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Original Article

Plasma markers of physiologic stress in human fetuses with intrauterine growth restriction and abnormal umbilical artery doppler velocimetry

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Abstract: Intrauterine Growth Restriction (IUGR) may be related to lifelong disease via mechanisms of in-utero programming. We compared IUGR fetuses with abnormal umbilical artery Doppler velocimetry (UA Dopplers) to normally-grown fetuses. Both singleton pregnancies (5 cases and three controls) and multiple pregnancies (4 cases and 5 controls) were compared. Singleton IUGR fetuses were compared to term, normally-grown fetuses. Multiple IUGR fetuses were compared to the other fetus(es) from the same pregnancies with normal growth and normal UA Dopplers. Plasma concentration from cord blood samples were measured for leptin, renin, and C-reactive protein. There were 17 placentas from 12 pregnancies. Singleton IUGR fetuses displayed lower leptin concentrations and greater renin activity. Fetuses from multiple pregnancies diagnosed with IUGR did not display differences from unaffected fetuses from the same pregnancies. There are metabolic differences in singleton fetuses with IUGR and abnormal UA Doppler velocimetry compared to normally-grown singleton fetuses with normal UA Dopplers. Differences between fetuses could not be demonstrated in multiple pregnancies.

Keywords: Renin, leptin, umbilical cord blood, intrauterine growth restriction, umbilical artery doppler velocimetry

Introduction

In developed countries intrauterine growth restriction (IUGR) complicates approximately 10 percent of screened pregnancies and predisposes the infant to lifelong health risks for metabolic disease [1, 2]. A major cause of growth restriction is poor placentation or abnormalities of the maternal-fetal interface [3]. Placental deficiencies increase the risk of abnormal umbilical artery (UA) Doppler indices [4, 5]. As the placental resistance increases, the systolic to diastolic (S/D) umbilical artery velocity ratio increases. The process may progress to absent end-diastolic flow (AEDF) followed by reverse end-diastolic flow (REDF). Detection of abnormal UA Doppler indices warrants further attention to the health of the fetus (in most institutions this would include antepartum fetal surveillance) and consideration of whether the fetus should be delivered to avoid continued oxygen and nutrient deprivation and mitigate the risk of stillbirth [5, 6].

Our knowledge about the intrauterine effects in growth restricted fetuses and the resultant neonates remains limited. The general assumption has been that after delivery, the neonate will 'catch up' in growth and progress to meet the physiologic milestones of its normally-grown counterparts. Indeed most of these infants do 'catch up', in growth, at least to their normal birth weight peers within 1-2 years from birth [7]. However, evidence continues to emerge showing that growth-restricted neonates have higher rates of morbidity and mortality when compared to their normally-grown counterparts born at a similar gestational age [8, 9]. Long term disorders of inflammation and oxygen deprivation, such as respiratory distress syndrome and resultant bronchopulmonary dysplasia, and necrotizing enterocolitis are more common in these neonates [5]. Additionally, longitudinal studies have found that intrauterine nutritional deprivation has lifelong consequences [1, 10, 11]. Low birth weight has been related to cardiovascular disease, diabetes and

cancer in several cohorts [1, 2, 10]. Together, these findings link IUGR to non-communicable cardiovascular and metabolic diseases and suggest an adaptive response in fetal life that portrays the life-long complications.

We investigated the association of IUGR with the metabolic and inflammatory condition of the fetus. Our hypothesis was that the IUGR fetus develops vascular and metabolic complications that alter hormone concentrations involved in metabolism, blood pressure regulation, and inflammation. We measured umbilical cord plasma concentrations of renin, leptin, and C-reactive protein. Renin is an enzyme secreted by the kidney in response to hypoperfusion, and may be a marker of blood shunting in poorly-perfused fetuses. Leptin is a metabolically active adipokine related to weight. CRP is a well-recognized systemic marker of inflammation elevated in a range of conditions.

Materials and methods

Subjects and sample collection

The University of Arizona Institutional Review Board approved this investigation on human subjects(#1412605183,#1406384521A002). Eligible patients for this prospective study were divided into four groups: 1) IUGR singletons, 2) control term singletons, 3) IUGR fetuses from dichorionic pregnancies in which only one fetus had IUGR (IUGR multiples) and 4) normally-grown fetuses from dichorionic pregnancies in which only one fetus had IUGR (control multiples). Patients were excluded if they were unable to read or write English or Spanish, if they were incarcerated or if the investigator felt that they were unable to obtain informed consent. Control patients were also excluded if they had been diagnosed with diabetes or if they were suspected to have abnormal fetal growth due to comorbidities.

Patients were identified by the investigators at the University of Arizona Health Sciences Center. After informed consent was obtained, an ultrasound was performed using GE machines to determine UA Doppler indices and anthropomorphic measurements of the fetus. Either the clinical investigator or one of the accredited sonographers at the University of Arizona performed the measurements.

Sonographic measurements of the fetus were used to determine IUGR and defined with predicted fetal weight less than the 10th percentile for gestational age. Gestational age was determined by dating criteria accepted by the patient's physician. At our institution an ultrasound performed before 20 weeks of gestation is usually used to confirm menstrual dating of gestational age. IUGR was confirmed using the Fenton 2013 growth calculator on the birth weight of the neonate after delivery [12]. If a fetus was estimated to be IUGR but found to have an actual birth weight above the 10th percentile, it remained in the cohort in the group to which it was originally assigned. Measurements of the UA Doppler were performed in a mid-segment of the cord, with the umbilical venous Doppler velocity also present. Both arteries were measured except in the case of a single umbilical artery. The lowest value measured of the S/D ratio was reported as this would reflect the best blood flow possible through the placental circuit. UA Doppler indices were calculated using nomograms for gestational age. At term, an S/D ratio <3.0 was considered normal, whereas at preterm gestational ages, a value >97.5th percentile for gestational age was considered abnormal as these are the values that are generally used clinically. Doppler velocimetry percentiles were calculated utilizing the perinatology.com online calculator [13].

Immediately after delivery of the fetus, the umbilical cord was clamped and cut. After delivery of the placenta arterial and venous blood was collected from the umbilical cord or placental vessels. Every attempt was made to collect both an arterial and venous sample from the umbilical cord or placental vessels, but in cases where we could not collect both, a single vessel sample was obtained for analysis. Blood was transferred into EDTA-lined tubes and centrifuged at 1600× g for 2 minutes. The plasma was aspirated and stored at -80°C for hormone and renin measurements.

Placental measurements were taken. Newborn growth indices were collected (**Table 1**).

Experimental design and endocrine measurements

Plasma concentrations were determined for total renin activity (ALPCO Diagnostics, Windham, NH; intra-assay coefficients of variation

Table 1. Fetuses included in cohort

	Gestational Age	Doppler Assessment*	Sex	Birth Weight grams**
		Singleton cases		
1	29 weeks	AEDF	Male	1005 g (13th percentile)
2	36 weeks	S/D ratio 3.7 (98th percentile)	Female	1860 g (2nd percentile)
3	37 weeks	S/D ratio 5.2 (>99th percentile)	Male	1900 g (1st percentile)
		Singleton controls		
1	39 weeks	S/D ratio 1.9 (8th percentile)	Female	3975 g (90th percentile)
2	39 weeks	S/D ratio 2.1 (26th percentile)	Female	3070 g (36th percentile)
3	39 weeks	S/D ratio 2.2 (40th percentile)	Male	3730 g (77th percentile)
4	39 weeks	S/D ratio 1.8 (3rd percentile)	Male	3585 g (66th percentile)
5	40 weeks	S/D ratio 2.8 (99th percentile)	Female	3955 g (84th percentile)
		Multiple cases and controls		
1	31 weeks (case)	AEDF	Female	630 g (1st percentile)
	31 weeks (control)	S/D 3.8 (92nd percentile)	Male	1240 g (16th percentile)
	31 weeks (control)	S/D 3.5 (86th percentile)	Male	1425 g (32nd percentile)
2	32 weeks (case)	REDF	Male	600 g (<1st percentile)
	32 weeks (control)	S/D 3.1 (75th percentile)	Male	2000 g (66th percentile)
3	35 weeks (case)	AEDF	Female	1585 g (1st percentile)
	35 weeks (control)	S/D 2.5 (52nd percentile)	Female	2305 g (27th percentile)
4	35 weeks (case)	REDF	Male	1425 g (<1st percentile)
	35 weeks (control)	S/D 2.7 (67th percentile)	Female	2780 g (76th percentile)

*Percentiles for Doppler Systolic/Diastolic Ratio are calculated utilizing perinatology.com [13] **Percentiles for fetal birth weight are calculated based on the online Fenton 2013 Growth Calculator for preterm infants [12]. AEDF Absent End Diastolic Flow, REDF Reversed End Diastolic Flow, S/D ratio Systolic/Diastolic ratio.

<12%), leptin (ALPCO Diagnostics; intra-assay coefficient of variation <20%), and C-reactive protein (CRP; Mercodia, Uppsala, Sweden) via enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

For statistical analysis subjects were assigned into IUGR singletons, IUGR multiples, control singletons and control multiples based on the criteria described. IUGR singletons were compared to control singletons and IUGR multiples were compared to control multiples. Plasma hormone concentrations were analyzed with a t-test with Welch's correction using GraphPad Prism v7.03 (Graphpad Software, La Jolla, CA) Group mean and standard error mean (SEM) are presented. Significant differences between comparisons were defined at $P<0.05$.

Results

Twelve women were recruited who had either singleton or multiple fetuses (n=17). The cohort collected had 5 singleton fetuses with IUGR and abnormal UA Doppler indices and 3 singleton controls with normal term birth weights and UA Doppler indices (**Table 1**). An elevated S/D ratio was noted in two of the IUGR singletons and AEDF in one. The cohort of multiple gestations included 9 fetuses in total with 3 sets of twins and 1 set of triplets (9 fetuses in total; **Table 1**). All multiple pregnancies had only one IUGR fetus with abnormal UA Doppler indices and one or more normally-grown fetuses for given gestational age. The abnormalities in Doppler indices included two fetuses with AEDF and two fetuses with REDF. One of the IUGR singleton fetuses was found to be at the 13th percentile at birth (but did have AEDF in utero). This fetus was kept in the cohort of singleton IUGR fetuses. One normally-grown singleton fetus was found to have an elevated Doppler S/D ratio for gestational age. This fetus remained in the cohort for singleton control fetuses.

The 17 pregnancies were measured for plasma renin activity and concentrations of leptin and CRP. Plasma renin activity was greater in IUGR singletons compared to control singletons

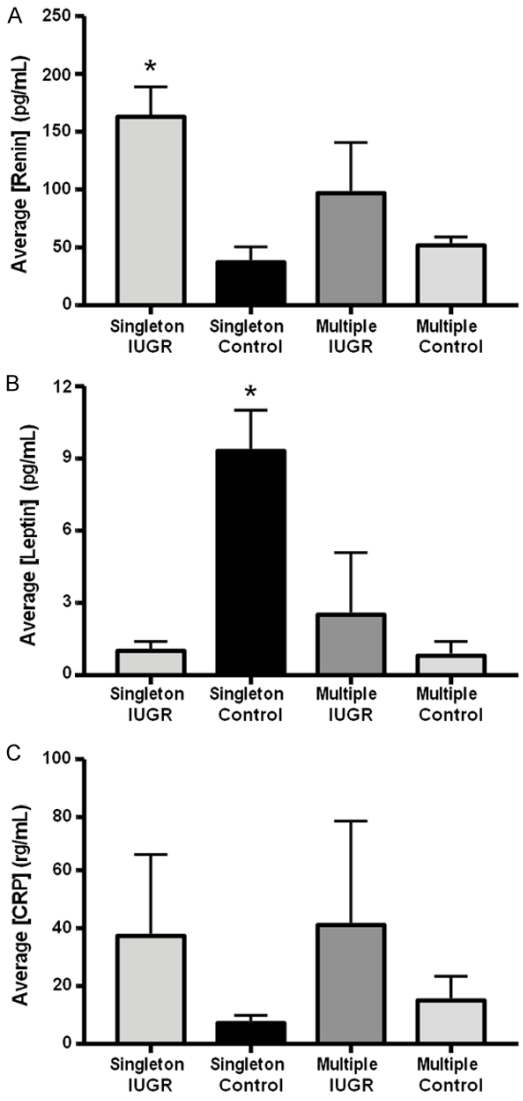

Figure 1. Plasma Renin activity and concentrations of Leptin and C-Reactive Protein in Cord Blood. Legend: A. Average Renin in pg/mL, B. Average Leptin in pg/mL, C. Average CRP in ng/mL. *Denotes P<0.05.

(164.9 ± 23.9 pg/mL vs 39.1 ± 11.4 pg/mL, P<0.01), but no difference was identified in multiple pregnancies (IUGR, 98.9 ± 41.9 pg/mL vs Control, 53.6 ± 5.5 pg/mL) (**Figure 1**). Plasma leptin concentrations were lower in IUGR singletons compared to control singletons (1.1 ± 0.3 ng/mL vs 9.4 ± 1.6 ng/mL, P<0.05). In multiple pregnancies the leptin concentrations were similar between IUGR and control fetuses (2.6 ± 2.5 ng/mL vs 0.9 ± 0.5 ng/mL) (**Figure 1**). Leptin was lower (P< 0.01) in multiple controls compared to singleton controls.

There were no significant differences in CRP between groups overall but wide variations in CRP concentrations. However, REDF was associated with a high CRP, 2 of the 3 highest CRP concentrations in this cohort occurred in fetuses with REDF. Significant arteriovenous differences were not found between umbilical cord samples for the hormones tested, so results were combined.

Discussion

This study identified metabolic differences in fetuses with IUGR and abnormal UA Doppler velocimetry compared to normally-grown fetuses with normal UA Dopplers. These hormones included leptin and renin, but did not include CRP in our study. These findings contribute to our understanding of the alterations in signaling related to control of metabolism, and perfusion as mediated by blood pressure, respectively.

We utilized multiple pregnancy twins to evaluate IUGR and abnormal UA Doppler velocimetry in fetuses without additional factors that may influence findings when using unrelated controls including maternal health, gestational age, genetic predisposition. The IUGR multiples had similar plasma concentrations of all substances tested in cord blood plasma to both their normally-grown counterparts and to the IUGR singletons. One can infer that the 'normal' fetus in these pregnancies is not in fact normal. This introduces the idea of the placenta as an organ with paracrine function. One interpretation of our results would be that the hormones secreted by the placenta of the growth-restricted fetus cause the same effects in the other pregnancy, irrespective of the normal fetal growth and normal placental circulation. This finding suggests that the unaffected twin may in fact be at an elevated risk for cardiovascular and metabolic disease because of in-utero programming.

The most striking findings were in singletons. Greater renin activity in IUGR singleton fetuses compared to control singletons likely reflects inadequate vascular perfusion of the fetal kidney in the setting of IUGR. This finding corroborates existing evidence that IUGR fetuses are born with fewer nephrons [14-16] and a propensity for hypertension both in the neonatal period and later in life [16, 17]. Additionally, it is possible that the IUGR fetus relying on a high

resistance placental circuit may require higher blood pressure to perfuse the organ. Renin homeostasis has been found to be altered in states of hypoxic stress during pregnancy [17, 18]. Our findings indicate that the increased renin could be a physiologic mechanism important for survival of the fetus in this setting.

There is evidence that IUGR and early nutrient deprivation predispose to heart disease and metabolic disease later in life [1, 2, 11, 14]. The elevated cord plasma renin activity could be a symptom of existing cardiovascular disease that has developed in fetal life [14, 17], but could also reflect the setting of a high steady state of secretion in the affected fetus [17]. This could lead to a predisposition to hypertension and resultant heart disease, renal disease and early death as the neonate ages. If the fetus is so predisposed, 'catch-up' growth would not mitigate this risk.

Leptin was decreased in IUGR singletons compared to control singletons. This is not surprising considering that leptin concentrations are related to newborn weight and adiposity and previous investigations revealed leptin concentrations in the IUGR neonate are decreased compared to normally-grown, full term neonates [19-21]. Leptin is released by adipose cells and the IUGR fetus weighs less and has a smaller proportion of mass made up by fat cells [22], as reflected by the weights of the fetuses studied (see **Table 1**). While fetal leptin concentrations correlate to gestational age in normally-grown fetuses, previous studies in the IUGR fetus have not found correlations in leptin levels as they relate to fetal growth [21]. This may indicate inappropriate leptin secretion in the IUGR fetus.

Though leptin has many functions in metabolic and neuroendocrine pathways, one of the most important functions is that of appetite regulation [23]. As leptin levels decrease, appetite tends to increase [23]. The low levels of leptin may program the fetus and then the neonate for excessive oral intake and may be part of the reason for the established relationship between IUGR and childhood obesity and diabetes [11]. This being said, leptin may have been affected by other factors (IUGR, maternal diabetes, maternal antenatal corticosteroid administration) [24]. There are established normal values for leptin across gestational ages and weights with leptin being produced both by the fetus and by the placenta [25]. Further study will need to confirm our findings in a larger number of subjects.

CRP was not elevated in the IUGR singleton fetuses. This presents several possibilities. The first is that the IUGR fetuses are not experiencing systemic inflammation. This is contrary to the findings of other studies that have shown an association between IUGR and markers of inflammation [26, 27]. The second possible explanation is that the process of birth is intrinsically related to inflammation (there is evidence that inflammation is required for normal parturition) and that CRP is elevated in both IUGR and the birth process. Lastly, the similar concentrations could mean that this is not specific enough a protein to be tested as a marker of vascular inflammation. Interestingly there was an association with REDF and elevated CRP. Our finding that CRP was not statistically significantly different could be related to the size of our cohort, the variation in mode of delivery or the severity of the abnormal UA blood flow. Further studies of inflammation in the IUGR fetus may further delineate the role of inflammation in these fetuses and the ongoing health of the newborn.

Strengths of this study include the prospective nature of the work, the selection of cases with IUGR related only to abnormal UA Doppler indices and the standardized approach taken for the collection of patient samples. Analysis of the cord blood from both the umbilical artery and vein, with similar values found for each vessel addressed the potential for concern that the plasma factors studied were being altered significantly by placental metabolism.

One limitation of this study is not having an age-matched control group of singletons because many of the IUGR fetuses were younger at delivery. We chose not to have gestational age-matched control fetuses as the comparison group because a true 'normal' preterm delivery does not exist. If a pregnancy is being delivered prematurely, it is because there is a complication, most likely because of preterm labor, preeclampsia, placental abruption or abnormal placental implantation. There is evidence that the pathological process leading to delivery for preeclampsia may be similar to that of IUGR in that it may have a placental origin or effect, so we determined that patients deliv-

ered early for pregnancy complications were not appropriate controls. Likewise, preterm labor may be related to a variety of factors, including infection and placental abruption, making these fetuses poor controls. As is a problem with many human studies, not all factors can be controlled for. We did our best in compensating for this by selecting term fetuses without any known comorbidities, including factors highly likely to affect fetal growth, such as maternal diabetes. We allowed cases to have comorbid conditions as this reflects the population occurrence of IUGR with abnormal UA Dopplers. The phenomenon is much more likely to occur with comorbid maternal conditions.

In our study the term and late preterm IUGR fetuses had similar findings to the early preterm fetuses, giving support to the notion that the findings are not due to gestational age differences alone. However, our group is now pursuing these same questions in this last group of patients (namely normally-grown fetuses delivered after idiopathic preterm labor or preterm premature rupture of the membranes). One factor that alleviates some concern about the lack of matching for gestational-age-matched controls is the fact that one of the singletons had reached a term gestation and the other was near-term at 36 weeks of gestation (a 2 and 3 week gap from the controls). In spite of the wide gestational age range observed, the IUGR fetuses had marked differences when compared to controls but not to each other suggesting an effect of the IUGR, not gestational age.

An additional limitation is the lack of control for confounding factors such as maternal pregnancy complications. Pre-eclampsia commonly occurs concomitantly with IUGR as was the case in many of these pregnancies. We did not control for fetal sex, mode of delivery or maternal and paternal ethnic background in this study. All of these factors may affect the findings and remain areas of future investigation.

In conclusion, IUGR with abnormal UA Doppler indices noted on an antenatal ultrasound heralds a fetus with altered metabolic signaling due to impaired placental blood perfusion and subsequent limitations in nutrient and oxygen transfer from mother to fetus. Our findings in singleton IUGR fetuses suggest that abnormal blood flow in the fetus is associated with programming reflecting a 'thrifty' phenotype with the metabolic profile of decreased leptin. Furthermore, increased renin activity may be a signal for hypertension and cardiovascular disease resulting from impaired renal responsiveness.

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Disclosure of conflict of interest

None.

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