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Chorionic vascular "fit" in the human placenta: Relationship to fetoplacental outcomes☆

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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: 916 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. The fetal-placental weight ratio (FPR) was calculated as birthweight/placental weight. Beta (beta) was calculated as ln(PW)/ln(BW). Chorionic disk perimeter was traced and chorionic surface shape (CS) area was calculated. "Fit" was defined as the ratio of the area of the vascular to the full chorionic surface area. 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) created three independent factors. Factors were used in regression analyses to explore relations to birth weight, trimmed placental weight, FPR, and beta. Specific measures of shape irregularity were also examined in regression analyses for interrelationships and to predict birth weight, placental weight, FPR, and beta.

Results: Variables related to disk size (CS area, perimeter) were correlated with BW, GA, trimmed PW and beta. "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 outcome variables. PCA yielded three factors that had independent effects on birth weight, placental weight, the fetal-placental weight ratio, and beta (each $p < 0.0001$). Addition of GA did not alter the factors' associations with outcomes. Chorionic "fit" (ratio of areas), also included within the factor analysis, was a positive predictor of birth weight ($p = 0.005$) and FPR ($p = 0.002$) and a negative predictor of beta ($p = 0.01$). Fit was statistically significantly associated with greater distances between the umbilical cord insertion site and the CS ($p < 0.001$) and CV centroids ($p < 0.001$), and to lesser displacement between CS and CV centroids ($p < 0.001$).

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

1. Introduction

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

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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., [2,3,20]], and a recent NIEHS request for applications to study the "Environmental Influences on the Placental Origins of Disease". (https://grants.nuh.gov/grants/guide/rfa-files/RFA-ES-17-005.html).

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 edge of the chorionic surface of the placenta. 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 fetoplacental vascular alterations with fetal growth restriction [14].

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. Here we test the relationships of measures of the chorionic surface shape (CS), measures of the chorionic plate covered by the CV, and their relationship to each other with birth weight, placental weight, and the fetoplacental weight ratio expressed as the linear ratio (FPR, [21]) and as beta, 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.

2. 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. 1159 women consented (94.6%); of these, 917 placentas (~80%) 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 (Fig. 1).

The following measurements were described with this method (Fig. 2, Table 2) for the chorionic surface shape and for the chorionic vasculature surface shape: perimeter, area, centroid (the weighted center of an irregular planar shape; if a circle/round, centroid is the geometric center), distance between centroid and umbilical cord insertion. 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. In the next step, these measures were used as the basis for quantifying the relationships between CS and CV parameters (Table 2). These parameters reflect the extent to which the entire chorionic surface (inclusive of surface without vasculature) aligns with the chorionic vasculature: ratio of CV and CS areas ("fit"); distance between the $Centroid_{CS}$ and $Centroid_{CV}$. In addition, while specific to the CS and CS, the distances between each type of centroid and the site of umbilical cord insertion can also be conceptualized as measures of displacement. The measures of fit and displacement of the features and shape of the chorionic (full) surface vis a vis the chorionic surface vasculature are of particular interest as these measures could be collected through prenatal ultrasound and not solely postpartum.

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 ("beta") was calculated as ln(PW)/(ln(BW)).

Placental measures are expected to be highly correlated with each other. Strong collinearity violates the assumptions of regression methods, making it difficult to determine independence of associations with outcomes. A number of statistical methods are available to reduce the number of variables in an analysis and simultaneously limit collinearity. We employed 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. In lay terms, PCA produces a smaller set of proxy variables, referred to as "factors"; the PCA method creates factors that are definitively not collinear, thus allowing us to input these factors as independent variables in our regression analyses to predict birth outcomes.

3. Results

Sample descriptive characteristics are presented in Table 1. The novel CS and CV shape measures and the sample means and standard deviations of measures for the cohort are described in Table 2. We examined the correlations between our novel measures and our key clinical outcomes (Table 3). All but one measure were significantly correlated with at least one and generally with all four outcomes. The exception was the distance between the $Centroid_{CV}$ and $Centroid_{CS}$; this variable was not significantly correlated with any of the outcomes.

Limiting the analysis to those measures correlated with one or more clinical outcomes, we used principal components analysis (PCA, see Methods above) to reduce these likely correlated variables into a smaller number of factors. Just three factors accounted for 82% of the data variance (43%, 23% and 16%respectively) (details available upon request from the authors). These 3 factors identified distinct placental patterns, e.g., Factor 1 is principally driven by the