Placental Volume at 11–13 Weeks' Gestation in the Prediction of Birth Weight Percentile

Walter Plasencia[a] Ranjit Akolekar[a] Themistoklis Dagklis[a] Alina Veduta[a]
Kypros H. Nicolaides[a, b]

[a]Harris Birthright Research Centre, Kings College Hospital, and [b]Department of Fetal Medicine, University College Hospital, London, UK

Abstract
Objective: To determine the value of placental volume measured by 3D ultrasound at 11–13 weeks' gestation in combination with maternal characteristics and serum pregnancy-associated plasma protein-A (PAPP-A) in the prediction of small and large for gestational age (SGA and LGA) neonates. *Methods:* Maternal serum PAPP-A and placental volume were measured at 11–13 weeks in 3,104 singleton pregnancies. Regression analysis was used to examine the contribution of maternal characteristics, placental volume and PAPP-A in the prediction of SGA and LGA neonates. *Results:* There was a significant association between placental volume and PAPP-A (r = 0.268, p < 0.0001). Median placental volume and PAPP-A, expressed as multiples of the median (MoM) in appropriate for gestational age (AGA) neonates, were reduced in the SGA group (placental volume 0.88 MoM, vs. 1.00 MoM in AGA, p < 0.0001; PAPP-A 0.92 MoM vs. 1.00 MoM in AGA, p = 0.019) and increased in the LGA group (placental volume 1.09 MoM vs. 1.00 MoM in AGA, p < 0.0001; PAPP-A 1.15 MoM vs. 1.00 MoM in AGA, p = 0.015). Maternal characteristics with either placental volume or PAPP-A detected about 30% of the SGA or LGA neonates, at a false positive rate of 10%. *Conclusion:* Measurement of placental volume and serum PAPP-A can improve the prediction of SGA or LGA neonates provided by maternal characteristics alone.

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Introduction

Birth weight is affected by gestational age at delivery and several maternal characteristics, including racial origin, age, body mass index, parity and cigarette smoking [1, 2]. There is also some evidence that birth weight is related to placental function in early pregnancy, reflected in the maternal serum concentration of the pregnancy-associated plasma protein-A (PAPP-A) and placental size, reflected in the 3D volume measurement at 11–13 weeks' gestation [1–5].

The aims of this study are (1) to examine the maternal characteristics which affect the placental volume, (2) to examine the association between placental volume and serum PAPP-A, and (3) to investigate whether the placental volume at 11–13 weeks is altered in pregnancies delivering small and large for gestational age (SGA and LGA) neonates.
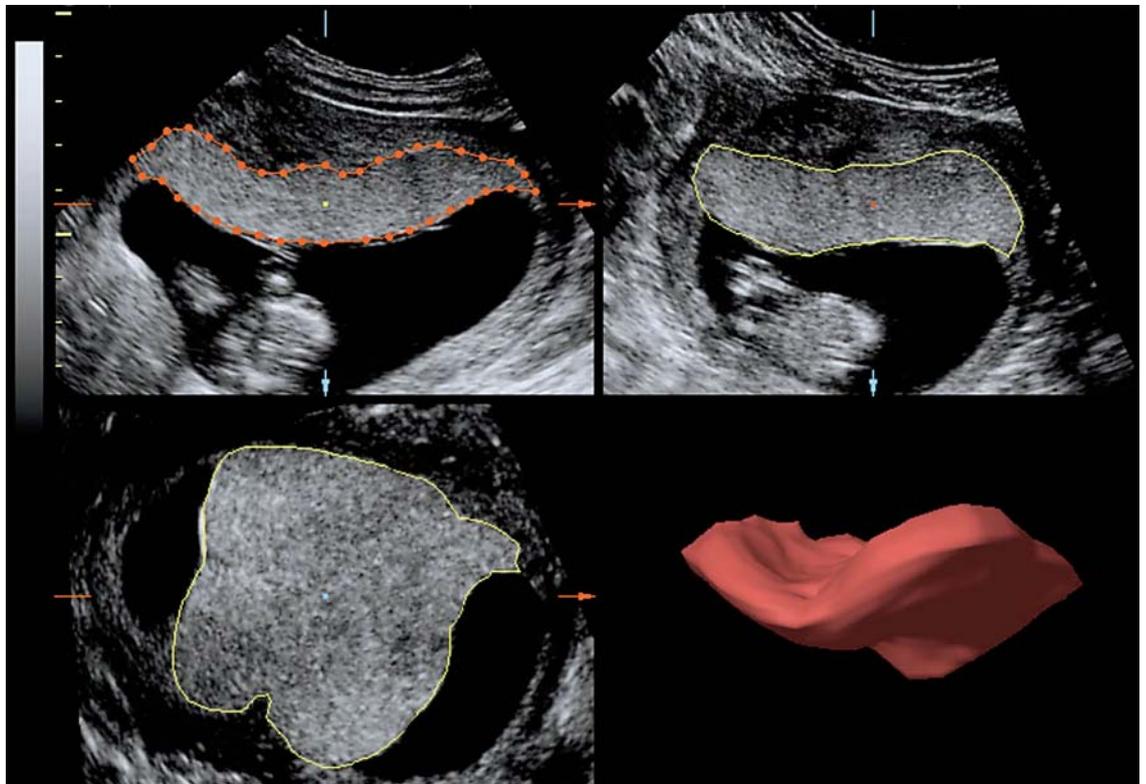
Prof. K.H. Nicolaides
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital
Denmark Hill, London SE5 9RS (UK)
Tel. +44 203 299 8256, E-Mail kypros@fetalmedicine.com

Fig. 1. 3D volume of the placenta obtained using the VOCAL technique.

Methods

The placental volume was measured in 3,104 singleton pregnancies at 11^{+0} to 13^{+6} weeks' gestation in women undergoing first-trimester combined screening for aneuploidies, by maternal age, fetal nuchal translucency thickness, and maternal serum PAPP-A and free β-human chorionic gonadotropin, at the Fetal Medicine Centre, London, UK [6, 7]. In each case we routinely acquired a 3D volume of the fetus and the placenta for offline analysis by transabdominal sonography (RAB 4–8L probe, Voluson 730 Expert; GE Medical Systems, Milwaukee, Wisc., USA) as previously described [8]. The sweep angle was set at 85° and it was aimed so that the probe was perpendicular to the placental plate. The VOCAL (Virtual Organ Computer-aided Analysis) technique was then used to obtain a sequence of 12 sections of the placenta, each after a 15° rotation from the previous one. In each of the 12 planes, the contour of the placenta was drawn manually, taking care to exclude the uterine wall, which at this gestation is usually thickened under the placenta either due to hypertrophy or contraction (Voluson 730 Expert Operation Manual, GE Medical Systems; fig. 1). Placental volume was automatically calculated by the built-in scanner software from the areas highlighted in each of the 12 planes. When the calculation was finished, the computed reconstruction of the organ was displayed together with the volume. All measurements were done offline by three operators who had certification from the Fetal Medicine Foundation for performing 11–13 week scans and had extensive experience in 3D ultrasound.

The neonate was considered to be SGA or LGA if the birth weight was less than the 5th or more than the 95th percentile, respectively, using a reference range of birth weight for gestation at delivery in our population [1]. Neonates between the 5th and 95th percentiles were considered to be appropriate for gestational age (AGA).

Statistical Analysis

Comparison between variables was done by a χ^2 test or Fisher's exact test for categorical variables, and a Mann-Whitney U test with post hoc Bonferroni correction for continuous variables.

The distribution of placental volume and PAPP-A were made Gaussian after logarithmic$_{10}$ transformation and normality was assessed using histograms and probability plots. Multivariate regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of $\log_{10}$ transformed placental volume in the AGA group. Then the distribution of $\log_{10}$ placental volume expressed as multiples of the median (MoM) of the AGA group, were determined in the SGA and LGA group. The measured concentration of PAPP-A was converted into MoM after adjustment for gestation, maternal age, racial origin, weight, parity, cigarette smoking status and method of conception as previously described [9]. Nonparametric analysis was used to examine the significance of association between placental volume MoM, PAPP-A MoM and birth weight percentile. Univariate logistic regression analysis was used to determine which of the factors amongst maternal

Table 1. Maternal and pregnancy characteristics in the study group

Characteristic	AGA (n = 2,811)	SGA (n = 144)	LGA (n = 149)
Maternal age in years, median (IQR)	35.6 (32.7–38.3)	35.7 (32.7–38.3)	36.2 (33.8–38.7)
Maternal weight in kg, median (IQR)	63.0 (57.0–69.0)	58.6 (53.7–64.0)*	70.0 (61.4–78.5)*
Maternal height in cm, median (IQR)	165.1 (162.6–170.2)	162.6 (157.5–167.6)*	167.6 (162.6–172.7)*
Crown-rump length in mm, median (IQR)	62.3 (57.3–68.0)	61.4 (56.7–66.8)	63.8 (57.3–70.2)
Ethnicity			
Caucasian, n (%)	2,607 (92.7)	119 (82.6)	141 (94.6)
African, n (%)	23 (0.8)	0	2 (1.3)
South Asian, n (%)	119 (4.2)	21 (14.6)*	2 (1.3)
Mixed, n (%)	25 (0.9)	1 (0.7)	1 (0.7)
Cigarette smoker, n (%)	37 (1.3)	3 (2.1)	3 (2.0)
Nulliparous, n (%)	1,221 (43.4)	84 (58.3)*	41 (27.5)*
Conception			
Spontaneous, n (%)	2,512 (89.4)	121 (84.0)	138 (92.6)
Assisted conception, n (%)	299 (10.6)	23 (16.0)	11 (7.4)
Birth weight percentile, median (IQR)	51.7 (32.5–71.2)	2.3 (0.7–3.5)*	97.5 (96.3–99.4)*

Comparison between outcome groups by Mann-Whitney U test with post hoc Bonferroni correction for continuous variables and χ^2-test or Fisher's exact test for categorical variables; corrected significance level * $p < 0.025$. IQR = Interquartile range.

characteristics, $\log_{10}$ PAPP-A MoM and $\log_{10}$ placental volume MoM provided a significant contribution in predicting the birth of SGA or LGA neonate. Multivariate logistic regression analysis was used to develop a model based on a combination of maternal characteristics and serum PAPP-A and placental volume was then added to the regression model to determine whether it provided a significant independent contribution. The detection and false positive rates were calculated as the respective proportions of SGA and LGA (detection rate) and AGA pregnancies (false positive rate) with MoM values above given cutoffs. The performance of screening was determined by receiver operating characteristic (ROC) curves analysis.

The statistical software package SPSS 17.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

The maternal and pregnancy characteristics in the study group are described in table 1. In the SGA group, compared to the AGA group, the median maternal weight and height were lower, there were more women of South Asian racial origin and more women were nulliparous. In the LGA group, compared to the AGA group, the median maternal weight and height were higher and more women were parous.

The median placental volume increased with fetal crown-rump length (CRL) from 45 ml at a CRL of 45 mm to 91 ml at 84 mm (fig. 2). Regression analysis demonstrated that $\log_{10}$ placental volume changed significantly with fetal CRL and maternal weight, but not maternal age (p = 0.199), height (p = 0.096), racial origin (p = 0.779), smoking status (p = 0.955), mode of conception (p = 0.848) or parity (p = 0.833). $\log_{10}$ placental volume MoM = $\log_{10}$ observed placental volume in millilitres – (1.218 + 0.008 × fetal CRL in millimetre + 0.001 × maternal weight in kilogram; R^2 = 0.244, p < 0.0001.

There were significant associations between placental volume MoM and PAPP-A MoM (Spearman's correlation coefficient ρ = 0.268, p < 0.0001), between placental volume MoM and birth weight percentile (ρ = 0.177, p < 0.0001), and between PAPP-A MoM and birth weight percentile (ρ = 0.111, p < 0.0001).

In the SGA group, compared to the AGA group, there was a significantly lower median placental volume MoM (0.88 vs. 1.00, p < 0.0001) and median PAPP-A MoM (0.92 vs. 1.00, p = 0.019), whereas in the LGA group, compared to the AGA group, there was a higher median placental volume MoM (1.09 vs. 1.00, p < 0.0001) and median PAPP-A MoM (1.15 vs. 1.00, p = 0.015; table 2, fig. 3).

In the prediction of SGA from maternal characteristics, there was a significant contribution from maternal weight (OR: 0.98, 95% CI: 0.96–1.00), maternal height (OR: 0.94, 95% CI: 0.92–0.97), nulliparity (OR: 1.79, 95% CI: 1.27–2.52) and South Asian racial origin (OR: 2.47, 95% CI: 1.46–4.17). In the prediction of LGA from maternal characteristics, there was a significant contribution from weight (OR: 1.04, 95% CI: 1.03–1.06), height (OR:

Table 2. Median (interquartile range) of PAPP-A MoM and placental volume MoM in the outcome groups

Variable	AGA (n = 2,811)	SGA (n = 144)	LGA (n = 149)
PAPP-A			
MoM	1.00 (0.71–1.39)	0.92 (0.64–1.23)*	1.15 (0.78–1.50)*
mIU/ml	3.48 (2.34–5.25)	3.38 (2.28–4.88)	3.58 (2.29–5.60)
Placental volume			
MoM	1.00 (0.83–1.16)	0.88 (0.74–1.08)*	1.09 (0.91–1.26)*
ml	61.7 (49.8–73.9)	52.4 (43.4–68.5)	70.7 (54.7–84.3)

Comparison between outcome groups by Mann-Whitney U test with post hoc Bonferroni correction; corrected significance level * p < 0.025.
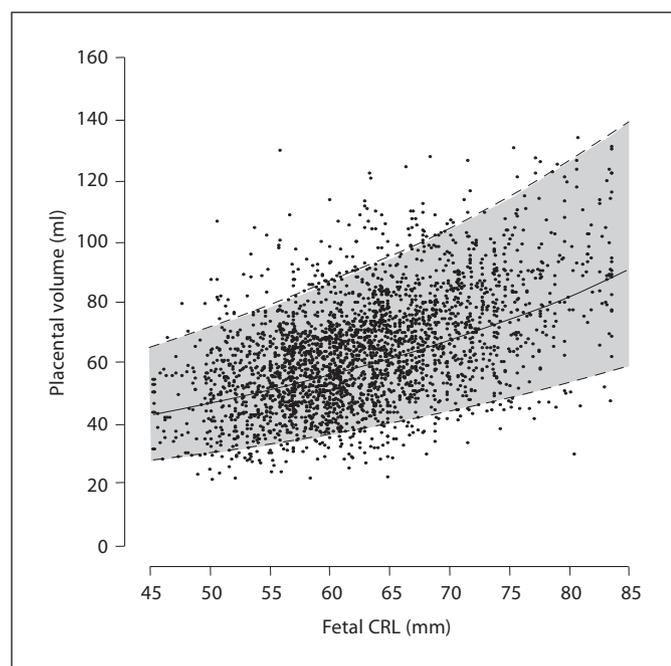

Fig. 2. Reference range of placental volume (millilitres) with fetal CRL (95th, 50th and 5th percentiles).
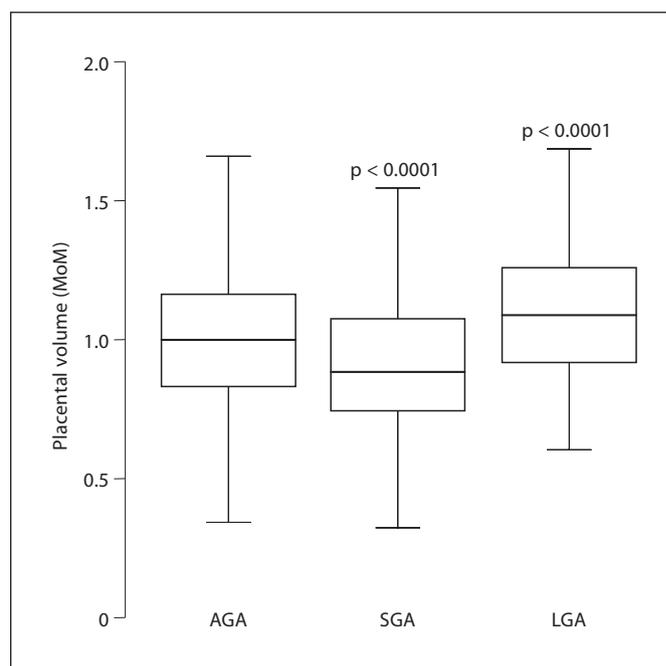

Fig. 3. Box (median, interquartile range) and whisker (range) plots of placental volume in MoM at 11–13 weeks' gestation in AGA, SGA and LGA neonates.

1.03, 95% CI: 1.01–1.06) and nulliparity (OR: 0.49, 95% CI: 0.34–0.71). Univariate logistic regression analysis demonstrated that in the prediction of both SGA and LGA, there were significant contributions from maternal characteristics (OR: 12.02, 95% CI: 6.52–22.15 and OR: 12.59, 95% CI: 6.93–23.21, respectively), $\log_{10}$ placental volume MoM (OR: 0.43, 95% CI: 0.01–0.18 and OR: 21.4, 95% CI: 4.48–102.3, respectively) and $\log_{10}$ PAPP-A MoM (OR: 0.35, 95% CI: 0.16–0.74 and OR: 2.70, 95% CI: 1.23–5.93, respectively).

The patient-specific risk for both SGA and LGA was calculated from the formula: odds/(1 + odds), where odds = e^Y and Y was derived from multivariate logistic regression analysis of the disease-specific maternal characteristics, $\log_{10}$ placental volume MoM and $\log_{10}$ PAPP-A MoM. The estimated detection rates of SGA and LGA at fixed false positive rates of 10% and their respective areas under the ROC (AUROC) curves in screening by maternal characteristics, $\log_{10}$ placental volume MoM and $\log_{10}$ PAPP-A MoM and their combinations are shown in table 3.

Table 3. Detection rates (DR) of SGA and LGA neonates at a fixed false positive rate of 10% and comparison of screening performance by ROC curve analysis in screening by maternal characteristics, PAPP-A, placental volume and their combinations

	DR (95% CI)	AUROC (95 % CI)
Prediction of SGA		
Maternal characteristics	27.8 (20.0–37.3)	0.678 (0.631–0.726)
Maternal serum PAPP-A	13.2 (7.9–21.2)	0.558 (0.511–0.605)
Placental volume	18.1 (11.8–26.8)	0.601 (0.552–0.651)
Maternal characteristics plus		
Serum PAPP-A	32.6 (24.2–42.3)	0.692 (0.646–0.738)
Placental volume	29.2 (21.2–38.8)	0.699 (0.653–0.746)
Maternal characteristics, serum PAPP-A, placental volume	34.7 (26.1–44.4)	0.706 (0.660–0.753)
Prediction of LGA		
Maternal characteristics	28.9 (20.9–38.4)	0.695 (0.652–0.738)
Maternal serum PAPP-A	14.8 (9.2–23.1)	0.559 (0.512–0.605)
Placental volume	20.8 (14.0–29.8)	0.598 (0.550–0.646)
Maternal characteristics plus		
Serum PAPP-A	29.5 (21.5–39.1)	0.704 (0.661–0.748)
Placental volume	32.9 (24.5–42.6)	0.715 (0.673–0.756)
Maternal characteristics, serum PAPP-A, placental volume	33.6 (25.1–43.3)	0.716 (0.673–0.758)

Multivariate regression analysis demonstrated that in the prediction of both SGA and LGA neonates, addition of placental volume to the combination of maternal characteristics and serum PAPP-A provided a significant independent contribution (SGA = OR: 0.10, 95% CI: 0.02–0.41, p = 0.001; LGA = OR: 12.92, 95% CI: 2.59–64.59, p = 0.002). However, placental volume did not improve significantly the performance of screening that was achieved by maternal characteristics and serum PAPP-A (SGA = AUROC: 0.692, 95% CI: 0.645–0.738 vs. AUROC: 0.706, 95% CI: 0.660–0.753, p = 0.160; LGA = AUROC: 0.704, 95% CI: 0.661–0.748 vs. AUROC: 0.716, 95% CI: 0.673–0.758, p = 0.254).

Discussion

The findings of our study demonstrate that (1) placental volume at 11–13 weeks is related to placental function, reflected in the maternal serum concentration of PAPP-A, and (2) the birth of SGA and LGA neonates can be predicted in the first trimester of pregnancy from a combination of maternal characteristics, placental volume and serum PAPP-A.

Placental volume at 11–13 weeks increases with maternal weight and gestational age. The increase in volume from a median of 45 ml at a CRL of 45 mm to about 90 ml at a CRL of 84 mm is similar to values reported in previous studies [8, 10]. The increase in placental volume with fetal CRL is reflected in an increase in serum PAPP-A with gestational age. The correlation coefficient for the association between placental volume and serum PAPP-A was 0.27, which is similar to the 0.28 reported in a previous study of 1,378 singleton pregnancies at 10–13 weeks [10].

The placental volume, corrected for maternal weight and fetal CRL, in pregnancies destined to deliver SGA and LGA neonates is smaller and larger, respectively, than in pregnancies with AGA neonates. An algorithm combining maternal characteristics with either placental volume or serum PAPP-A can potentially identify about 30% of pregnancies delivering SGA or LGA neonates, respectively, for a false positive rate of 10%. However, there was no significant improvement in the performance of screening for SGA and LGA neonates by the addition of placental volume to the combination of maternal factors and serum PAPP-A, reflecting the high association between placental volume and function. Two previous studies have also reported on prediction of SGA from first-trimester measurement of placental volume. Hafner et al. [11], examined 2,489 singleton pregnancies at 11–13 weeks and reported that the detection rate of SGA by measurement of placental volume alone was 27%, at a false positive rate of 10%. Similarly, Law et al. [4], examined 601 pregnancies and reported that the measurement of placental volume at 11–13 weeks identified 23% of SGA

neonates, at a false positive rate of 10%, and the prediction was not improved by uterine artery Doppler or fetal CRL. These studies did not report on performance of screening for SGA by combining placental volume with maternal characteristics and serum PAPP-A. There are no previous reports on the first-trimester prediction of LGA from placental volume.

Effective screening for fetal aneuploidies is provided in the first trimester of pregnancy by a combination of maternal age and the findings of ultrasonographic examination of the fetus and biochemical analysis of maternal blood. Recent evidence suggests that at the same hospital visit at 11–13 weeks, data from the maternal history can be combined with the results of biophysical and biochemical tests to estimate the patient-specific risk for a wide variety of pregnancy complications [12]. Early estimation of risks for these pregnancy complications could potentially improve pregnancy outcome by shifting antenatal care from a series of routine visits to a more individualized patient and disease-specific approach both in terms of the schedule and content of such visits. In this respect, the 11–13 weeks assessment is likely to be the basis for a new approach to antenatal care.

The findings of this study have shown that measurement of placental volume and serum PAPP-A can improve the prediction of the birth of SGA or LGA neonates based on maternal characteristics alone. Since serum PAPP-A is already routinely measured as part of screening for aneuploidies and the increase in performance of screening for fetal growth disorders provided from placental volume is only marginally better than that of PAPP-A, it is unlikely that measurement of placental volume will be incorporated into routine practice for this purpose.

Acknowledgment

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