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Placental Localization and Perinatal Outcome

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Placental Localization And Perinatal Outcome

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Lucy Emily Goddard Kalanithi

2007

– **ABSTRACT** –

PLACENTAL LOCALIZATION AND PERINATAL OUTCOME. Lucy E.G. Kalanithi, Jessica L. Illuzzi, and Errol R. Norwitz. Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT.

This retrospective case-control study was designed to investigate the relationship between placental localization and intrauterine growth restriction (IUGR). Pregnant women with an anatomic survey from January 1, 2000, to December 31, 2005, and delivery of the pregnancy at Yale-New Haven Hospital (YNHH) were identified using clinical and billing records. Multiple gestation, fetal anomaly, and incomplete medical information were reasons for exclusion. Cases (N=69) were consecutive pregnancies with evidence of IUGR (estimated fetal weight <10th percentile for gestational age) at last follow-up ultrasound. Randomly selected controls (N=258) from the same time period had no evidence of IUGR. Maternal, ultrasound, delivery, and perinatal data were collected by retrospective medical record review, and IUGR cases and non-IUGR controls were compared using the Student's *t*-test, Wilcoxon test, Chi-square analysis, Fisher's exact test, and ANOVA. Placental location was determined from the anatomic survey record (obtained at 18.4 ± 1.2 weeks' gestation in the IUGR group and 18.2 ± 1.0 weeks' gestation in the control group; $P=0.18$). Multivariate logistic regression with adjustment for confounders was used to investigate the association between IUGR and placental localization. Consistent with known predictors of IUGR, the IUGR group had a higher proportion of black women (36.4% vs. 19.8%, $P=0.03$), chronic hypertension (26.0% vs. 3.5%, $P<0.001$), and hypertensive disorders of pregnancy (36.2% vs. 5.0%, $P<0.001$). Mean birth weights of IUGR and non-IUGR pregnancies differed by 2 kilograms (3244 ± 625 grams vs. 1277 ± 637 grams, $P<0.001$). IUGR infants were more likely to receive antenatal steroids, deliver preterm, deliver by cesarean section, and be admitted to neonatal intensive care. In both IUGR and non-IUGR pregnancies, the placenta was most commonly anterior or posterior. Unilateral placentas were three times more common in the IUGR group than in the non-IUGR group (17.4% vs. 5.0%, $P=0.01$). IUGR pregnancies were over four times as likely as control subjects to have unilaterally-located placentas compared to anterior placentas (OR 4.8, 95% confidence interval, 1.9-11.7). Adjusting for ethnicity, chronic hypertension, and hypertensive disorders of pregnancy did not affect this finding (OR 4.6, 95% confidence interval 1.6-13.5). In conclusion, we compared a group of 69 IUGR pregnancies to 258 non-IUGR controls and found intrauterine growth restriction to be associated with unilateral placentation.

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Finally, to my mother, Jean Goddard, whose love for science was infectious, and to Paul Kalanithi, who knew I would pull it off.

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– INTRODUCTION –

Perhaps due in part to the well-publicized research efforts of March of Dimes, it is well appreciated that premature birth (birth before thirty-seven weeks' gestation) portends an elevated risk of perinatal mortality and long-term complications. Lesser appreciated is the risk to those neonates who, though they may attain adequate gestational age before delivery, achieve subnormal growth *in utero* compared to norms for gestational age. Lubchenco et al. (1) were the first to describe a greatly elevated risk of neonatal mortality in infants whose birth weight fell below the tenth percentile for gestational age, a finding that persisted at all gestational ages at birth: thus, their work suggested that regardless of prematurity, small size independently predicted neonatal mortality.

In the forty years since, Lubchenco's work has been corroborated and further elaborated by numerous studies demonstrating not only an elevated perinatal mortality rate – in the United States, six to ten times that of normal pregnancies (2) – in fetuses with size less than expected for gestational age, but increased neonatal morbidity and adverse long-term outcomes in those who survive. Natural and iatrogenic preterm birth, neonatal hypoxia, ischemic encephalopathy, poor feeding, and metabolic abnormalities including hypoglycemia have all been shown to occur more frequently in neonates who fail to achieve gestational-age-appropriate growth *in utero* (3). Long-term sequelae of restricted growth have been less clearly elaborated, but may include subnormal height (4) and neurodevelopmental abnormalities (5, 6). Additionally, regardless of gestational age, infants with subnormal growth *in utero* carry a higher risk of developing multi-organ system

adult disease later in life, including cardiovascular disease, hypertension, and type 2 diabetes mellitus (7-10).

Appropriate identification and careful management of pregnancies with fetal growth restriction may reduce mortality and adverse effects (11, 12). As such, pregnancies whose ultrasound-determined estimated fetal weight (EFW) is found to be below the tenth percentile for gestational age are now diagnosed with intrauterine growth restriction (IUGR) and followed closely. Such pregnancies undergo detailed surveillance, aggressive management of maternal disease, support for cessation of substance use and good nutrition, antenatal testing, and delivery at institutions with neonatology teams equipped to manage perinatal complications (13).

Since IUGR was first noted to be an important barrier to survival and health, many of its determinants have been described. IUGR affects well over 300,000 pregnancies per year in the United States (14, 15). Around two-thirds of these pregnancies are thought to be constitutionally small, with appropriate growth toward their genetic growth potential as determined by factors such as parental size and ethnicity (15-17). The remaining one-third of IUGR, or more than 100,000 pregnancies per year in the United States, is thought to result from pathologic factors. Fetal growth is affected by a combination of fetal factors, maternal factors, and placental factors; IUGR can result from abnormalities in any of these. Pathologic IUGR, therefore, does not represent one clinical phenomenon, but rather a manifestation of numerous disorders of pregnancy.

Fetal factors associated with IUGR

Genetic or structural anomalies. Chromosome or gene abnormalities, including sex chromosome disorders and aneuploidy, particularly trisomies 13 and 18, have been associated with IUGR (18). IUGR has also been shown to occur at elevated rates in fetuses with major structural malformations (19).

Maternal factors associated with IUGR

Maternal body habitus and nutrition. While growth is strongly influenced by genetic factors inherent to the fetus, maternal body habitus also strongly correlates with fetal size (20). Maternal weight less than one hundred pounds at conception is associated with a two-fold risk of IUGR (18). Further, even given adequate maternal pre-pregnancy weight, inadequate weight gain during pregnancy puts the fetus at risk for growth limitation, likely by limiting substrates available for fetal metabolism (21), a result strikingly shown in historical studies of war and famine (22, 23). In order to avoid an elevated risk of IUGR, weight gain of 20-25 pounds during pregnancy is necessary (15).

Maternal exposure. Maternal infection, particularly with cytomegalovirus or rubella virus prior to twenty weeks' gestation, is also thought to increase the risk of IUGR, an effect theorized to result via induction of cytolysis and capillary endothelial damage, which lead to stunted organogenesis (24, 25). The protozoan *Toxoplasma gondii*, parvovirus B19, HIV, and other infectious agents have also been associated with IUGR (2).

Degree of maternal exposure to certain chemical agents, including prescription and non-prescription medications, drugs of abuse, and occupational or environmental chemicals, strongly predicts fetal growth. While prenatal and

postnatal growth delay are important features of fetal alcohol syndrome (26) resulting from excessive alcohol use during the first trimester, alcohol use during the second and third trimesters (27, 28), perhaps as few as one to two alcoholic drinks per day (29) may restrict growth. One proposed mechanism of action of growth restriction, shown in alcohol (24), tobacco (30), and cocaine (31, 32) use, is reduction of maternal appetite. Tobacco and cocaine, furthermore, decrease oxygen delivery to the fetus due to vasoconstrictive effects (24). Other chemical agents, including additional drugs of abuse [e.g., heroin (25)], anticonvulsants [e.g., phenytoin (33, 34)], anticoagulants [e.g., warfarin (35, 36)], folic acid antagonists [e.g., methotrexate (37, 38)], and occupational or environmental chemicals (39) have been associated with IUGR as well.

Environmental factors. Characteristics of the maternal environment, including both geographic location and altitude, have been shown to influence fetal growth, as demonstrated by higher average birth weights in populations at sea level compared with birth weights in high altitude populations (24, 40). Similarly, characteristics of the fetal environment within the uterus are important to growth and development. IUGR occurs in up to a quarter of twin pregnancies (22), making it ten times more common among twins than among singleton gestations. Defects in placental implantation, placental crowding within the uterus, and twin-to-twin transfusion are possible mechanisms for this effect (2).

Maternal disease. Numerous forms of acute and chronic maternal disease have been implicated in the development of IUGR, including both pregnancy-induced hypertension and chronic, or prepregnancy, hypertension, both related perhaps to uteroplacental vascular insufficiency (41, 42). Maternal vascular disease

may be the most common cause of IUGR in nonanomalous infants (25). Preeclamptic pregnancies, also falling in this category, have four times the risk of producing an IUGR fetus than do normal pregnancies (43).

Maternal congenital or acquired thrombophilic disorders, including the antiphospholipid antibody syndrome (25) and the prothrombin gene mutation (44, 45) have likewise been associated with IUGR. Similarly, while gestational diabetes and type 2 diabetes, by virtue of maternal and fetal hyperinsulinemia, predispose to fetal macrosomia (24), diabetic women with diabetes-related vascular disease, particularly in the setting of long-standing type 1 diabetes, are predisposed to intrauterine growth restricted pregnancies (46). It is thought that diabetic vasculopathy may extend to the placenta, causing pathologic changes that compromise placental circulation and thereby restrict fetal size (47). Maternal hemoglobinopathies, maternal cyanotic heart disease, and maternal chronic pulmonary disease (e.g., cystic fibrosis) also increase the risk of IUGR, possibly by limiting fetal oxygenation (48-50).

Placental factors associated with IUGR

As described above, numerous factors associated with IUGR, including maternal malnutrition, infectious agents, and maternal vascular disease, are hypothesized to exert their effects on fetal growth by constraining fetal resources, whether by restricting metabolic substrates, limiting oxygen availability, or curbing fetal blood supply. Given the placenta's role in fetal blood supply, and hence in both fetal nutrient and oxygen delivery, it comes as little surprise that abnormalities of the placenta itself elevate the risk of IUGR (51-54). IUGR fetuses often have small

placentas, abnormal placental function, or both (55, 56). Chronic placental abruption has been associated with IUGR and fetal demise (57). Placenta previa, placental infarction, chorioangioma, circumvallate placenta and velamentous cord insertion have also been implicated in the development of IUGR (18, 25).

The worst outcomes have been shown to occur in those growth-restricted pregnancies with the highest degree of compromise in uteroplacental blood flow (58, 59). Simulation models of uteroplacental circulation (60, 61) and studies examining the association between placental location and uterine artery Doppler velocimetry (62-65) suggest that site of placental attachment in the uterus may be an important determinant of placental blood flow. With some variation, such studies have tended to classify the site of placental implantation as previa; low-lying (attached in the lower uterine segment but not previa); fundal; right, left, or generally “unilateral”; or anterior, posterior, or generally “central.” Their findings suggest that abnormal uterine artery blood flow is more likely to occur in pregnancies with unilaterally located placentas (62, 64, 66). This suggests the possibility that placental location might affect fetal growth.

Site of placental attachment within the uterus has been associated with perinatal outcome according to such measures as length of gestation (67, 68), fetal position and presentation (69, 70), and development of preeclampsia (64, 71-73)]. Despite these findings, the association, if any, between placental localization and fetal growth has not been clearly defined. Several studies (74, 75) have found an elevated incidence of IUGR in pregnancies with low-lying or previa placentas. Kofinas et al. (64) reported that pregnancies with growth restriction and/or preeclampsia were more likely than normal pregnancies to have had unilateral

placentas compared with central (i.e., anterior or posterior) placentas. Vaillant et al. (66), similarly, found increased fetal distress, cesarean deliveries, and IUGR in women with unilateral placentas compared with centrally implanted placentas. However, Magann et al. (67) studied the relationship between placental location and neonatal outcome and, while they found an association between unilateral placental location and low Apgar scores, they found no link between placental location and IUGR.

This study was designed to further investigate the relationship between intrauterine growth restriction and placental localization in the uterus.

– **STATEMENT OF PURPOSE** –

This retrospective case-control study was designed to investigate the relationship between ultrasound-documented placental localization and intrauterine growth restriction (IUGR) in singleton pregnancies.

Specific aims of the study:

To determine whether there is an association between placental localization and IUGR status after adjusting for factors known to affect fetal growth, such as maternal disease.

Hypothesis examined:

We hypothesized that there exists an association between placental localization and IUGR.

– METHODS –**Study design**

We carried out a retrospective case-control study in which pregnancies with persistent IUGR were compared to pregnancies without any evidence of IUGR. We reviewed maternal and neonatal medical records to discern placental location, maternal demographic and clinical data, and delivery and neonatal outcome data. Multivariate logistic regression analysis was used to determine the relationship between IUGR and placental location, adjusting for potential confounders. The study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Subjects

Subject selection is illustrated in **Figure 1**. Inclusion criteria were pregnancy with an ultrasound performed between 16 and 20 weeks' gestation (hereafter called the "anatomic survey") at the Yale-New Haven Hospital (YNHH) Perinatology Unit or its affiliate at the Long Wharf Medical Center during the period from January 1, 2000 to December 31, 2005 (in the case of more than one ultrasound between 16 and 20 weeks, anatomic survey was defined as the ultrasound performed nearest 18 weeks); and either delivery of the pregnancy at YNHH or, in the case of intrauterine fetal demise, management at YNHH. Cases, furthermore, were required to have evidence of persistent IUGR. IUGR was defined as estimated fetal weight below the 10th percentile for gestational age using growth charts appropriate for our patient population. Persistent IUGR was defined as evidence of IUGR at the last follow-up

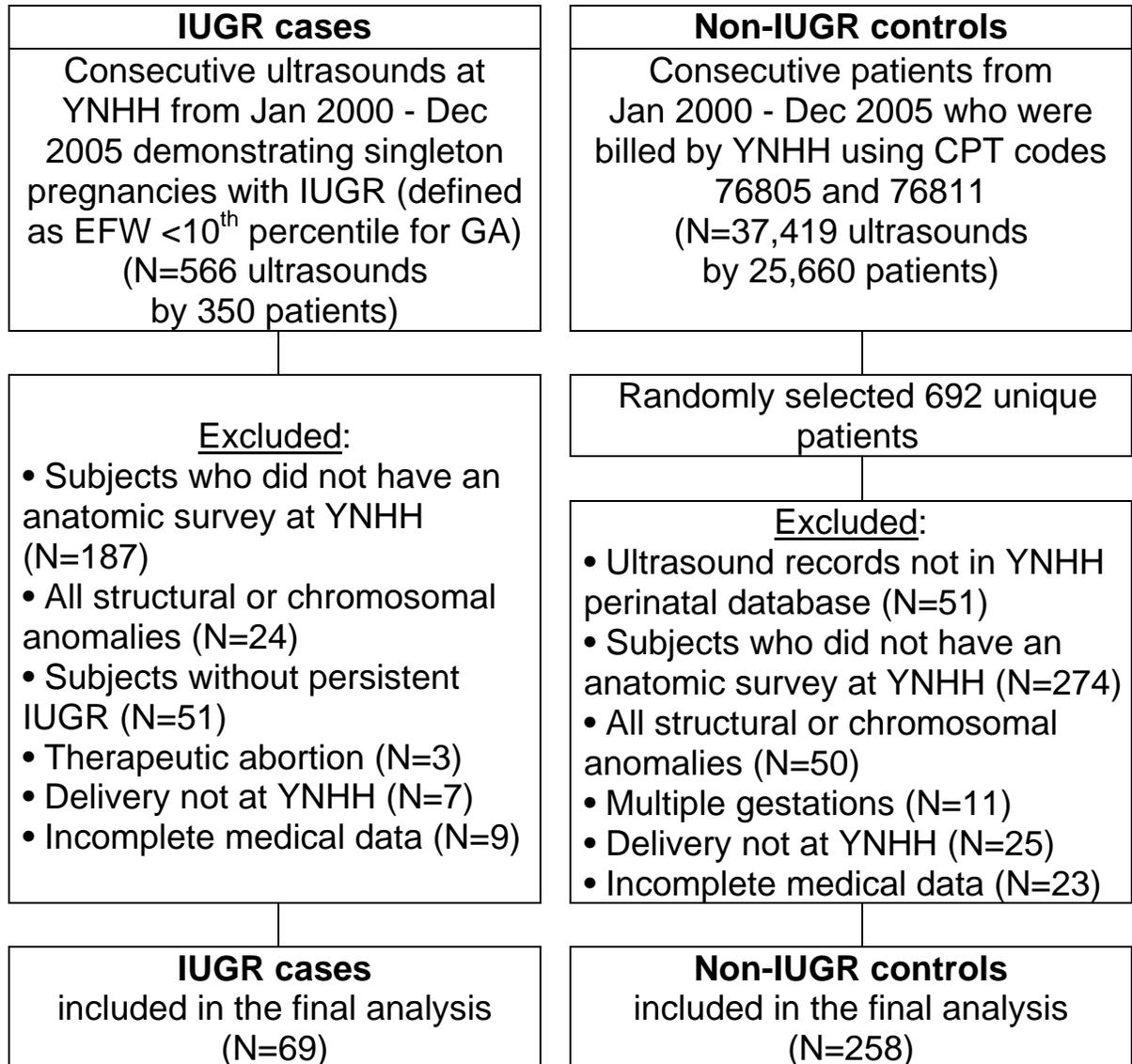
ultrasound of the pregnancy. Controls were required to have no evidence of IUGR at any ultrasound. Multiple gestations, fetal chromosomal or structural anomalies, termination by therapeutic abortion, or incomplete medical data were reasons for exclusion.

Potential IUGR cases were identified using the perinatal ultrasound database at Yale-New Haven Hospital. During the study time period, 566 consecutive ultrasounds performed at the YNHH Perinatology Unit revealed an EFW <10th percentile for gestational age. These ultrasounds corresponded to 350 patients. Of these, 69 were included in the study. Of the 281 excluded patients, 187 did not have an anatomic survey at YNHH, 24 had structural or chromosomal anomalies, 51 did not have evidence of persistent IUGR, 3 ended the pregnancy by therapeutic abortion, 7 did not deliver at YNHH, and 9 had incomplete medical data available.

Given 69 IUGR cases, using $P < 0.05$, we calculated that in comparing placental location between cases and controls, we would have >80% power to detect an odds ratio of 3.0 if we had a 3:1 ratio of controls to cases. To identify potential controls, we used the integrated financial and clinical information system (Resource Information Management System) at Yale-New Haven Hospital's Operational Finance department. All patients (N=25,660) who were coded and/or charged (regardless of ability to pay) for pregnancy ultrasounds during the study time period were identified by CPT-4 code (codes 76805 and 76811, delineated in **Figure 1**). To ensure an adequate number of controls, 692 patients were randomly selected from among this group. We subsequently excluded 51 patients who did not have records in the YNHH perinatal ultrasound database, 274 who did not have an anatomic survey at YNHH, 50 patients whose pregnancies had structural or chromosomal anomalies,

11 because the pregnancy was not delivered at YNHH, and 23 because there was incomplete medical data available. Therefore, a total of 258 controls were included in the study. None of the control pregnancies had any evidence of IUGR.

Figure 1: Method of subject selection



Reasons for exclusion are listed in order of application (e.g., after potential subjects without anatomic surveys at YNHH were excluded, the remaining potential subjects were examined for structural or chromosomal anomalies). Thus, while a pregnancy may have had more than one reason for exclusion from the study, the first reason encountered is designated here. Abbreviation: IUGR, intrauterine growth-restricted; YNHH, Yale-New Haven Hospital; EFW,

estimated fetal weight; GA, gestational age. CPT-4 code 76805 is defined as "Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation." CPT-4 code 76811 is defined as "Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation."

Measurements

For each pregnancy, we recorded placental location as noted at the anatomic survey and additionally, if the anatomic survey was not the last ultrasound, as noted at the last follow-up ultrasound. In the multivariate analysis, placental location was determined by the anatomic survey. We chose to define placental location using anatomic survey for several reasons. Many healthy pregnancies have only one ultrasound around 18 weeks' gestation, without further follow-up ultrasounds unless clinically indicated. Choosing only control pregnancies with later ultrasounds, therefore, might have skewed the control group to include a higher proportion than would be expected of complicated pregnancies, limiting the power to detect a difference between the two groups or to generalize any findings to healthy populations. Thus, the anatomic survey was used to determine placental location in all pregnancies studied, despite many pregnancies having one or more follow-up ultrasounds after the anatomic survey. Determining placental location for all subjects at the same gestational age ensured that our findings were not influenced by a possible association between gestational age and assessment of placental location.

In each ultrasound report, one or more of the following placental locations was noted: anterior, posterior, unilateral, fundal, low-lying, and previa. If there was any confusion about reported placental location, or if placental location was not noted in the anatomic survey report, images were reviewed by a single perinatologist (E.R.N.)

Maternal race (white; black; Hispanic; Asian; or other, including Native American, southeast Asian, and mixed race) was abstracted from the Resource Information Management System database. All other clinical, demographic, and pregnancy outcome data were abstracted from maternal and neonatal medical records, including maternal age at anatomic survey; gravity; parity; chronic (pregestational) hypertension; pregestational or gestational diabetes mellitus; hypertensive disorders of pregnancy (including pregnancy-induced hypertension, preeclampsia, and HELLP); alcohol, tobacco, or illicit substance (e.g., cocaine, heroin) use as determined by patient report; methadone use; gestational age at anatomic survey, last follow-up ultrasound, and delivery; intrauterine fetal demise; intrapartum steroid administration to promote fetal lung maturity (whether one dose or a full course); indication for delivery; mode of delivery; birth weight; Apgar scores at 1 and 5 minutes; admission to neonatal intensive care; and neonatal demise (defined as death prior to hospital discharge).

Analytic methods

Statistical analyses were performed using the SAS 9.1 statistical program. The Chi-square test, Wilcoxon test, ANOVA, Student's *t*-test, or Fisher's exact test were used to compare characteristics of the case and control groups. Continuous variables were examined for normal distribution; if found to be normal, means and standard deviations were compared using the Student's *t*-test or Fisher's exact test. For continuous variables that were not normally distributed, results were reported as median (interquartile range), where interquartile range is the range of values spanning the 25th to 75th percentile, and compared using the Wilcoxon test.

Multivariate logistic regression analysis was used to examine the relationship between placental location and IUGR, adjusting for potential confounders after creating the most parsimonious model using backwards stepwise elimination. We estimated 95% confidence intervals and results were considered significant at $P<0.05$.

Distribution of work

Contact with the Human Investigation Committee of the Yale School of Medicine regarding initial and ongoing study approval was by Errol Norwitz, M.D., Ph.D., of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the Yale School of Medicine, and Lucy Kalanithi. Lists of potential subjects were generated by Wendy Shaffer, RDMS, of the Yale Perinatal Unit via the Yale-New Haven Hospital perinatal ultrasound database and by Joan Rimar, D.N.SC., Clinical Coordinator, Finance, Yale-New Haven Hospital, via the Resource Information Management Systems database. Controls were randomly selected using SAS 9.1 by Jessica Illuzzi, M.D., M.S., of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the Yale School of Medicine. Data were collected by Lucy Kalanithi. Data analysis was performed by Jessica Illuzzi and Lucy Kalanithi.

- RESULTS -**Study population**

Table 1 compares the maternal demographic and clinical characteristics of the IUGR and non-IUGR pregnancies. The groups did not differ with respect to maternal age, gravity, parity, and body mass index. Racial characteristics of the groups did differ, however. Though each group was made up of about half white women, black women made up a higher proportion of the IUGR group (36.4% vs. 19.8%, $P=0.03$).

Table 1. Maternal demographic and clinical characteristics of the 327 pregnancies, by IUGR status

| | Non-IUGR (N=258) | IUGR (N=69) | <i>P</i> |
|--------------------------------------------|---------------------|------------------|--------------------------------|
| Maternal age (years) | 29.2 ± 6.8 | 29.4 ± 5.9 | $P=0.75$ |
| Gravity* | 3 (1) | 2 (3) | $P=0.29$ |
| Parity [†] | 1 (2) | 1 (1) | $P=0.12$ |
| Race [‡] (% [N]) | | | $P=0.03$ |
| White | 48.5% [125] | 47.0% [31] | |
| Black | 19.8% [51] | 36.4% [24] | |
| Hispanic | 22.9% [59] | 12.1% [8] | |
| Asian | 2.3% [6] | 1.5% [1] | |
| Other | 6.6% [17] | 3.0% [2] | |
| Gestational age at anatomic survey (weeks) | 18.2 ± 1.0 | 18.4 ± 1.2 | $P=0.18$ |
| Gestational age at last ultrasound (weeks) | 29.1 (19.0-35.0) | 32.0 (28.9-35.3) | $P<0.001$ |

| | | | |
|-----------------------------------------------------------|--------------------|-------------------|--------------------------|
| Total number of ultrasounds | 2 (1-4) | 4 (3-7) | <i>P</i><0.001 |
| Body mass index[¶] | 30.5 (27.5-35.0) | 29.3 (27.1-36.1) | <i>P</i> =0.39 |
| Diabetes (% [n]) | | | |
| No diabetes | 93.0% (240) | 94.2% (65) | <i>P</i> =0.18 |
| Pregestational DM | 0.8% [2] | 2.9% [2] | |
| Gestational DM | 6.2% [16] | 2.9% [2] | |
| Chronic HTN (% [N])** | | | |
| No hypertension | 96.9% [250] | 75.4% [52] | <i>P</i><0.001 |
| Untreated hypertension | 1.6% [4] | 4.4% [3] | |
| Treated hypertension | 1.6% [4] | 20.3% [14] | |
| Hypertensive disorder of pregnancy (% [N]) | 5.0% [13] | 36.2% [25] | <i>P</i><0.001 |
| Smoking^{††} (% [N]) | 22.0% [54] | 28.8% [19] | <i>P</i> =0.25 |
| Alcohol use^{‡‡} (% [N]) | 2.8% [7] | 6.0% [4] | <i>P</i> =0.26 |
| Illicit drug or methadone use^{§§} (% [N]) | 4.8% [12] | 7.4% [5] | <i>P</i> =0.37 |

Results are expressed as mean \pm standard deviation, median (interquartile range), or % [N]. Abbreviation: IUGR; intrauterine growth-restricted; DM, diabetes mellitus; HTN, hypertension.

* 3 controls did not have gravity recorded.

† 5 controls and 2 cases did not have parity recorded.

‡ 3 cases did not have race recorded.

¶ 38 controls and 22 cases did not have height and/or weight recorded.

** In all, there were 9 controls with chronic hypertension and 18 cases with chronic hypertension; of those, 1 case and 1 control did not have medication information available.

†† 13 controls and 3 cases did not have smoking status recorded.

‡‡ 10 controls and 2 cases did not have alcohol use recorded.

§§ 10 controls and 2 cases did not have illicit drug and/or methadone use recorded.

Anatomic surveys are generally performed between the sixteenth and twentieth week of gestation; we excluded any subjects who did not have an

ultrasound during this time period. As expected, therefore, our subjects underwent anatomic survey at 18.2 ± 1.0 weeks' gestation (non-IUGR controls) and 18.4 ± 1.2 weeks' gestation (IUGR cases, $P=0.18$). After the anatomic survey, 66% (170/258) of the control pregnancies underwent one or more follow-up ultrasounds [with a median of 2 ultrasounds total (interquartile range 1-4)]. Thus, gestational age at the last ultrasound was bimodally distributed for the control group, with a peak at around 18 weeks' gestation and a peak at around 35 weeks (median 29.1 weeks, interquartile range 19.0-35.0). Follow-up ultrasounds for the non-IUGR group did not detect IUGR; they were done for reasons such as history of cervical incompetence, abnormal triple serum screening, maternal exposure to teratogenic medications, and placenta previa. In the IUGR group, every pregnancy had at least one follow-up ultrasound after anatomic survey, with a median of 4 (3-7) ultrasounds total ($P<0.001$ compared with controls, Wilcoxon test) and the last follow-up ultrasound occurring at 32.0 (28.9-35.3 weeks' gestation ($P<0.001$ compared with controls, Wilcoxon test) [both distributed normally but reported as median (interquartile range) as for the non-normally distributed controls].

The groups had comparable proportions of mothers with diabetes mellitus: 7.0% (18/258) of the control mothers and 5.8% (4/69) of the mothers with IUGR pregnancies had either pregestational or gestational diabetes ($P=0.73$). There was a trend toward a higher proportion of pregestational diabetic mothers among IUGR cases (2.9% of all cases vs. 0.8% of controls) and a higher proportion of gestational diabetic mothers in the control group (6.2% of all controls vs. 2.9% of cases) ($P=0.21$).

There was a marked difference between the two groups in the incidence of maternal hypertensive disorders. While fewer than 1 in 20 (9/258, or 3.5%) of control mothers had chronic, or pregestational, hypertension, 1 in 4 of the mothers in the IUGR group did (18/69, or 26.1%, $P<0.001$). In the control group, 1.6% of all mothers were hypertensives who took no medication to control their blood pressures and 1.6% were hypertensives on antihypertensive treatment. The IUGR group was quite different ($P<0.001$): 5 out of every 6 hypertensive mothers in that group, or 20.3% of the entire IUGR group, were on antihypertensive medications.

Similarly, hypertensive disorders of pregnancy (including pregnancy-induced hypertension, preeclampsia, and HELLP) occurred in 36.2% (25/69) of the IUGR pregnancies, a rate 7 times higher than in the non-IUGR group (in which 13/258 pregnancies, or 5.0%, were complicated by hypertensive disorders of pregnancy; $P=<0.001$).

The proportion of women who used tobacco, alcohol, or illicit drugs was comparable between the two groups: 28.8% (19/69) of the IUGR group and 22.0% (54/258) of the control group and reported smoking at some point during the pregnancy ($P=0.25$); 6.0% (4/69) of the IUGR group and 2.8% (7/258) of the control group reported drinking alcohol at some point during the pregnancy ($P=0.26$, Fisher's exact test); and 7.4% (5/69) of the IUGR group reported illicit drug and/or methadone use, while 4.8% (12/258) of the cases did ($P=0.37$, Fisher's exact test).

Placental localization

The distribution of placental locations, as determined at anatomic survey, differed between the two groups (**Table 2**). In both the IUGR and non-IUGR pregnancies,

placentas were most commonly located anteriorly, with anterior accounting for roughly half (48.1%) of placental locations in the non-IUGR group and around a third (34.8%) of the IUGR group. Unilateral placentas were three times more common, however, in the IUGR group than in the non-IUGR group (17.4% vs. 5.0%).

Table 2. Placental location as determined by 16-20 week anatomic survey, by IUGR status

| | Non-IUGR (N=258) | IUGR (N=69) | <i>P</i> |
|-------------------|-----------------------------|------------------------|----------------------|
| Anterior | 48.1% [124] | 34.8% [24] | <i>P=0.01</i> |
| Posterior | 35.2% [91] | 31.9% [22] | |
| Fundal | 7.0% [18] | 10.1% [7] | |
| Unilateral | 5.0% [13] | 17.4% [12] | |
| Low-lying | 2.7% [7] | 1.5% [1] | |
| Previa | 1.9% [5] | 4.4% [3] | |

Results are expressed as % [N]. Abbreviation: IUGR, intrauterine growth-restricted.

Posterior placentas accounted for 35.2% of the non-IUGR group and 31.9% of the IUGR group; fundal placentas 7.0% of the non-IUGR group and 10.1% of the IUGR group; low-lying placentas 2.7% of the non-IUGR group and 1.5% of the IUGR group; and placenta previa 1.9% of the non-IUGR group and 4.4% of the IUGR group.

We also analyzed the data to determine if the designation of placental location persisted from 18-weeks' gestation to the last follow-up ultrasound. As stated previously, only 66% of control group pregnancies had a follow-up ultrasound performed after the anatomic survey. Using data from follow-up ultrasounds, 89.7%

(70/78) of placentas classified as anterior at anatomic survey continued to be classified as anterior at the last follow-up. Of posterior placentas, 75.4% (46/61) remained posterior at last follow-up ultrasound, while only 11.1% (1/9) of unilateral placentas remained unilateral, and no fundal (0/10), low-lying (0/7), or previa (0/5) placentas persisted. All 69 of the IUGR pregnancies had at least one follow-up ultrasound; 3 of them, however, did not have placental location recorded at the last follow-up ultrasound. In the rest of the IUGR group, 70.8% (17/24) of anterior placentas remained anterior, 81.0% (17/21) of posterior placentas remained posterior, 18.2% (2/11) of unilateral placentas remained unilateral, and 33.3% (2/6) of fundal placentas remained fundal. One low-lying placenta was identified in the IUGR group; it did not persist. Of three previa placentas, one continued to have evidence of previa at last follow-up ultrasound.

Delivery and neonatal outcomes

Mean birth weights between the two groups of pregnancies differed by 2 kilograms: the non-IUGR infants weighed 3244 ± 625 grams, while the growth restricted infants weighed 1277 ± 637 grams ($P < 0.001$). By several other measures, the IUGR pregnancies were more complicated than the non-IUGR pregnancies (see **Table 3**). Prior to delivery, over half the IUGR group (57.6%) received at least one dose of intrapartum steroids, while fewer than 1 in 20 (3.1%) of the controls were given steroids ($P < 0.001$). The control pregnancies tended to be delivered at term (mean 39.1 ± 2.2 weeks' gestation), while the IUGR pregnancies delivered prematurely (mean 32.5 ± 4.4 weeks, $P < 0.001$). Over two-thirds of IUGR pregnancies (70.4%)

were delivered by cesarean section, compared with fewer than one-third (28.3%) of the non-IUGR group ($P < 0.001$).

Table 3. Delivery and perinatal characteristics of the 327 pregnancies, by IUGR status

| | Non-IUGR (N=258) | IUGR (N=69) | P |
|----------------------------------------------------------|-----------------------------|------------------------|-------------|
| IUFD | 0.4% [1] | 2.9% [2] | $P=0.11$ |
| Antenatal steroids* | 3.1% [8] | 57.6% [38] | $P < 0.001$ |
| Cesarean delivery | 28.3% [73] | 72.5% [50] | $P < 0.001$ |
| Gestational age at delivery (weeks) | 39.1 ± 2.2 | 32.5 ± 4.4 | $P < 0.001$ |
| Birth weight (grams) | 3244 ± 625 | 1277 ± 637 | $P < 0.001$ |
| Gender (female) | 55.8% [144] | 58.0% [40] | $P=0.75$ |
| Apgar score[†] | | | |
| <5 at 1 minute | 2.3% [6] | 16.7% [11] | $P < 0.001$ |
| <5 at 5 minutes | 1.2% [3] | 4.6% [3] | $P=0.10$ |
| Neonatal intensive care admission[‡] | 16.0% [41] | 92.5% [62] | $P < 0.001$ |
| Neonatal demise | 0.8% [2] | 4.4% [3] | $P=0.07$ |

Results are expressed as mean ± standard deviation or % [N]. Abbreviation: IUFD, intrauterine fetal demise; IUGR, intrauterine growth-restricted.

* For 3 cases, data on whether antenatal steroids were administered was not available.

† 2 controls and 3 cases did not have Apgar scores recorded.

‡ For 1 control and 3 cases, data on the necessity of NICU admission was not available.

The indications for delivery in each of the two groups were as follows: in the control group, 53.4% of deliveries followed spontaneous labor (135/253), 12.5% were electively delivered at term (32/253), 5.5% were delivered for oligohydramnios (14/253), 5.1% for non-reassuring fetal testing (13/253), 4.7% for hypertensive disorders of pregnancy (12/253), 4.3% for failure to progress (11/253), 4.3% because they were post-due (11/253), 2.4% for premature rupture of membranes (PROM) (6/253), 1.6% for preterm premature rupture of membranes (pPROM) (4/253), and 7.9% other reasons (including abruption and polyhydramnios). In the IUGR group, 38.2% were delivered due to IUGR (26/68), 51.5% due to non-reassuring fetal testing (35/68), 22.1% for hypertensive disorders of pregnancy (15/68), 7.4% for oligohydramnios (5/68), 5.9% for placental abruption (4/68), 4.4% for spontaneous labor (3/68), 2.9% for preterm premature rupture of membranes (pPROM) (2/68), 2.9% following intrauterine fetal demise (2/68), and 1.5% (1/68) spontaneously at term (percentages add up to greater than 100% because some pregnancies had more than one delivery indication).

The IUGR infants had less stable neonatal periods as well (**Table 3**). They were more likely to have Apgar scores of less than 5 at 1 minute of life (16.7% in the IUGR group vs. 2.3% in the non-IUGR group, $P < 0.001$ by Fisher's exact test), though by 5 minutes of life they did not differ from the non-IUGR group by this measure. Greater than 9 out of 10 of the IUGR infants received immediate postnatal care in the neonatal intensive care unit, while greater than 8 out of 10 of the other group went to the well baby nursery following delivery (92.5% vs. 16.0% admitted to neonatal intensive care, $P < 0.001$). Though the proportion did not reach statistical significance, 2.9% (2/69) of IUGR pregnancies ended in intrauterine fetal demise,

compared with 0.4% (1/258) of control pregnancies ($P=0.11$, Fisher's exact test). Similarly, 4.4% (3/69) of IUGR infants died before hospital discharge, compared with 0.8% (2/258) of controls ($P=0.07$, Fisher's exact test).

Placental localization and intrauterine growth restriction

Pregnancies with IUGR were over four times as likely as control pregnancies to have had unilaterally-located placentas compared to anterior placentas (odds ratio 4.8, 95% confidence interval, 1.9-11.7) (**Table 4**). Adjusting for ethnicity, chronic hypertension, and hypertensive disorders of pregnancy (no other variables were found to be statistically significant confounders) did not affect this finding (odds ratio 4.6, 95% confidence interval 1.6-13.5).

Table 4. Association between intrauterine growth restriction at latest follow-up ultrasound and placental location as determined at 16-20 week anatomic survey: multivariate logistic regression

| | Unadjusted | Adjusted* |
|--|------------|-----------|
|--|------------|-----------|

| Placental location | OR | 95% CI | OR | 95% CI |
|---------------------------|------------|-----------------|------------|-----------------|
| Anterior | 1.0 | Reference | 1.0 | Reference |
| Posterior | 1.3 | 0.7-2.4 | 1.0 | 0.4-2.2 |
| Fundal | 2.0 | 0.8-5.3 | 3.1 | 1.0-9.6 |
| Unilateral | 4.8 | 1.9-11.7 | 4.6 | 1.6-13.5 |
| Low-lying | 0.7 | 0.1-6.3 | 0.4 | 0.0-4.7 |
| Previa | 3.1 | 0.7-13.8 | 2.6 | 0.4-18.7 |

*Adjusted for ethnicity, chronic hypertension, and hypertensive disorders of pregnancy

– **DISCUSSION** –

This retrospective case-control study compared intrauterine growth-restricted (IUGR) pregnancies with non-growth-restricted pregnancies and found IUGR to be associated with attachment of the placenta to a lateral (i.e., right or left) uterine wall during the second trimester. More specifically, the odds of having had a unilateral placenta (versus the most common placental location, anterior) were over four times greater in IUGR pregnancies compared with non-IUGR controls. IUGR was not associated with other placental locations (anterior, posterior, fundal, low-lying, or previa).

Our finding suggests that lateral placentation predisposes to IUGR. Alternative explanations for the finding seem less likely. Given its statistical significance (odds ratio 4.6, 95% confidence interval 1.6-13.5), which persists after adjustment for potential confounders, the result is unlikely to be due to chance. We were careful to record and include in our multivariate logistic regression analysis a number of important clinical characteristics (e.g., hypertensive disorders of pregnancy) that are associated with IUGR in the medical literature and which could potentially confound our analysis, and in the final analysis we adjusted for all significant confounders (chronic hypertension, hypertensive disorders of pregnancy, and ethnicity). It is possible that our results could be confounded by a known factor associated with IUGR not included in our data (e.g., presence of maternal thrombophilia), but this would be less likely given that such factors are not known to be linked to placental location. There may also exist an as-yet-unknown confounder (for example, a characteristic of the uterine myometrium) that predisposes to both

unilateral placentation and IUGR, and which would thereby discount a cause-effect relationship between unilateral placentation and IUGR. Prior studies have not revealed such a mechanism.

Therefore, we believe our findings suggest that some aspect of placental implantation in the lateral uterus makes it less favorable for fetal growth than implantation in other sites. One possible explanation for this is grounded in prior studies demonstrating differential placental blood flow according to placental location. Prior studies have suggested, using Doppler velocimetry, an association between unilaterally-located placentas and abnormal uterine artery flow velocity (64).

The maternal blood supply to the placenta derives mainly from the uterine arteries, with additional supply from the ovarian arteries. The right and left uterine arteries each have many branches that supply the ipsilateral side of the uterus (76). In some patients, arcuate branches of the right and left uterine arteries cross to the contralateral side and create major anastomoses (77). In pregnancies with unilateral placentas, uterine artery resistance is lower in the ipsilateral vs. contralateral uterine artery, while in pregnancies with centrally located placentas resistance is similar between the two uterine arteries (62, 65, 66). Ito et al. (62) interpreted this finding in the context of an electrical equivalent circuit model of uteroplacental circulation (61) and suggested that the decreased placental-side uterine artery resistance may reflect decreased uteroplacental blood flow volume in unilaterally situated placentas. Kofinas (64), further, suggested an anatomic mechanism by which decreased blood flow to a unilaterally located placenta could occur. Perhaps centrally located placentas receive adequate blood flow from both uterine arteries by virtue of their

position. In contrast, unilaterally located placentas may depend on a high degree of anastomosis between the ipsilateral and contralateral uterine arteries in order to receive adequate blood supply. Therefore, any deficiency in collateral circulation could lead to decreased blood flow, and, therefore, a higher risk of growth restriction, in pregnancies with unilateral placentas.

Indeed, the abnormal waveforms in the uterine and uteroplacental circulation that were demonstrated to occur more commonly with unilateral placentation have since been associated with placental ischemia on postpartum placental pathologic examination (78) and have been corroborated as important predictors of IUGR (63, 79). Thus, given that uteroplacental insufficiency is a well-established and common cause of growth restriction *in utero*, abnormal blood flow is a feasible mechanism by which unilateral placentation could predispose to IUGR. This theory is bolstered by analogous reports in the medical literature regarding preeclampsia, which shares with IUGR the common pathologic mechanism of uteroplacental insufficiency and has also associated with unilateral placental implantation (71).

The association of placental location and IUGR has been examined before with contradictory results. Kofinas et al. (64) used a case-control design to compare placental location in pregnancies with IUGR and/or preeclampsia to placental location in normal pregnancies. No odds ratio was reported, but they found that in the presence of preeclampsia and/or IUGR, up to 75% of pregnancies had unilaterally located placentas and 25% central placentas, whereas in the absence of these two conditions, 51% of the patients had unilateral and 49% central placentas ($P<0.02$). Similarly, Vaillant et al. (66) found an increased history of fetal distress,

cesarean deliveries, and IUGR in women with unilateral placentas compared with centrally implanted placentas.

A more recent study by Magann et al. (67), however, examined second trimester placental location and a variety of adverse pregnancy outcomes, with a result contradictory to the prior studies'. Though this group found an association between unilateral implantation and low Apgar scores (<7) at 1 and 5 minutes, they found no association between any placental location and IUGR. In fact, they found unilateral placentas to be associated with an increased risk of macrosomia, suggesting larger neonates in this group.

Several additional studies have looked specifically at the relationship between IUGR and low-lying or previa placentas via retrospective analysis of large groups of pregnancies with these uncommon placental locations. Strong associations between IUGR and low-lying (75) or previa (74, 80) placentas were found in some of these studies. Others found a weak association (81) or no association (82, 83) Our study did not find an association between low-lying or previa placentas and IUGR. Because of the very small number of low-lying (8 total) and previa (8 total) placentas included in our study, we may have lacked statistical power to detect an association.

Our study lends weight to the findings associating IUGR with unilateral placentation. We believe our data set to be robust and our finding to be valid, particularly given its significance despite a relatively small sample size and our strict definition of IUGR (with growth <10th percentile required to persist through the latest follow-up ultrasound), which may have increased our ability to detect an association.

As regards the clinical and demographic variables we measured, we found several differences between the IUGR and non-IUGR groups. Race was associated with IUGR, with a significantly higher proportion of black mothers in the IUGR group. The association between black race and IUGR has been demonstrated in at least one large epidemiologic study (84). Our observations that hypertensive disorders and pregestational diabetes were more common among IUGR pregnancies than non-IUGR controls are consistent with well-described associations of IUGR with maternal vascular disease (25, 41, 43) and diabetic vasculopathy (46).

There was also a trend toward a higher proportion of gestational diabetic mothers in the control group, and a trend toward a higher proportion of pregestational diabetic mothers in the IUGR group. Interestingly, these trends are consistent with known associations between gestational diabetes and fetal macrosomia (24), and between diabetes-related vascular disease (of the type that develops in the setting of longer-standing diabetes) and fetal growth restriction (46). Perhaps due to a relatively small number of mothers with diabetes, however, these differences were not significant.

Smoking (30), alcohol use (27-29), and illicit substance use (25, 31, 32) have been associated with IUGR in large epidemiologic studies. Substance use was not, however, associated with IUGR in this study. This may be because we measured substance use as a categorical variable (i.e., any substance use at all vs. no substance use at all). For example, women who reported drinking until they learned they were pregnant, as well as those who reported drinking one drink per week, one drink per day, or many drinks per day throughout pregnancy were all classified together as drinkers. Nondrinkers were those without any alcohol use at all. A dose-response

effect of alcohol use in pregnancy has been reported (29) such that the percentage of IUGR newborns increases sharply with increasing maternal alcohol intake, while the consumption of less than one drink daily may have little effect on intrauterine growth. Therefore, because we could not analyze substance use as a continuous variable or a categorical variable indicating substantial use, a relatively high proportion of low-dose substance users may have diluted our ability to detect an association with IUGR if one existed.

Not surprisingly, we found a marked difference in birth weight between the IUGR and non-IUGR pregnancies. The mean birth weight of the IUGR infants fell well below the clinically significant category of low birth weight (<2500g), which, like IUGR, portends a substantially increased risk of morbidity and mortality (85, 86). The observation that pregnancies with IUGR received intrapartum steroids and were delivered earlier than non-IUGR infants is consistent with current obstetric management, which encourages active intervention and delivery of IUGR fetuses once a favorable gestational age is reached or fetal growth ceases. The great majority of IUGR neonates we studied were admitted to the neonatal intensive care unit; this is also consistent with current management of IUGR pregnancies, though this may also have been related to the group's low gestational ages, given that IUGR pregnancies tended to deliver prematurely. The high proportion of IUGR pregnancies delivered by cesarean section is likely related to the high proportion of deliveries in that group (51.5%) for non-reassuring fetal testing.

We identified placental location by retrospective review of the anatomic survey performed between 16 and 20 weeks' gestation. Because many healthy pregnancies have no further follow-up scans after that time, we chose to determine

placental location during the second trimester so that our method remained constant among all pregnancies. At least two more recent studies investigating the effects of placental location on pregnancy outcome have used a similar approach, with placental location determined at 18 weeks (87) or between 14 and 22 weeks (67).

The distribution of placental locations in the pregnancies we studied was consistent with several large studies of second trimester placental location (73, 88, 89), in which most placentas were found to be located anteriorly or posteriorly in the upper uterine segment. We found, as prior studies have, that anterior and posterior implantation sites were not associated with IUGR. It may be that blastocysts are more likely to implant in uterine sites that are favorable to fetal growth, or that implantation in sites less favorable to growth [as has been shown, for example, in studies of implantation in the region of a uterine septum (90)] is associated with spontaneous abortion, making placental attachment in such areas less common. Further studies could expand on this observation.

Though our study investigated the relationship between second trimester placental location and IUGR, we were interested to see if there was some degree of placental “migration” following the anatomy scan. A prior case-control study (64) evaluated 300 pregnancies and found no difference in the incidence of placental laterality (vs. centrality) between pregnancies <28 weeks’ gestation and those of >28 weeks. In contrast, a larger prospective study (88) identified placental location at 18 weeks and compared it to results of serial assessments throughout the pregnancy, demonstrating that 16.9% of non-low-lying posterior placentas and 4.9% of anterior placentas migrated to a fundal position by 34 weeks. Of low-lying placentas (called anterior low or posterior low in the referenced study) identified at 18 weeks, 97.8%

were no longer low-lying toward the end of the pregnancy; 55.5% of previas at 18 weeks remained previa by 34 weeks' gestation. We found similar rates of shifting classification of placental location over time. Perhaps placental location is more difficult to identify in a smaller gravid uterus, and therefore assessment of location becomes more specific and thus may change as the uterus grows. Further studies may better elucidate placental "migration" and determine if there is also an association between IUGR and placental location in the third trimester, which, like the second trimester, is an important period of fetal growth.

We regard the validity of the data set to be a major strength of our study. The IUGR group differed significantly from the control group with respect to maternal race, chronic hypertension, hypertensive disorders of pregnancy, gestational age at delivery, and birth weight, among other variables. These characteristics have well-known associations with IUGR, as previously demonstrated in the medical literature. The validity of our data set by these measures gives us confidence in the validity of the association we detected between IUGR and second trimester placental location.

Our study had several limitations. The case-control design allowed us to detect an association between IUGR and unilateral placentation. Though we discussed the possibility of a cause-effect relationship, our study design precludes anything beyond speculation. Further, a number of subjects (N=19) were excluded from the multivariate regression analysis, in which we controlled for potential confounders, because one or more data points were missing (e.g., maternal race). Ideally, we would have included all subjects in this adjusted analysis, though we do not suspect that the excluded subjects were different from included subjects in a way that would affect our findings.

In summary, we completed a retrospective case-control study comparing 69 pregnancies with intrauterine growth restriction (IUGR) to 258 non-growth-restricted pregnancies treated at the same institution during the same time period. We found, as two prior studies have, an association between IUGR and second trimester unilateral placentation. After adjusting for confounders, IUGR pregnancies were over four times as likely as control subjects to have had unilaterally located placentas compared to anterior placentas, an association we believe may relate to differential placental blood flow according implantation site. Additional research is necessary to further confirm this observation, and if confirmed, to elucidate its mechanism and determine whether pregnancies with unilateral placentas require more intensive monitoring.

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