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Placental abnormalities associated with isolated single umbilical artery in small-for-gestational-age births☆

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ABSTRACT

Background: Previous studies have shown that pregnancies complicated by placentas with an isolated single umbilical artery (iSUA) are at increased risk for small-for-gestational-age (SGA) births. The etiology of SGA in this population, however, remains unknown.
Objective: The primary objective of this study was to evaluate whether placental abnormalities in pregnancies with SGA births differ according to the presence of iSUA.
Study design: This was an observational study of all women with pathologic examination of the placenta after delivering a non-anomalous, singleton SGA neonate between January 2009 and August 2015. SGA was defined as birthweight less than 10th percentile for gestational age. Women were categorized according to whether they had an iSUA or a three-vessel cord. The following placental pathologies were compared between the groups using bivariable and multivariable analyses: SGA placenta, maternal vascular malperfusion, high grade fetal vascular malperfusion, and chronic villitis.
Results: 1833 women were included in the analysis: 34 with iSUA and 1799 with three-vessel cord. More than 85% of women in both groups had at least one placental abnormality. After adjusting for nulliparity and neonatal gender, the presence of iSUA was associated with increased odds of high grade fetal vascular malperfusion (adjusted odds ratio 2.8, 95% confidence interval 1.1–7.5) and decreased odds of maternal vascular malperfusion (adjusted odds ratio 0.2, 95% confidence interval 0.1–0.9). There was no significant association with other pathologic findings.
Conclusion: Pathologic placental findings associated with SGA birth differed based on umbilical cord composition. The presence of iSUA in an SGA birth was associated with a higher odds of high grade fetal vascular malperfusion abnormalities and lower odds of maternal vascular malperfusion abnormalities, compared to SGA birth with a 3VC.

1. Introduction

A single umbilical artery (SUA) is diagnosed in 0.5–5% of all pregnancies and is thought to result from primary agenesis or thrombotic atrophy of one umbilical artery [1,2]. SUA frequently has been associated with other fetal anomalies [3], but even in the setting of a normal anatomic survey, an isolated SUA (iSUA) is still associated with small-for-gestational age (SGA) birth [4–6]. The etiology of reduced birthweight in this population remains unknown. Recent studies evaluating umbilical cord blood flow have demonstrated that the remaining artery in a two-vessel cord is able to compensate and carry twice the typical blood volume of an artery in a three-vessel cord [7,8]. Based on this evidence, it has been suggested that SGA birth in pregnancies complicated by an iSUA is not caused by the difference in the umbilical cord blood flow itself, but rather from a wider pathologic process involving the placenta.

Specific placental patterns of injury such as SGA placenta, maternal vascular malperfusion, high grade fetal vascular malperfusion, and chronic vilittis have been associated with different

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pathophysiologic mechanisms of fetal growth restriction [9,10]. Maternal vascular malperfusion, for example, has been associated with injury during early pregnancy which prevents normal placental implantation, commonly seen in SGA births in pregnancies complicated by preeclampsia [9]. Previous studies have noted an association between iSUA and abnormal placental findings on ultrasound such as succenturiate lobes, velamentous cord insertion, and placenta previa [4,6]; however, few studies have evaluated perfusion abnormalities on placental pathology that might be related to SGA birth. Therefore, the primary aim of this study is to evaluate pathologic placental abnormalities associated with iSUA in pregnancies complicated by fetal growth restriction.

2. Materials and methods

This was an observational study of all women who had pathologic examination of the placenta after delivery of a non-anomalous, singleton SGA neonate between January 2009 and August 2015. SGA was defined as birthweight less than 10th percentile based on a recent United States reference encompassing the time period of our cohort [11]. Women with multiple gestations or singleton gestations with a major fetal anomaly were excluded from further analysis.

Baseline demographics, antepartum characteristics, and delivery data including birthweight were abstracted from maternal and neonatal records. Indications for placental examination by pathology established by institutional guidelines in 2009 include obstetrical complications such as intrauterine growth restriction, preterm delivery, preeclampsia with severe features, and chorioamnionitis, as well as gross abnormalities at the time of delivery such as single umbilical artery, velamentous insertion of the umbilical cord, placental infarct or mass. Pathologic gross examination of the placenta was performed in a systematic fashion with standardized sampling to include sections of the umbilical cord and membranes, along with two full thickness parenchymal sections and one additional cassette containing three parenchymal sections with maternal surface along their long axis. Additional sections were submitted if gross lesions were identified. All placental pathology reports were individually reviewed and data were abstracted for umbilical cord and placental abnormalities such as: SGA placenta, maternal vascular malperfusion (formerly maternal vascular underperfusion), high grade fetal vascular malperfusion (formerly fetal thrombotic vasculopathy) and chronic villitis. Placental pathologic diagnoses were defined based on the established criteria [12] with terminology adjusted based on recent consensus [13]. Briefly, maternal vascular malperfusion was diagnosed if vascular pathology, such as acute atherosis, persistent muscularization of basal plate arterioles, or mural hypertrophy of membrane arterioles or villous pathology such as infarcts (>2 cm), increased syncytial knots, or distal villous hypoplasia was present. High grade fetal vascular pathology was considered present if > 45 avascular villi ± fetal vascular thrombi were observed. Chronic villitis was recognized as chronic inflammatory infiltrates, typically lymphohistiocytic, in and around chorionic villi and was graded as low grade if < 10 villi were involved in any focus, and high grade if multiple foci were present, at least one of which involved 10 or more villi.

We hypothesized that the etiology behind SGA birth in pregnancies complicated by ISUA is different from that in the setting of three-vessel cord. In order to test this hypothesis we compared placental pathology between SGA pregnancies with and without iSUA. Student's *t*-test, χ^2, and Fisher's exact test were used for bivariable analysis, as appropriate, to compare characteristics and outcomes of SGA births between these two groups. Multivariable logistic regressions were performed for the outcomes that were significantly different between the two groups in bivariable analysis. Covariates were entered into the regression equations if they differed between groups in bivariable analysis at a level of $p < 0.05$. Odds ratios with 95% confidence intervals were estimated from the regressions. All tests were two-tailed and $p < 0.05$ was used to define significance. Approval for this study was obtained from the Northwestern University Institutional Review Board (STU00201676).

3. Results

Of 13,451 placentas from non-anomalous singleton births sent to pathology for evaluation, 1833 resulted in an SGA birth. iSUA was present in 34 pregnancies and three-vessel cord in 1799 pregnancies.

In bivariable analysis, women with pregnancies complicated by an iSUA were more likely to be nulliparous (44.1% vs. 68.5%, $p < 0.01$) and less likely to deliver a male neonate (61.8% vs. 43.3%, $p = 0.03$) (Table 1). The frequency of preterm birth less than 28, 34 and 37 weeks was 2.4%,15.0%, and 32.0%, respectively in the 3VC group and 0%, 14.7%, and 32.4%, respectively, in the iSUA group. There were 67 antenatal and postnatal demises in the study cohort: 66 (3.7%) in the three-vessel cord group and 1 (2.9%) in the iSUA group, $p = 0.82$. On placental pathology, there was no statistically significant difference between groups in the frequency of having an SGA placenta, chronic villitis, or umbilical cord abnormalities (Table 2). Conversely, iSUA was associated with an increased frequency of high grade fetal vascular malperfusion (14.7% vs. 6.0%, $p = 0.04$) and decreased frequency of maternal vascular malperfusion (5.9% vs. 21.6%, $p = 0.03$).

After adjusting for parity and neonatal gender as potential confounding factors in multivariable logistic regression, the presence of an iSUA remained associated with a higher odds of high grade fetal vascular malperfusion (aOR 2.8, 95%CI 1.1–7.5) and lower odds of maternal vascular malperfusion (aOR 0.2, 95%CI 0.1–0.9) (Table 3).

4. Comment

In this study we have shown that among women with SGA births, the presence of an iSUA is associated with higher odds of

Table 1
Maternal and pregnancy characteristics stratified by presence of iSUA.

	3VC (n = 1799)	iSUA (n = 34)	p-value
Maternal age (years)	31.3 ± 6.0	31.7 ± 6.3	0.72
BMI (kg/m^2)	29.8 ± 6.1	30.3 ± 7.9	0.66
Race/ethnicity			0.91
Non-Hispanic white	709 (45.4)	12 (46.2)	
Non-Hispanic black	269 (17.2)	5 (19.2)	
Hispanic	99 (6.3)	2 (7.7)	
Asian	351 (22.5)	4 (15.4)	
Other	135 (8.6)	3 (11.5)	
Nulliparous	1233 (68.5)	15 (44.1)	<.01
In vitro fertilization	28 (1.6)	1 (2.9)	0.52
Gestational or Pregestational DM	24 (1.3)	1 (2.9)	0.42
Chronic HTN	85 (4.7)	3 (8.8)	0.27
Gestational HTN or Preeclampsia	339 (18.8)	3 (8.8)	0.14
Tobacco use	31 (1.7)	0 (0.0)	0.44
Prior PTB	100 (5.6)	1 (2.9)	0.51
Gestational age at delivery (weeks)	37.2 ± 3.4	36.8 ± 3.0	0.50
Birthweight (grams)	2222 ± 629	2096 ± 535	0.24
Male gender	777 (43.3)	21 (61.8)	0.03

Data presented as n (%) or mean ± SD.
Abbreviations: 3VC, 3-vessel cord; iSUA, isolated single umbilical artery; BMI, body mass index, DM, diabetes mellitus; HTN, hypertension; PTB, preterm birth.