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Chorionic vascular ‘fit’ in the human placenta: Relationship to gestational age and birth weight

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Abstract

Background—Novel measures of the chorionic plate and vessels are used to test the hypothesis that variation in placental structure is correlated with reduced birth weight (BW) independent of placental weight (PW), suggesting functionally compromised placentas.

Methods—917 mothers recruited to the Pregnancy, Infection and Nutrition Study delivering singleton live born infants at >30 gestational weeks had placentas collected, digitally photographed and weighed prior to formalin fixation. Beta (β) was calculated as $\ln(PW)/\ln(BW)$. Chorionic disk perimeter was traced and chorionic surface shape (CS) area was calculated. The sites at which chorionic vessels dived beneath the chorionic surface were marked to calculate the chorionic surface vessel (CV) area. The centroids of shapes, the distance between centroids and other measures of shape irregularities were calculated. Principal components analysis (PCA)

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created three independent factors to explore relations to BW, GA, trimmed PW, and β with $p < 0.05$ considered significant.

Results—Variables related to disk size (CS area, perimeter) were correlated with BW, GA, trimmed PW and β . “Fit” (the ratio of CV area to CS area), measures of shape irregularities, and the distance between the cord insertion and the centroids of surface and vascular areas were also correlated with one or more of the clinical variables. PCA yielded three factors that had independent effects on β (each $p < 0.0001$). Addition of GA did not alter the factors’ association with β .

Conclusions—Measures of CS and CV account for variation in placental efficiency defined by β , independent of GA. Macroscopic placenta measurements can identify suboptimal placental development.

Keywords

chorionic plate; birth weight; placental weight; placenta efficiency

INTRODUCTION

The placenta is the sole source of oxygen and nutrients for the fetus and thus is essential to healthy fetal life. Normal placentas will grow uniformly out from the umbilical cord insertion resulting in a round to oval disk with a centrally inserted cord. [1] However, placentas are frequently not round and alterations in shape may reflect suboptimal intrauterine environments. A variable maternal uteroplacental environment affects macroscopic placental structure by modifying the normal trajectories of chorionic surface shape (CS) including chorionic surface vessel (CV) development. (e.g., [4–6]) Irregularities in disk outline, in the site of umbilical cord insertion and recently, the orientation and distribution of the chorionic surface branching vessels, have been well characterized. [7–11]

Variation in the patterns of CV extension is considered to be “not random, although we do not understand the mechanisms that govern their growth”. [12] In general, the CV will course nearly to the placental edge. However, there is great variability in the distributions of the CV. Kaufmann speculated that a principal influence on the final anatomy of the CV is chorionic vascular perfusion. [13] Studies have shown some associations of these with fetal growth restriction. [14] The role of the placenta in “fetal programming” deserves a detailed and thorough evaluation, given the public health ramifications of adult diseases originating in failure of the placenta to optimally and efficiently meet fetal needs. [15–17] Extremes in placental efficiency have been related to cardiovascular disease later in life [18] that may have transgenerational effects. [19] The issue of the mechanisms and the implications of altered placental efficiency for post-natal consequences have been the subject of much scrutiny. [e.g., 20], and a recent NIEHS request for applications to study the “Environmental Influences on the Placental Origins of Disease”. (<https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-17-005.html>).

We hypothesize that, barring any perturbations of its environment, the average placenta is round with a centered umbilical cord [20] from which will extend chorionic surface vessels

uniformly about the chorionic surface, but that Here we test the relationships of measures of the chorionic surface shape (CS), the area of the chorionic plate covered by the CV, and their relationship to each other with birth weight, placental weight, gestational age and the fetoplacental weight ratio expressed as the linear ratio (FPR, [21]) and as β , the ratio of the logarithm of PW to the logarithm of BW [22–29]. We hypothesize that poor fit of CV area to the underlying CS area, and cord displacement relative to these two shapes are readily measurable markers of abnormal placental growth that impact placental function and efficiency.

MATERIALS AND METHODS

The Pregnancy, Infection, and Nutrition Study is a cohort study of pregnant women recruited at mid pregnancy from an academic health center in central North Carolina. Our study population and recruitment techniques are described in detail elsewhere [30]. Beginning in March 2002, all women recruited into the Pregnancy, Infection, and Nutrition Study were requested to consent to detailed placental examination. 1150 women consented; of these, 917 placentas were collected intact for digital photography of the fresh placenta. Image analyses were performed at EarlyPath Clinical and Research Diagnostics, a New York State-licensed histopathology facility under the direct supervision of Dr. Salafia. The institutional review board from the University of North Carolina at Chapel Hill approved this protocol.

Placental gross processing

Post delivery, the placenta was oriented so that the margin of the placenta closest to the ruptured edge of the extraplacental membranes was at 6 o'clock. A digital photograph of the fresh placenta was taken with the study identification number and at least 3 cm of a ruler in the field of view. From the digital placental photographs, the perimeter of the chorionic plate was traced as previously reported. [31] The “clicks” on the graphics tablet that defined the CS perimeter, marked the cord insertion, and marked the most distant end points of CV, were recorded in an Excel spreadsheet that graphically depicts and stores the x-y coordinates in an analyzable format. (Figure 1).

The following four variables were calculated (Figure 2):

1. Chorionic surface shape (CS);
2. CS centroid (the weighted center of an irregular planar shape);
3. CV shape; and
4. CV centroid

From these we derived four additional variables:

- (1) Ratio of CV and CS areas (“fit”);
- (2) Distance between the CS and CV centroids;
- (3 & 4) Distances between the CS and CV centroids and the site of umbilical cord insertion

Measures of shape irregularity for both CS and CV include:

- Compactness as $4\pi\text{Area}/\text{Perimeter}^2$ with 1= round shape
- Roughness as $\text{Perimeter}/\text{Perimeter of the smallest convex hull that includes the whole shape}$
- Radial standard deviation (RSD) as the standard deviation of 360 radii from cord insertion to CS or CV shapes, or from CS and CV centroids to their respective shapes.

We also counted the number of distal vascular end points that demarcated the CV shape, a proxy for the complexity of the chorionic vascular surface network.

The trimmed placental weight (PW), gestational age at delivery (GA), birth weight (BW) were retrieved from the data set. Fetoplacental weight ratio (FPR) was calculated as BW/PW . The allometric scaling coefficient (“ β ”) was calculated as $\ln(\text{PW})/(\ln(\text{BW}))$. We elected to use conservative non-parametric tests (Spearman’s correlation) in analyses of these novel variables. Bonferroni corrections were used for multiple comparisons, specific to each outcome analyzed.

Data reduction was performed using principal components analysis (PCA) using SPSS V20 (IBM, Chicago, IL). PCA is a statistical procedure that converts a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called factors, each of which accounts for a portion of the variance of variable values in the data set. Each factor is the sum of a series of coefficients (or weights) that are multiplied by the value of the respective variables. Since factors are calculated to be normally distributed, parametric tests (Pearson’s correlation, multivariable regression) were used in tests of relationships of factors to outcomes.

RESULTS

Population descriptive characteristics are presented in Table 1. The novel CS and CV shape measures are described in Table 2. Of the 17 novel variables, 11 had independent relationships with one or more of GA, BW, PW, FPR and β (Table 3).

We took the 11 variables that had independent relationships to one or more of the 5 outcomes, and used PCA to reduce these likely intercorrelated variables into a smaller number of factors. Three factors accounted for 85% of the data variance (44%, 28% and 13%, respectively). Factor scores were calculated from the coefficient matrix (Table 4). These 3 factors identified distinct placental patterns, e.g., Factor 1 is principally driven by the CS and CV perimeters and areas, in other words “size” and “fit” and other parameters with lesser contribution. By contrast, Factor 2 is negatively correlated with size but strongly correlated with greater irregularity of the CV shape, and displacement of both the CS and CV shapes from the umbilical cord insertion, the putative center of the primitive placenta. Finally, Factor 3 is principally driven by “fit”, the ratio of CV and CS areas. Representative images of placentas with high and low scores for the 3 factors are shown in Figures 3(a–f). The three factors have varying patterns of correlations with GA, BW, PW, and FPR (Table 5). Factor scores are calculated to be normally distributed, so linear regression was used to test the relationships among the 3 factors and BW, PW, GA and FPR (Table 6). The factors

accounted for 12% of BW variance, 4% of GA variance, 13% of PW variance, 2% of FPR and 5% of β , each p overall <0.0001 . Because β changes with GA, we re-analyzed the data including GA with the three factors as predictors of BW, PW, FPR and β . The significant relationships of the factors with BW, PW, FPR and β were generally unaffected by the addition of GA as a predictor. (Table 6)

Finally, we attempted to test a hypothesis that the extent of poor “fit” of the CV shape relative to the CS shape, reflecting an early perturbation of placental vascular growth relative to the achieved placental growth by delivery, would also be associated with displacement of the umbilical cord relative to the CS and CV centroids, and displacement between CS and CVS centroids. The smaller the CV relative to the CS areas, i.e., the poorer the “fit”, the greater displacement of the cord relative to both the CS and CV centroids ($r=.13$, $r=.15$, each $p < 0.0001$ respectively), and negatively correlated with displacement between the two centroids ($r = -0.30$, $p < 0.0001$); in other words, the better the “fit” between the CS and CV areas, the smaller the distance between the centroids of the CS and CV areas.

Discussion

We have tested novel measures of the placental chorionic surface shape, and the shape of the area covered by the chorionic surface vessels. Previously we have shown that measures of the surface vasculature at term are highly correlated with placental ultrasonographic measures obtained at 11–14 weeks, including displacement of the umbilical cord from the disk center, and the area of the placental chorionic surface. [32] Deviations of the placenta from its average round shape [33] have been associated with reduced placental efficiency, either as an altered FPR [33] or as a reduced β [5, 34]. Here we demonstrate that measures that are simple to collect (with clicks on a graphics tablet) have predictive value for the BW and the PW at delivery, and their relationship expressed either as the linear FPR or as the ratio of logarithms that is β . The stronger correlations with β than with FPR (see Tables 3 and 5) support that the birth to placental weight relationship is better expressed as a ratio of logarithms. Further, these features, while related to GA, are associated with outcomes independent of GA.

It is well known that placental growth is responsive or “tropic” to its maternal uterine environment that can be reflected in histologic maternal and/or fetal vascular pathology. [35] Placental growth can be directional based on local uterine pathology that may limit receptivity (such as scars) or alter perfusion (such as myomata). We have shown here that our novel measures of perturbations of placental growth have specific and different significant associations with GA, BW, PW, FPR and β . Additional study of these measures of poor “fit” will move us closer to understanding how placental growth and development, directly responsive to the maternal environment, is “translated” into fetal growth and birth weight.

Assessment of the macroscopic measurements of the placenta has received little attention, despite the evidence that alterations of the placental shape are likely to reflect an altered intrauterine environment and function, [36–38] that may account, at least in part, for the gender dimorphism of fetal programming. [39] These studies support the ongoing

assessment of the macroscopic features of a placenta, and also provide an insight into intrauterine environment and placental adaptation.

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Highlights

The chorionic surface shape and chorionic surface vessels may occupy very different areas, and be off-center relative to each other and to the umbilical cord.

Novel measures of these areas and their centroids provide insights in differences in birth and placental weights, and placental efficiency as quantified by beta.

These measures could be captured as a shape of Doppler color and analyzed, as a potential marker of preclinical fetal jeopardy.

Figure 1.
Sample schematic of the Kurta graphics representation of the placental perimeter tracing. The red star at the lower edge identifies the edge of the placenta closest to the free edge of the ruptured membranes (the site of rupture, or SoR); the red circle marks the site of the umbilical cord insertion.

Figure 2.

These schematics represent types of “mis-fit” of the chorionic vascular area (in red) and the chorionic disk surface area (in blue), and displacement of area centroids relative to the cord insertion. **A.** The chorionic vascular area (red) is smaller than the chorionic disk area (blue) but their centroids (red and blue circles, respectively) are closely concordant, with a short inter-centroid distance. **B.** The chorionic vascular area (red) and chorionic disk area (blue) are identical to **A** but they are displaced. **C.** shows the displacement from the side view.

Figure 3. Visual representations of the 3 factors. All images are to the same scale. **(a)** Low score on Factor 1; **(b)** High score on Factor 1; **(c)** Low score on Factor 1; **(d)** High score on Factor 2; **(e)** Low score on Factor 3; **(f)** High score on Factor 3.

Table 1

Sample cohort descriptives for birth outcomes.

	Mean ±Standard Deviation (Range)
Gestational Age at Birth(days)	272 ± 14 (177–298)
Birth Weight (grams)	3301 ±585 (778–5018)
Trimmed placental weight (grams)	445 ± 101 (120–870)
Fetal-placental weight ratio (FPR) ¹	7.60 ± 1.39 (2.91–12.97)
Beta ²	0.75 0.02 (0.66–0.85)

¹Birth weight/Placental weight

²Beta calculated as Ln (placental weight)/(Ln (birth weight) [23,24]

Description of Novel Chorionic Surface Shape (CS), Chorionic Surface Vessel Shape (CV), and “Fit” (CV relative to CS)

Table 2

Chorionic Surface Shape (CS)			Chorionic Surface Vessel Shape (CV)			“Fit” (CV relative to CS)	
Variable	Units	Mean $\pm$ SD (Range)	Variable	Units	Mean $\pm$ SD (Range)	Variable	Mean $\pm$ SD (Range)
Perimeter _{CS} (Figure 1)	Cm	62.4 $\pm$ 9.4 (42.3–113.2)	Perimeter _{CV} (Figure 1)	cm	51.9 $\pm$ 9.6 (26.5–105.8)		
Area _{CS}	cm ²	280.6 $\pm$ 64.9 (130.8–652.3)	Area _{CV}	cm ²	172.2 $\pm$ 49.6 (41.7–438.2)	Area _{CV} /Area _{CS} ratio	0.61 $\pm$ 0.09 (0.25–0.98)
Centroid _{CS}	x, y coordinate cm		Centroid _{CV}	x, y coordinate cm		Distance between Centroid _{CV} and Centroid _{CS}	0.55 $\pm$ 0.038 (0.01–3.29)
Distance between Centroid _{CS} and umbilical cord insertion (UCI)	cm	3.56 $\pm$ 2.23 (0.10–24.28)	Distance between Centroid _{CV} and umbilical cord insertion (UCI)	cm	3.51 $\pm$ 2.13 (0.04–22.49)		
			Distal vascular endpoints marked to delimit the CV area	Number	24.5 $\pm$ 5.3 (12–56)		

Table 3

Correlations of novel CS and CV variables with birthweight (BW), placental weight (PW), fetoplacental weight ratio (FPR) and beta

	Spearman Correlation Coefficients			
	BW (grams)	PW (grams)	FPR	beta
Perimeter _{CS}	0.381 ***	0.418 ***	-0.115 ***	0.215 ***
Area _{CS}	0.456 ***	0.510 ***	-0.0161 ***	0.282 ***
Perimeter _{CV}	0.331 ***	0.349 ***	-0.083 #	0.171 ***
Area _{CV}	0.376 ***	0.388 ***	-0.096 **	0.172 ***
Area _{CV} /Area _{CS} ratio ("fit")	ns	ns	0.089 **	-0.081 #
Distal vascular endpoints marked to delimit the CV area	.094 **	0.111 **	0.067 #	ns
Distance between Centroid _{CS} and UCI	ns	0.119 ***	-0.108 **	0.118 ***
Distance between CSV centroid and UCI	ns	0.110 **	-0.093 **	0.103 **
Distance between CSS and CSV centroids	ns	ns	ns	ns

p<0.0001;

**
p<0.001;

*
p<0.01,

p<0.05

ns: not significant (p>0.05)

CS: chorionic surface shape; CV: chorionic vascular surface shape

UCI: umbilical cord insertion

Table 4

Linear regression models testing placental predictors of birth outcomes

	Birth Outcomes (Dependent Variables)							
	Birth Weight (BW) (grams)		Placental weight (PW) (grams)		Fetoplacental weight ratio (BW/PW)		Beta (ln(PW)/ln(BW))	
	regression coefficient (95% CI)		regression coefficient (95% CI)		regression coefficient (95% CI)		regression coefficient (95% CI)	
	Unadjusted	Adjusted for GA	Unadjusted	Adjusted for GA	Unadjusted	Adjusted for GA	Unadjusted	Adjusted for GA
Regression models of factors from principal components analysis 1,2								
Factor 1	213.9 **** (178.8, 249.0)	135.5 **** (107.5, 162.7)	37.5 **** (31.4, 43.6)	33.0 **** (26.9, 39.1)	-0.14 *** (-0.24, -0.04)	-0.25 **** (-0.33, -0.17)	0.004 **** (0.002, 0.006)	0.005 ± .001 **** (0.003, 0.007)
Factor 2	5.8 (-32.2, 43.8)	12.7 * (15.5, 40.9)	9.6 ** (3.1, 15.9)	9.6 ** (3.3, 15.9)	-0.13 ** (-0.23, -0.03)	-0.13 ** (-0.21, -0.05)	0.002 **** (0.00004, 0.004)	0.002 **** (0.00004, 0.004)
Factor 3	-63.9 **** (-101.5, -26.3)	30 * (1.58, 58.2)	-18.7 **** (-25.2, -12.2)	-16.4 **** (-22.7, -10.1)	0.13 * (0.03, 0.23)	0.13 ± .04 * (0.05, 0.21)	-0.003 **** (-0.004, -0.001)	-0.004 **** (-0.006, -0.002)
Regression models of chorionic area "fit"								
Area _{CV} /Area _{CS}	304.9 (-126.3, 736.1)	213.1 (-68.9, 495.1)	-9.5 (-74.5, 55.5)	-34.9 (-97.0, 27.2)	1.4 ** (0.42, 2.38)	1.0 * (0.22, 1.78)	-0.023 **** (-0.04, -0.007)	-0.020 * (-0.06, -0.03)

GA: gestational age
CI: confidence interval
¹ One model including all 3 factors;
² Principal components analysis
* p<0.05;
** p<0.01;
*** p<0.001;

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Table 5

Linear regression models testing predictors of chorionic fit

	Chorionic “fit”: Area_{CV}/Area_{CS}	
	regression coefficient (95% CI)	
Models for Shape Irregularity Predictors^{1, 2}	Unadjusted	Adjusted for GA
Distance (cm) between umbilical cord insertion and centroid_{CV}	0.004 (0.002, 0.006) **	0.004 (0.002, 0.006) **
Distance (cm) between umbilical cord insertion and centroid_{CS}	0.003 (0.001, 0.005) *	0.003 (0.001, 0.005) *
Distance (cm) between Centroid_{CV}, Centroid_{CS}	-0.08 (-0.09, -0.07) ****	-0.08 (-0.09, 0.07) ****

¹ Models consider each variable individually;² See Table 2 for descriptions.Centroid_{CV}: Centroid for the chorionic vascular surface shapeCentroid_{CS}: Centroid for the chorionic (full) surface shape

GA: gestational age

CI: confidence interval

p<0.001;***
p<0.01;**
p<0.05;*
p<0.10