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Identifying fetal growth disorders using ultrasound in women with diabetes

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Abstract

Objective—We evaluated the ability of third trimester ultrasound to diagnose disorders of fetal growth among women with diabetes mellitus.

Study design—This is a retrospective cohort study of women with diabetes who delivered term singleton neonates at a single academic medical center who had an ultrasound within 5 weeks of delivery. We characterized the sensitivity, specificity, positive predictive value and negative predictive value of ultrasound to detect large-for-gestational age (LGA) and small-for-gestational age (SGA) infants. LGA or SGA were defined as an ultrasound estimated fetal weight > 90% or < 10% based on the Hadlock formula, respectively; ultrasound estimates of LGA or SGA were compared to postnatal findings of LGA or SGA based on gestational age-based weight percentiles. Test characteristics were analyzed for the total cohort and by type of diabetes. We compared the area under the curve for receiver-operating characteristic (ROC) curves for different types of diabetes.

Results—Of 521 women, 3 (0.6%) screened positive for SGA and 64 (12.3%) delivered an SGA neonate. In contrast, 129 (24.8%) screened positive for LGA and 61 (11.7%) delivered an LGA neonate. The ROC curves did not differ significantly for different types of DM ($p = 0.68$).

Conclusion—Ultrasound in women with diabetes and term or late preterm pregnancies has a high specificity but poor sensitivity for SGA, and a low positive predictive value for LGA. Diagnostic capability of ultrasound to detect fetal growth abnormalities did not differ significantly by type of diabetes.

Keywords

ultrasound; diabetes; fetal growth disorders

Introduction

Due to the obesity epidemic, the proportion of pregnant women with either pre-gestational or gestational diabetes in pregnancy has increased in recent years.^{1,2} Women with

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gestational and pre-gestational diabetes are at increased risk of delivering a neonate that is large-for-gestational age (LGA).³ Diabetes and LGA fetuses are independent risk factors for a number of obstetric complications at the time of delivery, including shoulder dystocia,⁴ higher-order perineal lacerations,⁵ and cesarean delivery.⁶ Thus, a majority of women with diabetes undergo an ultrasound to assess fetal weight in the third trimester to assist with delivery planning.

Several technical challenges to ultrasound accuracy often exist in the diabetic pregnant patient. Ultrasound is known to be less accurate with increasing fetal weight⁷ and at later gestational ages.⁸ Many women with diabetes are also obese; maternal adiposity poses a challenge to an accurate ultrasonographically estimated fetal weight (US-EFW).⁹ Much previous literature on ultrasound in the diabetic population focuses on detection of macrosomia, with most studies showing that ultrasound performs relatively poorly in accurately detecting macrosomia.⁷ Overdiagnosis of macrosomia can lead to unindicated elective cesarean delivery or other interventions.¹⁰ Moreover, the diagnostic ability of ultrasound to detect SGA status among women with diabetes remains unclear.

Given these challenges but yet the common frequency of ultrasound in this population, it is important to understand the test characteristics of ultrasound for estimated fetal weight in this population. Additionally, it is unclear from previous studies whether the type of diabetes (gestational vs. pre-existing) affects the diagnostic accuracy of ultrasound to detect macrosomia. Thus in this paper, we used a large, tertiary care center cohort to characterize the diagnostic capability of a third trimester ultrasound to detect LGA and SGA fetuses in pregnant women with diabetes and to determine if there are differences in test characteristics by type of maternal diabetes.

Materials and methods

This is a retrospective cohort study of women aged 18 or greater with gestational or pre-gestational diabetes who delivered term (37.0 weeks' gestation or greater), singleton gestations and received sonographic examinations at Northwestern Memorial Hospital in Chicago, IL between 1/1/2010 and 12/31/2015. Women were included in the study if they had an ultrasound performed for fetal weight estimate within 5 weeks of delivery. Women were excluded if they had a fetus with a major anomaly, as this may impair accurately measuring fetal weight. Women who had ultrasounds performed solely for biophysical profile, fluid volume, or fetal presentation, but without assessment of estimated fetal weight, were excluded. Women who had informal "bedside" ultrasounds not read by the Division of Maternal-Fetal Medicine were additionally excluded. Clinical and demographic data were abstracted from the electronic medical record and ultrasound database, including information on estimated fetal weight and ultimate birthweight.

All ultrasounds were performed by trained sonographers calculating estimated fetal weight using the Hadlock formula incorporating head circumference, biparietal diameter, abdominal circumference, and femur length.¹¹ For the purposes of consistent terminology, the phrases SGA and LGA refer to both fetuses and neonates at the extremes of growth, as terms such as "macrosomia" do not have consistently accepted definitions. We defined fetuses as SGA if

the US-EFW was < 10% for gestational age at the time of ultrasound using the percentiles generated by Brenner et. al.¹² and embedded into the AS ultrasound software package (AS Software Inc., Englewood Cliffs, NJ), and the corresponding neonate as SGA if birthweight was < 10% for gestational age at birth, using standardized growth curves for U.S. birthweights generated by Oken et. al.¹³ Similarly, we defined fetuses as LGA if the US-EFW was > 90% for gestational age at the time of ultrasound, and the corresponding neonate as LGA if birthweight was > 90% for gestational age at birth, again using the Brenner et. al. values for fetal growth curves and the standardized values generated by Oken et. al. for neonatal growth percentiles.^{12,13}

We defined different types of gestational diabetes using the White criteria, with A1 gestational diabetics being those who were diet-controlled during pregnancy and A2 gestational diabetics those women that required medication.¹⁴ Women with pre-gestational diabetes were classified as either Type 1 or Type 2 using the diagnoses made prior to pregnancy according to patients' previous primary care physicians or endocrinologists; however, our institution follows recommended guidelines for early screening and diagnosis of type 2 diabetes during pregnancy.¹⁵

Patient demographic and clinical characteristics were compared by type of diabetes. We calculated the sensitivity, specificity, positive predictive value, and negative predictive value of an ultrasound performed within 5 weeks of delivery to detect SGA and LGA neonates for the overall sample, as well as for each type of diabetes. We also calculated the receiver-operating characteristic curve (ROC) associated with each type of diabetes, comparing the area under the curve (AUC) to see whether diagnostic performance varied across types of diabetes. The AUC values associated with different types of diabetes were compared for equality using the methods suggested by DeLong et. al.¹⁶

In order to determine the consequences of antenatal LGA and SGA diagnoses based on US-EFW, we also examined neonatal outcomes, including admission to the neonatal intensive care unit (NICU), shoulder dystocia, and third and fourth degree perineal laceration. We performed bivariable comparisons of neonatal outcomes based on weight category (SGA, appropriate for gestational age [AGA], or LGA) using chi square analysis and Fisher's exact test. Comparisons were considered statistically significant at the $p < 0.05$ level for two-sided hypotheses. All analyses were carried out in STATA (version 14.2, StataCorp, College Station, TX). Approval for this study was obtained from the Northwestern Institutional Review Board with a waiver of informed consent.

Results

Of 877 women with diabetes who otherwise met the study inclusion criteria, 59.5% (N=521) had an ultrasound within 5 weeks of delivery and comprised the population of interest. In this population, 0.6% (N=3) screened positive for SGA and 12.3% (N=64) delivered an SGA neonate. Thus, the overall sensitivity of ultrasound for SGA was 4.7%, and specificity was 100%. In contrast, 24.8% (N=129) screened positive for LGA and 11.7% (N=61) delivered an LGA neonate. The overall sensitivity of ultrasound for LGA was 80.3% and the specificity was 82.6%. The overall AUC was 0.82 for LGA and 0.52 for SGA. Table 1 shows

there are no significant differences in demographic or obstetric characteristics between women whose fetuses were diagnosed accurately as compared to those who ultimately delivered a fetus in a different birthweight class than that predicted by ultrasound.

In assessing test characteristics by type of diabetes (Table 2), we identified that the sensitivity of ultrasound for the detection of LGA was lowest for women with type 2 diabetes mellitus (57.1%) and highest for women with type 1 diabetes mellitus (94.7%). In contrast, the specificity of ultrasound for LGA was greatest for women with GDMA1 (85.6%) and lowest for women with type 1 diabetes (68.6%). The positive predictive value of ultrasound for LGA was below 40% for all women except for those with type 1 diabetes, whereas the negative predictive value for LGA approached 100% for all women. With regard to SGA status, the sensitivity of ultrasound for SGA was universally poor, whereas specificity was universally 100%. The positive and negative predictive values for SGA were high for women with all types of diabetes.

Figure 1 shows the receiver – operating characteristic for each type of diabetes in the detection of LGA. The ROC curves for the detection of LGA did not differ significantly by type of diabetes ($p = 0.68$). Further, adding type of diabetes to the predictive model did not improve the ability of ultrasound to detect LGA ($p = 0.07$). Given the overall poor performance of ultrasound to diagnose SGA, we did not compare ROC curves across types of diabetes for SGA.

Of the 389 women with fetuses determined to be appropriate for gestational age (AGA) on ultrasound, 15.7% ($N=61$) ultimately delivered an SGA neonate and 3.1% ($N=12$) delivered an LGA neonate. Of the 61 SGA neonates incorrectly identified as AGA on ultrasound, 31.2% ($N=19$) were admitted to the NICU compared to 21.2% ($N=67$) of the appropriately grown neonates ($p = 0.09$). Of the 12 women whose fetuses were identified as AGA but ultimately delivered LGA neonates, 5 delivered vaginally. Of these 5 women, 40.0% ($N=2$) experienced a third degree laceration, compared to 4.3% ($N=8$) of 185 women who were identified on ultrasound as having an AGA fetus and ultimately delivered an AGA fetus ($p < 0.001$). Of these 5 women, 20.0% ($N=1$) experienced a shoulder dystocia, compared to 3.6% ($N=7$) of women with AGA fetuses/neonates ($p = 0.07$). Of the 5 women who delivered vaginally, all 5 delivered an infant weighing $> 4,000$ grams, but only one woman delivered a neonate weighing > 4500 grams.

Discussion

Women with diabetes often undergo a growth ultrasound in the third trimester to aid in glycemic control and delivery planning.¹⁷ However, the diagnostic accuracy of ultrasound for estimated fetal weight in women with diabetes, for whom there is greater risk of LGA status but also potentially greater risk of error in ultrasound measurements, has not been well described. We characterized the diagnostic accuracy of ultrasound to detect fetal growth disorders, namely SGA and LGA, in a diverse population of women with both gestational and pre-gestational diabetes. Similar to other studies in older cohorts and in women without diabetes,^{7,18-20} the positive predictive value of a growth ultrasound for LGA in this population was low. This study confirms that the primary value of a third trimester growth

ultrasound may be to rule out LGA. Women in this study who delivered an LGA fetus that was missed on prenatal diagnosis were more likely to experience shoulder dystocia and a third degree perineal laceration, although only one of these infants would have met the antepartum criteria of 4,500 grams for a primary cesarean delivery.²¹

A novel finding in this analysis is the low sensitivity of ultrasound for SGA in this sample of diabetic patients, which is considerably worse than in nondiabetic pregnancies.²²⁻²⁴ The underdiagnosis of SGA neonates in this population is concerning. While maternal diabetes is classically associated with fetal overgrowth, women with diabetes, particularly those with longstanding vascular disease, remain at risk of developing intrauterine growth restriction (IUGR),²⁵ leading to a small for gestational age (SGA) neonate. Such risk can be compounded in the context of other risk factors for growth restriction, including inadequate gestational weight gain,²⁶ hypertension, or renal disease.²⁷ These infants are at higher risk of stillbirth, neonatal morbidity, and neonatal mortality.²⁸ A recent study among women with uncomplicated pregnancies indicates that SGA fetuses that are not properly diagnosed and monitored are at higher risk of stillbirth, neonatal mortality, and neonatal morbidity.²⁸ While the majority of women in this population are already undergoing antenatal testing with either biophysical profiles or nonstress tests due to maternal diabetes, monitoring specific to intrauterine growth restricted fetuses, such as Dopplers of the umbilical artery, would not be performed. As clinicians likely have a higher index of suspicion for macrosomia, rather than IUGR, in this population, a substantial number of SGA infants may be missed despite frequent growth ultrasounds, an assertion that could be tested in other diabetic cohorts

The strengths of this analysis include study of a large cohort of women with multiple subtypes of diabetes. All ultrasounds were performed at a single institution by a small number of highly trained obstetric sonographers with ultrasounds read by a discrete group of maternal-fetal medicine physicians. However, this paper also has several limitations. First, the number of fetuses screening positive for SGA is low, which may make estimates of test characteristics unstable. Second, not all diabetic patients at our institution undergo third trimester growth studies (especially women with A1 gestational diabetes); thus, there may be selection bias in who received an ultrasound, although presumably women at greatest risk of LGA fetuses were the most likely to undergo a scan. Third, these results may not be generalizable to a broader population, as this study was performed at a tertiary care academic medical center, with highly trained obstetric sonographers. Finally, our study was underpowered to detect significant differences in rare adverse outcomes such as shoulder dystocia, as well as differences in the AUC for different ROC curves based on different subtypes of diabetes.

In summary, although ultrasound for estimated fetal weight in the third trimester is commonly performed for women with gestational or pre-gestational diabetes, the test characteristics of such an ultrasound suggest these estimates are far from perfect. Specifically, while ultrasound had a high negative predictive value for LGA, the sensitivity, specificity and positive predictive value for LGA are suboptimal. Moreover, ability to detect LGA did not differ by type of diabetes, although again, our study is likely underpowered to detect such differences. Further work is required to understand how clinicians can optimize

the performance of ultrasound – such as by specific growth curves or other alterations in ultrasound performance – for this population.

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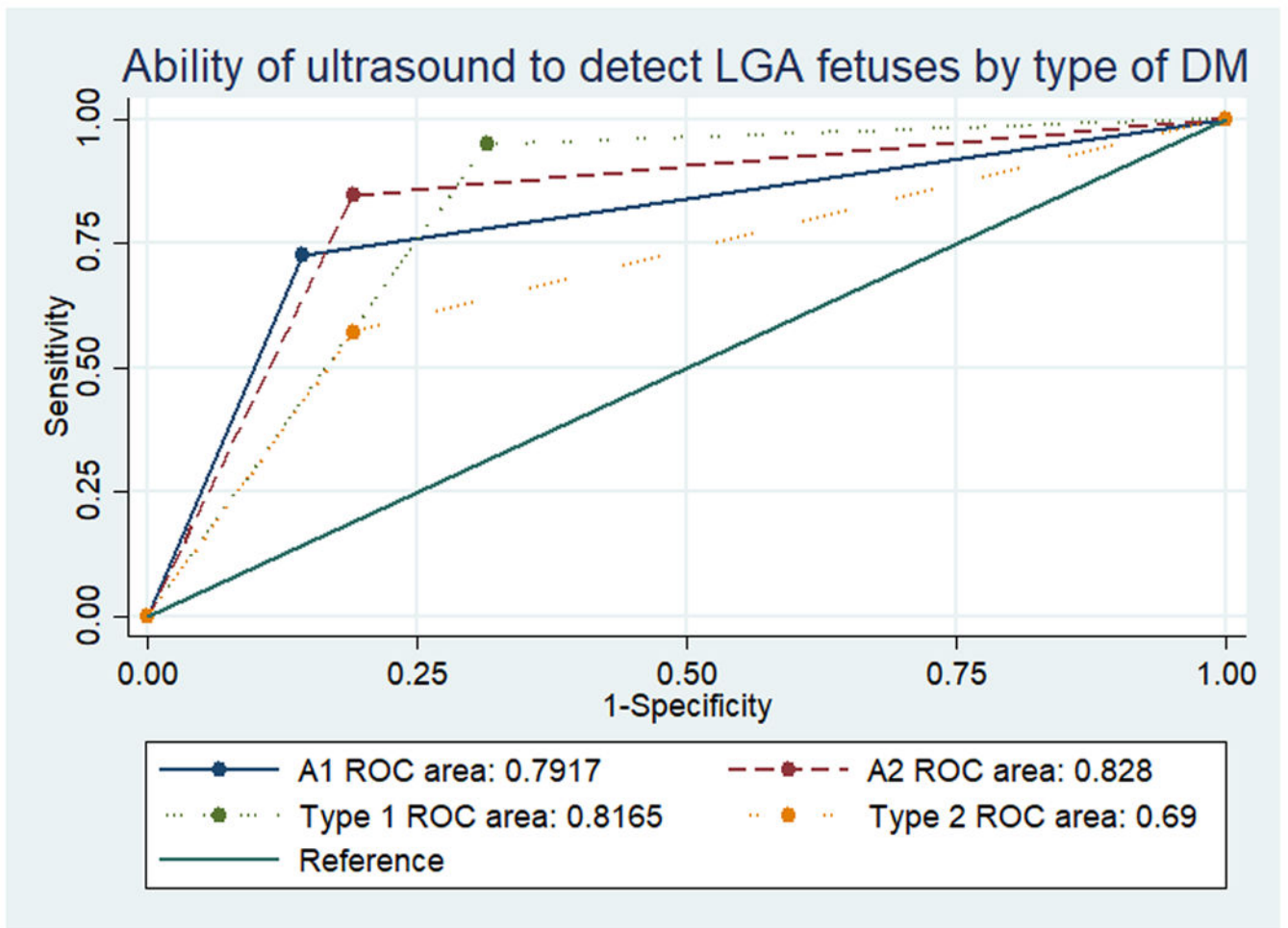


Figure 1.

AUC values for different types of diabetes were not found to be significantly different, using the methods of DeLong et. al.¹⁶

Table 1
Cohort characteristics

Variable	Accurately predicted birthweight category ^c (N = 368)	Inaccurately predicted birthweight category (N = 153)	P value
Maternal age (years)	31.5 ± 5.4	31.0 ± 5.4	0.29
Maternal race/ethnicity:			0.20
Non Hispanic white	123 (38.4)	45 (33.1)	
Non Hispanic black	45 (14.1)	30 (22.1)	
Hispanic	76 (23.8)	32 (23.5)	
Other	76 (23.8)	29 (21.3)	
Maternal BMI at delivery (kg/m ²)			0.40
< 30	143 (38.9)	69 (45.1)	
30 – 39.9	151 (41.0)	58 (37.9)	
40	74 (20.1)	26 (17.0)	
Type of diabetes:			0.64
A1 GDM ^b	193 (52.5)	86 (56.2)	
A2 GDM	94 (25.5)	40 (26.1)	
Type 2 DM	39 (10.6)	15 (9.8)	
Type 1 DM	42 (11.4)	12 (7.8)	
Gestational age at delivery (weeks)	39.0 ± 1.0	39.0 ± 1.1	0.44
Gestational age at ultrasound (weeks)	37.1 ± 1.4	37.2 ± 1.4	0.24
Time between last ultrasound and delivery (weeks)	1.7 ± 1.3	1.5 ± 1.3	0.06
Birthweight category at delivery:			< 0.001
Small for gestational age	3 (0.82)	61 (39.9)	
Appropriate for gestational age	316 (85.9)	80 (52.3)	
Large for gestational age	49 (13.3)	12 (7.8)	

^aNumbers presented are either mean ± standard deviation or N(%).

^bGDM: gestational diabetes mellitus

^c'Accurate' and 'inaccurate' here refer to whether the predicted birthweight category (SGA, AGA, LGA) based on the ultrasound-estimated fetal weight was concordant with the actual birthweight category (SGA, AGA, LGA).

Table 2

Diagnostic performance of ultrasound in the diabetic population

	Any DM (N = 521)	A1 GDM (N = 279)	A2 GDM (N = 134)	Type 2 DM (N = 50)	Type 1 DM (N = 50)
Large for gestational age:					
Screen positive	129	53	34	13	29
True positive	61	22	13	7	19
Sensitivity	80.3%	72.7%	84.6%	57.1%	94.7%
Specificity	82.6%	85.6%	81.0%	80.9%	68.6%
Positive predictive value	38.0%	30.2%	32.4%	30.8%	62.1%
Negative predictive value	96.9%	97.3%	98.0%	92.7%	96.0%
AUC ^a	0.82	0.79	0.83	0.69	0.82
Small for gestational age:					
Screen positive	3	2	0	1	0
True positive	64	45	15	4	0
Sensitivity	4.7%	4.4%	0.0%	25.0%	-
Specificity	100%	100%	100%	100%	-
Positive predictive value	100%	100%	-	100%	-
Negative predictive value	88.2%	84.5%	88.8%	94.3%	-
AUC	0.52	0.52	-	0.63	-

^a AUC: area under the curve