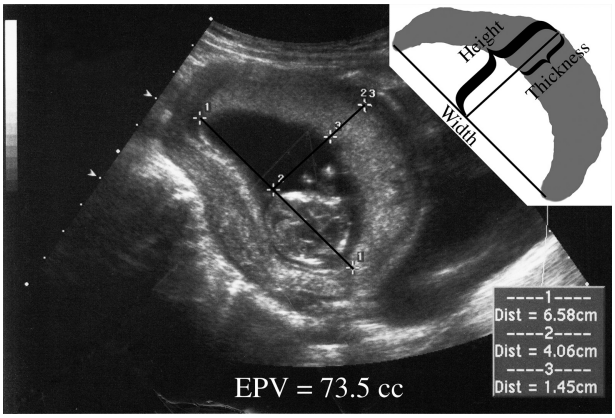

Fig. 1 Representative gray-scale two-dimensional ultrasound image demonstrating the placental width (1–1), height (2–2), and thickness (3–3) measurements used to calculate an EPV. Distances in cm are shown in lower right corner, resulting in an EPV of 73.5 cc. Inset shows a diagrammatic version of the placental outline with the key measurements used to generate an EPV. Note that the height is always greater than the thickness whenever the placenta has any curvature. When the placenta is flat, the thickness and height are of the same measurement. EPV, estimated placental volume.

EPV readings (defined as below the 10th or above the 90th percentiles); the birth weights of the babies born to these patients were then also graphed against their GA at delivery to determine their birth weight percentile using Center for Disease Control and Prevention (CDC) growth charts.

Results

In this study, 423 patients were scanned between 9.7 and 39.3 weeks GA to generate a total of 627 EPV calculations. Readings were clustered at 12 and 20 weeks, times of routine scanning. The mean EPV at 12.5 $\pm$ 1.5 weeks ($n = 444$) was 73 $\pm$ 47 cc and the mean EPV at 20 $\pm$ 2 weeks ($n = 151$) was 276 $\pm$ 106 cc. The data best fit a parabolic function as follows: EPV $=$ (0.384 GA – 0.00366GA^2)^3 (►**Fig. 2**, green line). The 10th and 90th percentile lines were generated with $\pm$ 1.28 SE offset from the 50th percentile green line (►**Fig. 2**, red lines). An R^2 correlation of 0.978 and a p value of $< 2.2 \times 10^{-16}$ were calculated with this best fit equation. Because some patients had two or more EPV measurements performed over their gestations, we also performed a subanalysis to evaluate the potential confounding affect of having multiple readings from some of the patients. We randomly selected one reading from patients with multiple readings, combined these data with all the patients with only one EPV reading and recalculated the best fit analysis, generating an equation with a first term (GA) within 2.2% of the original equation, an R^2 correlation within 0.2% of the original equation, and a p value that was identical to the original equation. The similarity between the best fit curves demonstrated that the patients with multiple readings did not bias the resultant curve generated when all the data points were used.

When the results of all patients with two or more EPV readings were plotted against GA, a series of uniform growth

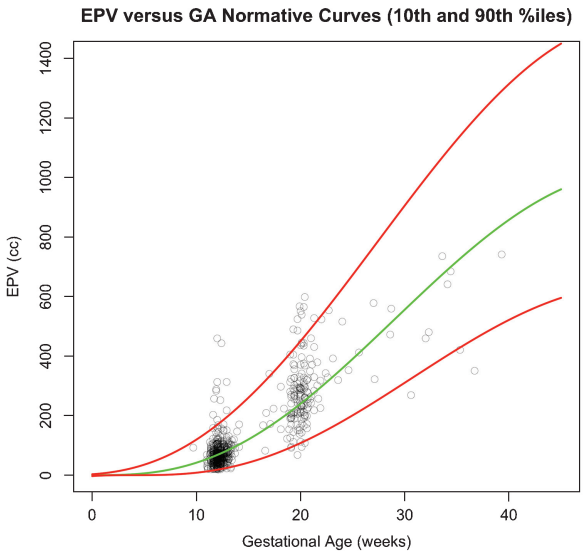

Fig. 2 Six hundred and twenty-seven EPV calculations versus GA demonstrating normative curves with 10th (lower red line), 50th (green line), and 90th (upper red line) percentile lines calculated based on the following parabolic relationship: EPV = $(0.384GA - 0.00366GA^2)^3$ with the 10th and 90th percentile lines being generated with ± 1.28 SE offset. An R^2 correlation of 0.978 and a p value of $< 2.2 \times 10^{-16}$ were calculated using the above parabolic equation. EPV, estimated placental volume; GA, gestational age.

lines was revealed (►**Fig. 3**), illustrating marked consistency in growth of the placentas from this patient cohort.

Only 21 patients fell either below or above the 10th and 90th percentile lines, respectively. Although this number was not sufficient to determine whether there was a statistically significant correlation between outlying EPV readings and birth weight, the data appear to reveal a trend (►**Table 1**). Of the four patients with EPV readings below the 10th percentile, three gave birth to babies with notably low birth weight percentiles (10th, 12th, and 20th percentiles). Although the fourth gave birth to a baby with a birth weight at the 80th percentile, interestingly, this mother had gestational diabetes. On the other end of the spectrum, 17 patients had EPV readings above the 90th percentile. Of the 13 with birthweight data available in the electronic medical record, three gave birth to babies with notably high birth weight percentiles (90th, 95th, and 99th percentiles), while two had gestations associated with a genetic abnormality (Dandy–Walker and fragile X intermediate risk).

Discussion

This research used 2D US during routine prenatal surveillance and a validated mathematical equation to develop normative EPV growth curves. This represents an advance in clinical knowledge, as it is the first such placental growth chart to be developed. The implications for patient care are important: just as the CDC recommends that pediatricians use growth charts to monitor growth for infants and children,[9] such an EPV growth chart could be used by obstetricians to monitor the growth of the placenta in utero, in addition to the developing fetus, for risk stratification purposes.

As the growth of a fetus is dependent on the placenta, a small for GA placenta (defined as an EPV reading below the 10th percentile on an EPV growth chart) could be an *earlier* indication of a small for GA newborn than waiting until a fetus is noted to be in the 10th percentile or less on standard fetal growth charts. A small for GA fetus is at increased risk for adverse peri- and postnatal outcomes.[10] Therefore, if there is an easily usable and accessible screening test to potentially identify such fetuses as early as possible, then earlier interventions to optimize outcome may be a possibility. EPV represents such a screening test: in our experience, sonographers can quickly be taught to measure the placental length, width, and height of routine 2D prenatal US images. The EPV can be easily calculated using a free iPhone

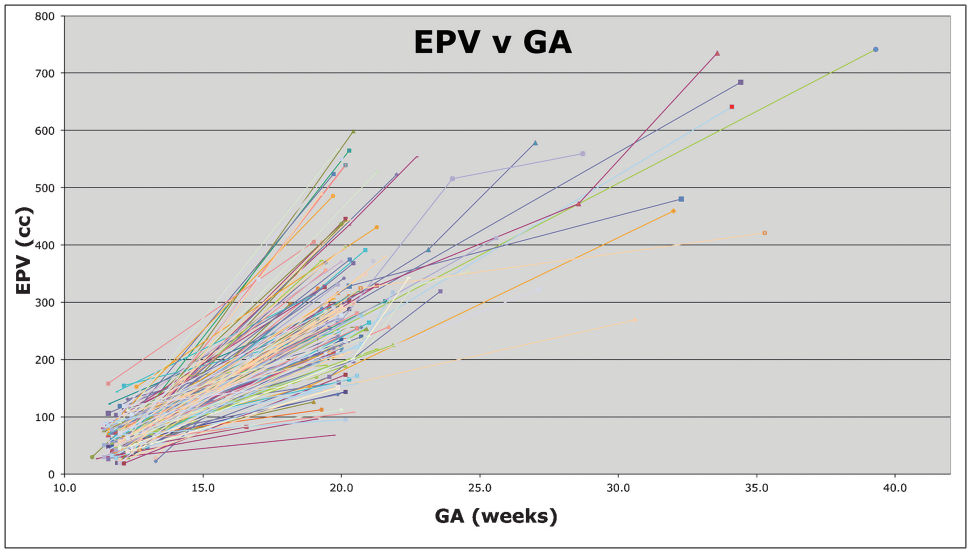

Fig. 3 Individual growth plots of all the patients with multiple EPV readings illustrating a marked uniformity in growth of the placentas from this cohort of patients. EPV, estimated placental volume.

Table 1 EPV readings and birth weight

GA (wk) at time of EPV	EPV (cc)	EPV percentile[a]	GA (wk) at the time of delivery	Birth weight (g)	Birth weight percentile[b]	Notes
30.6	269	< 10th	38 + 1	2,675	10th	
36.7	351	< 10th	38 + 1	2,835	20th	
19.7	68	< 10th	38 + 1	3,526	80th	Maternal diabetes
20.1	95	< 10th	38 + 0	2,679	12th	
12	459	> 90th	39 + 6	3,204	25th	
12.4	443	> 90th	41 + 4	3,420	20th	
12	313	> 90th	39 + 1	3,635	60th	
11.9	283	> 90th	39 + 1	3,785	70th	
11.9	288	> 90th	39 + 1	4,865	99th	Preeclampsia
12.3	252	> 90th	38 + 1	3,210	50th	
12.9	218	> 90th	37 + 6	3,545	80th	
11.6	203	> 90th	37 + 0	3,205	60th	Fragile X, intermediate
19.9	567	> 90th	20 + 0	Unknown	Unknown	Termination at 20 wk for Dandy–Walker malformation
20.3	565	> 90th	41 + 2	4,430	90th	
20	551	> 90th	39 + 3	3,915	80th	
19.3	490	> 90th	40 + 6	3,845	55th	
12.9	313	> 90th	39 + 1	4,264	95th	
12	459	> 90th	39 + 6	3,204	25th	
12.4	443	> 90th	41 + 4	3,420	20th	

Abbreviations: EPV, estimated placental volume; GA, gestational age; wk, weeks.
[a]Determined using the curves in ►**Fig. 2**.
[b]Determined using the fetal–infant growth chart for preterm infants from COC growth charts, based on Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr. 2003;3(1):13.

application (►**Fig. 4**), an Excel spread sheet, or even directly on US machines that have the EPV equation programmed into the user options. In short, an EPV reading can be achieved within a minute or two, thus quickly providing reassurance that a placenta is within normal limits (10th–90th percentile) or flagging it as an outlier (below the 10th percentile or above the 90th percentile).

Although the literature contains several studies on placenta weight percentile curves for singleton and twin studies,[11,12] the placental weights in these studies were taken in pathology departments after delivery; thus, a strength of the present study is that placental volume—while estimated—was obtained prenatally, and the accuracy has been validated.[1] Other studies in the literature describing the estimation of placental volume in the prenatal period use three-dimensional (3D) US,[13,14] which is not always available; thus, another strength of the present study is that our method of EPV calculation uses routine 2D US, which has widespread availability. Despite this distinction, the recent publication by Collins et al[13] using 3D US is related to the present study in that their goal was also to see if IUGR could be predicted as early as possible: they found that their semi-automated image processing technique from a 3D image obtained at the time of a nuchal scan could be used to predict growth restriction in both low- and high-risk populations (with a fixed false-positive rate of 10%, sensitivity of 44%), albeit with sample size ($N = 145$) smaller than ours ($N = 423$).

The objective of this study was to use 2D US to develop normative EPV growth curves, but having achieved this objective, this research begs the next question to be studied: can EPV predict IUGR and prevent IUFD? Although this study was not powered to investigate outcomes, review of the outliers suggests that this question is worthy of further investigation. For example, there was trending in the same direction for low outlying EPV readings: three out of four patients with low outlying EPV readings had newborns with notably low birth weight percentiles, demonstrating—if not a statistically significant correlation—at least a consistent trend. The one newborn that was not small for GA was the product of a mother with gestational diabetes. On the other end of the spectrum, there was an enrichment of notable outcomes (5) in patients with high outlying EPV reads with known outcomes (13) as well: of the 13, 3 delivered babies with high-birth-weight percentiles and 2 delivered babies with an associated genetic abnormality. Attention to outliers in future studies is recommended.

Fig. 4 Screenshot of the free iPhone EPV application demonstrating the calculation of the EPV at 11 + 0 weeks from width, height, and thickness measurements in centimeters of the placenta illustrated in ►**Fig. 1**. EPV, estimated placental volume.

The main limitation of our study is its sample size: ideally, such a study should be replicated on a much larger scale, comparable to the large population-based studies used to establish the World Health Organization growth standards and CDC growth charts,[9] with multiple, more frequent EPV readings per patient. This was not fiscally possible for this research; therefore, we chose to do a feasibility study with the results providing preliminary pilot data in favor of a larger scale approach. Furthermore, as discussed above, because there were relatively few outlying EPV readings, a statistically significant correlation between abnormal EPV reading and postnatal outcome could not be determined. Our study was not powered to do this—rather, it was organized to generate normative growth curves. However, Pomorski et al[14] found a statistically significant difference in placental volume between normal and IUGR pregnancies, with placental volume in normal pregnancies 92 cc larger (on average) than in IUGR pregnancies, albeit with a sample size ($N = 120$) smaller than ours, when employing a 3D Power Doppler and VOCAL technique in patients 22 to 42 weeks GA. In addition, since ours is a high volume institution employing multiple obstetrical sonographers, inter- and intra-observer variabilities in obtaining EPV measurements may have been present to some degree; however, all sonographers performing EPV measurements received prestudy training by the senior author and periodic checks by the head sonographer and first author to optimize measurements and minimize such variability. Finally, while the measurement method has some limitations in the third trimester, with the validation study demonstrating technical difficulties with large placentas when the GA was more than 36 weeks,[1] there were the fewest measurements in this trimester compared with the earlier two.

In conclusion, this study used 2D US during routine prenatal surveillance to develop normative EPV growth curves, the first ever generated. In clinical practice, these EPV curves could be used to flag a pregnancy for closer follow-up or further evaluation if an EPV reading is in the bottom or top 10th percentile. The next step is to investigate whether EPV can predict IUGR and prevent IUFD, and the pilot data from this study support the hypothesis that it may be able to do so.

Acknowledgments

The authors acknowledge with gratitude the sonographers of the Department of Obstetrics and Gynecology at the New York Presbyterian Hospital, Weill Medical College of Cornell University, who took all of the EPV measurements and thus made this study possible; Frank A. Chervenak, MD, Professor, Chairman, and Director of Maternal Fetal Medicine of the Department of Obstetrics and Gynecology at the New York Presbyterian Hospital, Weill Medical College of Cornell University, for his support of this study; John A. Hartigan and Saier Ye, both from the Department of Statistics, Yale University, for their help and insights in developing the best fit models and R programs to analyze the presented data.

References

1 Azpurua H, Funai EF, Coraluzzi LM, et al. Determination of placental weight using two-dimensional sonography and volumetric mathematic modeling. Am J Perinatol 2010;27(2):151–155
2 Kinare AS, Natekar AS, Chinchwadkar MC, et al. Low midpregnancy placental volume in rural Indian women: A cause for low birth weight? Am J Obstet Gynecol 2000;182(2):443–448
3 Hafner E, Metzenbauer M, Höfinger D, et al. Comparison between three-dimensional placental volume at 12 weeks and uterine artery impedance/notching at 22 weeks in screening for pregnancy-induced hypertension, pre-eclampsia and fetal growth restriction in a low-risk population. Ultrasound Obstet Gynecol 2006; 27(6):652–657
4 Metzenbauer M, Hafner E, Schuchter K, Philipp K. First-trimester placental volume as a marker for chromosomal anomalies: preliminary results from an unselected population. Ultrasound Obstet Gynecol 2002;19(3):240–242
5 Elchalal U, Ezra Y, Levi Y, et al. Sonographically thick placenta: a marker for increased perinatal risk—a prospective cross-sectional study. Placenta 2000;21(2–3):268–272

6 Baschat AA, Harman CR. Antenatal assessment of the growth restricted fetus. Curr Opin Obstet Gynecol 2001;13(2):161–168
7 Harkness UF, Mari G. Diagnosis and management of intrauterine growth restriction. Clin Perinatol 2004;31(4): 743–764, vi
8 Gilbert WM, Danielsen B. Pregnancy outcomes associated with intrauterine growth restriction. Am J Obstet Gynecol 2003;188(6): 1596–1599, discussion 1599–1601
9 Center for Disease Control (CDC) Pediatric Growth Charts. Available at: http://www.cdc.gov/growthcharts/. Accessed April 3, 2013
10 Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population-based study. BJOG 2008;115(5):590–594
11 Almog B, Shehata F, Aljabri S, Levin I, Shalom-Paz E, Shrim A. Placenta weight percentile curves for singleton and twins deliveries. Placenta 2011;32(1):58–62
12 Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. Placenta weight percentile curves for singleton deliveries. BJOG 2007; 114(6):715–720
13 Collins SL, Stevenson GN, Noble JA, Impey L. 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(2):253–260
14 Pomorski M, Zimmer M, Florjanski J, et al. Comparative analysis of placental vasculature and placental volume in normal and IUGR pregnancies with the use of three-dimensional Power Doppler. Arch Gynecol Obstet 2012;285(2):331–337