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Antenatal fetal adrenal measurements at 22–30 weeks gestation, fetal growth restriction, and perinatal morbidity

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Abstract

Objective: Our objective was to test the association of fetal adrenal size with perinatal morbidity among fetuses with fetal growth restriction (FGR, estimated fetal weight <10th percentile).

Study design: This was a secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) adrenal study, which measured fetal adrenal gland size at 22–30 weeks' gestation. We analyzed the transverse adrenal area (TAA) and fetal zone area (absolute measurements and corrected for fetal size) and the ratio of the fetal zone area to the total transverse area using a composite perinatal outcome of stillbirth, NICU admission, RDS, NEC, ROP, sepsis, mechanical ventilation, seizure, or death. Among fetuses with FGR, adrenal measurements were compared between those that did and did not experience the composite perinatal outcome.

Results: There were 1709 eligible neonates. Seven percent (n=120) were diagnosed with FGR at the time of adrenal measurement, and 14.7% (n=251) experienced perinatal morbidity. EFW-corrected and absolute adrenal measurements were similar among fetuses with and without FGR

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as well as among those who did and did not experience morbidity. The AUC for cTAA was 0.52 (95% CI 0.38–0.67).

Conclusion: In our cohort, adrenal size was not associated with risk of morbidity among fetuses with FGR.

Keywords

fetal growth restriction; perinatal morbidity; adrenal gland; placental insufficiency; prenatal ultrasound

Introduction

Fetal growth restriction (FGR) describes pathologic fetal growth wherein a fetus does not achieve its inherent growth potential and is predisposed to adverse outcomes such as respiratory distress, admission to the neonatal intensive care unit (NICU), perinatal death, and cerebral palsy.[1,2] In addition to the associated short-term morbidity and mortality, growth restricted fetuses undergo compensatory metabolic programming and cardiovascular remodeling that persist into adulthood. These intrauterine adaptations predispose to a host of enduring morbidities, including metabolic disease, hypertension, stroke, and death from coronary heart disease.[3,4] With 7–10% of pregnancies affected by poor fetal growth, the contribution of fetal growth restriction to the global burden of morbidity and mortality across the lifespan is substantial.[5]

Clinical management of FGR is plagued by an inability to accurately identify fetuses with true growth pathology at highest risk of perinatal morbidity. The diagnosis traditionally is based on a calculated estimated fetal weight (EFW) which is below a population-based percentile cutoff for a given gestational age. This is problematic because it both under- and over-diagnoses FGR, missing fetuses with growth pathology who measure above the cutoff, as well as including constitutionally small fetuses that are not at increased risk of morbidity. The use of umbilical artery (UA) Doppler studies is helpful to identify the most severely “at-risk” fetuses, but data demonstrating increased risk of morbidity among FGR fetuses with normal UA Doppler studies illustrate that additional methods of risk stratification are needed.[6,7]

One of the principal fetal adaptations to adverse intrauterine conditions is preferential direction of blood to the heart, brain, and adrenal glands. In a sheep model of chronic hypoxemia, the largest increase in blood flow is directed to the fetal adrenal glands.[8] Indeed, there has been some, albeit inconsistent, evidence that fetuses with growth restriction develop sonographically-larger adrenal glands on average, whereas a lack of this change is associated with more frequent adverse neonatal outcomes.[9,10] This suggests that increased adrenal size may serve as an indicator of fetal compensation for adverse intrauterine conditions, and that the absence of such a response indicates either an intrinsic adrenal insufficiency or fetal compromise severe enough to interrupt physiologic autoregulation, both of which would plausibly predispose to morbidity. Thus, the utility of adrenal gland measurements to stratify risk of morbidity from FGR is uncertain. The purpose of this study

was to determine whether adrenal gland measurements are associated with neonatal morbidity among fetuses with growth restriction.

Study Design

This was a secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b). In this study, 10,038 nulliparous women with a singleton gestation had comprehensive demographic, clinical, and biomarker data prospectively collected across pregnancy, with the goal of developing an observational data set that could be used to predict adverse pregnancy outcomes. Women were recruited from eight centers, and study participation included study visits at 3 separate time points during pregnancy, with outcomes abstracted from the medical records after delivery. Prior to study initiation, institutional review board approval was obtained at each site and the data coordinating center.[11]

From within the nuMoM2b cohort, women were recruited for a sub-study to evaluate the utility of fetal adrenal gland measurements by ultrasound to predict preterm birth, the results of which have been previously published.[12] For the adrenal sub-study, study sonographers underwent standardized training and centralized certification, and were required to demonstrate the ability to identify and measure the fetal adrenal gland in a transverse plane and, when possible, sagittal and coronal planes. Accordingly, sonographers identified the closest adrenal gland in the transverse plane and measured the lengths and widths of both the whole gland and the fetal zone. Three measurements of each parameter were measured, with the mean values used for analysis. Examination quality was centrally assessed on an ongoing basis. Additional methodologic details for this study are available.[12]

For our analysis we included data from non-anomalous neonates born to women enrolled in the adrenal sub-study. In addition to the exclusion criteria of the parent NuMoM2b study, we excluded neonates delivered prior to 24 weeks' gestation or with missing gestational age at delivery, fetal weight or adrenal size measurements, or neonatal outcome data. Major anomalies were defined as those potentially requiring neonatal surgery or predisposing to adverse neonatal outcomes (e.g., cardiac anomaly, abdominal wall defect, skeletal dysplasia).[12]

At the 3rd nuMoM2b study visit, which occurred between 22–30 weeks' gestation, EFWs were performed and orthogonal adrenal measurements (length and width) were collected in the transverse plane, with the depth measured in the sagittal plane when possible. Adrenal measurements are illustrated in Figure 1. Because depth measurements were obtained only in a minority of study participants, the parameters included in our analyses were based on transverse adrenal area rather than gland volume. The formula for transverse adrenal area (TAA) is π x length x width. Because the analysis focused on whether the adrenal gland is disproportionately large or small, we accounted for fetal size by dividing the transverse area or gland volume by the EFW, giving the corrected transverse area as a ratio, which was then multiplied by 100 in order improve ease of use (cTAA = TAA/EFW x 100). Fetal zone measurements were used to calculate the absolute and corrected fetal zone area (FZA, cFZA). Finally, the ratio of the FZA to the TAA was used to compute the fetal zone ratio.

Because study ultrasounds measured only pre-specified parameters and not clinically-indicated parameters, umbilical artery and middle cerebral artery Doppler velocimetries were not performed. Furthermore, data from clinically-indicated ultrasound examinations were not collected for analysis by the nuMoM2b study. Clinicians were blinded to the study ultrasound adrenal measurements.

Composite perinatal outcome was defined as a composite of stillbirth, respiratory distress syndrome (RDS), grade III/IV intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), sepsis, mechanical ventilation, seizure, NICU admission, or neonatal death. EFWs were calculated using the Hadlock EFW formula, and EFW percentiles were assigned using the Hadlock fetal growth standard. FGR was defined as EFW <10th percentile at the time of adrenal measurement.[13] Data are reported according to STROBE guidelines for observational studies. This study was approved by our institutional review board.

Statistical Analysis

We summarized demographic characteristics of our analytical population using frequency and percentage for categorical measures, and mean for continuous measures (reported with standard deviation, or 95% confidence interval with geometric mean for log-transformed values). Two-sample t-tests on log-scale adrenal measures were used to compare measurements from neonates with and without morbidity. To determine the association between corrected transverse adrenal area (cTAA) and perinatal morbidity for fetuses with FGR, a logistic regression model was estimated from which the receiver-operator characteristics curve (ROC) curve, area under the curve (AUC) and 95% confidence interval are reported. The ideal cTAA cutoff for morbidity prediction was derived using the Youden index.[14] The diagnostic properties of the ROC-identified cTAA cutoff are reported. AUC and 95% confidence interval for each adrenal gland measurement are reported using a similar approach for EFW deciles higher than the 10th percentile as well.

Exploratory analyses included assessing whether the relationship between cTAA and morbidity differed by preeclampsia, preterm birth, neonatal sex, or antenatal corticosteroid administration. These factors were chosen for exploration because preeclampsia and preterm birth have been associated with decreased and increased adrenal size, respectively, fetal sex is known to mediate morbidity in a variety of contexts, and a differential effect of betamethasone is plausible in the presence of altered adrenal function.[15–17] Among the subset of FGR fetuses, a logistic regression model of morbidity was estimated with an interaction between cTAA and preeclampsia. This was repeated for preterm birth, neonatal sex, and antenatal corticosteroid administration.

Significance was defined as a two-sided p-value < 0.05. Tests with an AUC of 0.8 were considered to have good discriminatory value. This analysis was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS, Inc., Cary, NC). Graphics were created using GraphPad Prism version 8.0 for Windows (GraphPad Software, La Jolla California).

Results

Of the 10,038 nuMoM2b study participants, 1709 were eligible for inclusion in the current analysis (Fig. 2). Baseline cohort characteristics are described in Table 1. The rate of sonographically-diagnosed FGR was 7% (n=120), and the overall rate of composite perinatal morbidity was 14.7% (n=251). Among fetuses designated as FGR, 19 (15.8%) experienced composite perinatal morbidity. This was driven primarily by NICU admission (n=16) and RDS (n=5), as there were no cases of stillbirth, neonatal death, IVH grade III/IV, ROP, sepsis, seizures, or NEC. Among fetuses with FGR, those with EFW <5th percentile (n=6) were not more likely than those with EFW 5th-10th percentile (n=13) to experience composite morbidity (p=0.6). However, fetuses with EFW < 5th percentile did have longer NICU stays that those with EFW 5th-10th percentile (median 11 vs 5 days, p=0.04).

When analyzing all study participants irrespective of neonatal morbidity, cTAA was weakly correlated to EFW percentile (Spearman correlation coefficient = −0.1, p<0.01, Fig 3). EFW-corrected and absolute adrenal areas were similar among FGR neonates who did and did not experience composite morbidity, however (Table 2). This was unchanged when only fetuses with EFW <5th percentile were analyzed (data not shown). For our primary outcome, the cTAA did not have good discriminatory value to identify fetuses at risk of composite neonatal morbidity in FGR (AUC 0.52; 95% CI 0.38, 0.67, Fig 4). We did not calculate an AUC for adrenal volume measurements because the small number (n=41) of FGR cases among those with all three orthogonal adrenal measurements did not allow for a meaningful statistical comparison. The poor utility of the cTAA to predict morbidity in FGR did not improve when the ROC-derived cTAA cutoff of 44.3 was applied to fetuses in the other 9 fetal weight deciles (Fig. 5). None of the additional fetal adrenal ratios or parameters were better than chance at identifying fetuses at risk of composite perinatal morbidity (Table 3). Among the FGR subset, morbidity differed significantly by preterm birth, neonatal sex, antenatal corticosteroid administration, and preeclampsia, however none were significantly associated with a difference in the relationship between cTAA and morbidity.

Discussion: Summary of findings and comparison with existing data

In this analysis, we tested the hypothesis that adrenal size measured at 22–30 weeks is associated with perinatal morbidity in fetuses with FGR. Using a variety of measured adrenal parameters and calculated ratios, we found no association between adrenal gland parameters and neonatal morbidity in this cohort. There was a very weak relationship between adrenal size and EFW percentile, though this was not clinically significant given the lack of association with morbidity. These findings contrast with those of other investigators. In a convenience sample of 63 FGR and 343 normally grown fetuses, Heese et al found that FGR was associated with larger adrenal width measurements and a higher ratio of total width to medulla (the corollary to our fetal zone ratio).[10] While our study did demonstrate a weak association between adrenal size and EFW percentile, the negligible strength of the association and the lack of association of adrenal size with morbidity do not support its use in clinical practice. Our study methods were similar with respect to adrenal measurement technique, gestational age at the time of ultrasound, and the definition of FGR. However, potential reasons for the disparate findings may include differing fetal growth

standards used to define FGR or distinct study populations. In addition, we had a much larger sample size and focused on perinatal morbidity rather than growth. Though the severity of FGR in their cohort is not explicitly described, it is possible that their study population was more severely affected than ours.

Another study by Mohajeri et al compared adrenal measurements in 48 fetuses with FGR and abnormal umbilical artery (UA) Doppler pulsatility index (PI) to those of 49 healthy controls at 28–36 weeks' gestation.[9] They found that fetuses with FGR had relatively larger total and fetal zone adrenal volumes and smaller fetal zone ratios. They also found that among fetuses with FGR, those that went on to experience morbidity had smaller adrenal size than those that did not. Our study had several important methodologic differences. Their use of abnormal UA PI as an inclusion criterion for the FGR group likely selected a group at higher risk for adverse outcomes. It may be that adrenal size is only a useful predictor of morbidity in more severe cases of FGR (defined by abnormal UA Doppler studies). However, this does not explain why we found no difference in adrenal size between fetuses that did or did not go on to experience morbidity, as those experiencing morbidity presumably would have been the most severely affected FGR cases.

Strengths and Weaknesses

Strengths of our analysis include the measurement of fetal adrenal glands in a large, unselected sample during an epoch in pregnancy when fetal growth is commonly assessed. Also, we used a robust analysis of neonatal morbidity that leveraged the standardized, pre-defined, and prospective methodology of the NuMoM2b study. Clinicians managing the patients' care were blinded to the adrenal measurements on study ultrasounds, and because FGR was not part of the original hypothesis in the primary NuMoM2b adrenal study, sonographer bias in measuring adrenal size in smaller or larger fetuses is unlikely. A final strength, which accounted for the inherent limitations of FGR criteria based on fetal size, was the analysis of adrenal size across all EFW deciles. A weakness was the lack of routine umbilical artery Doppler assessments to confirm the diagnosis of FGR and stratify severity. These were only collected for clinical indications at the discretion of clinicians, and so allowed for a more heterogeneous FGR cohort. Because adrenal measurements were taken only once and potentially far in advance of delivery or FGR progression, our study cannot inform the utility of adrenal measurements when assessed serially or later in gestation to identify disease progression or deterioration of fetal status. Finally, the small number of fetuses with EFW < 5^{th} percentile limited our ability to assess those at highest risk of morbidity.

Clinical implications and future directions

We found no relationship between fetal adrenal gland size, early onset FGR and neonatal morbidity. While we cannot definitively rule out such an association given the long ultrasound to delivery interval, the high data quality conferred by a large sample size, prospective enrollment, uniform training with centralized image review support a conclusion that adrenal size is not useful to predict morbidity when FGR is diagnosed prior to 30 weeks. Also, while we only analyzed adrenal area, our findings can likely be extrapolated to adrenal

volume since it is unlikely that adaptive adrenal hypertrophy disproportionately alters adrenal depth. For the time being, the utility of fetal adrenal size to risk stratify fetuses with FGR is uncertain at best, and fetal adrenal measurements in the setting of FGR should remain experimental rather than clinical.

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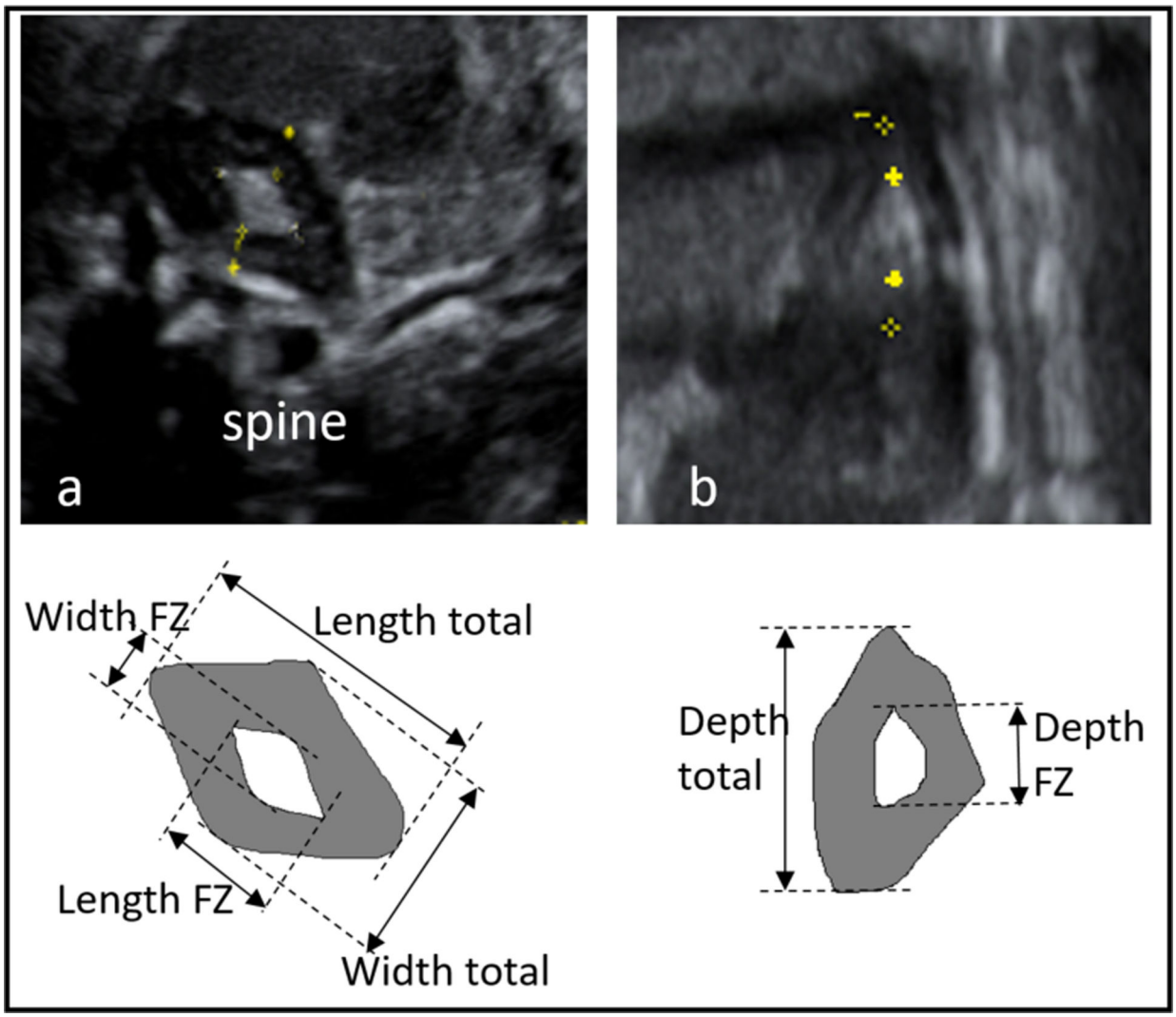
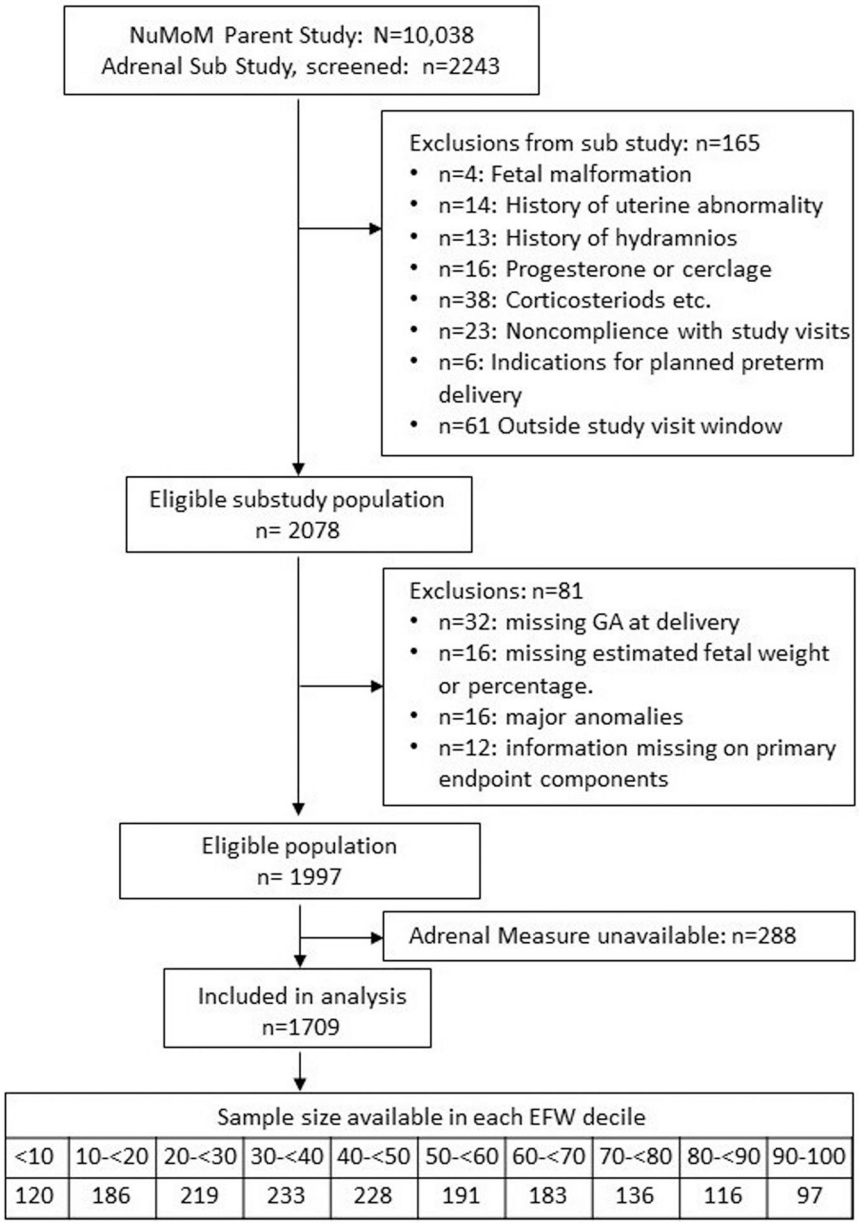


Figure 1 : Fetal adrenal measurement technique.
panel A: adrenal gland as assessed in the axial plane. Panel B: adrenal gland in the longitudinal plane. FZ, fetal zone.



Sample size available in each EFW decile									
<10	10-<20	20-<30	30-<40	40-<50	50-<60	60-<70	70-<80	80-<90	90-100
120	186	219	233	228	191	183	136	116	97

Figure 2 . CONSORT diagram of study participant inclusion.

nuMoM2b, Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be; GA, gestational age.

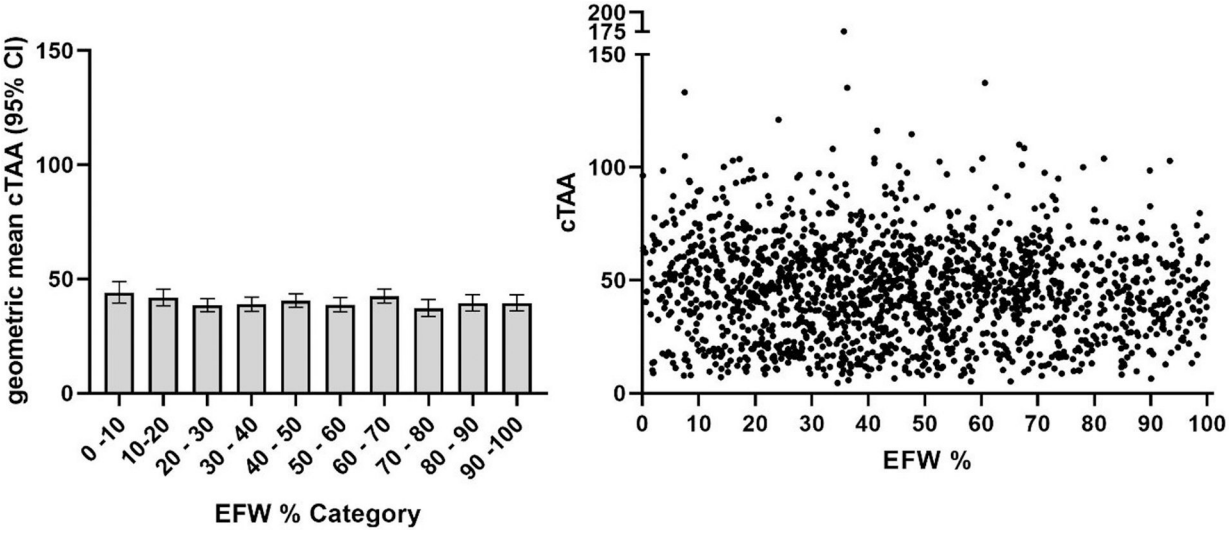


Figure 3 : cTAA according to EFW percentile.

2a: Mean cTAA across EFW deciles with 95% Cis; 2b: scatter plot of log-scale cTAA by EFW percentile (Spearman correlation (−0.1, 95%CI −0.11 to −0.02, p=0.007) the slight negative correlation is significant. cTAA, corrected transverse adrenal area; EFW, estimated fetal weight, CI, confidence interval, %, percentile.

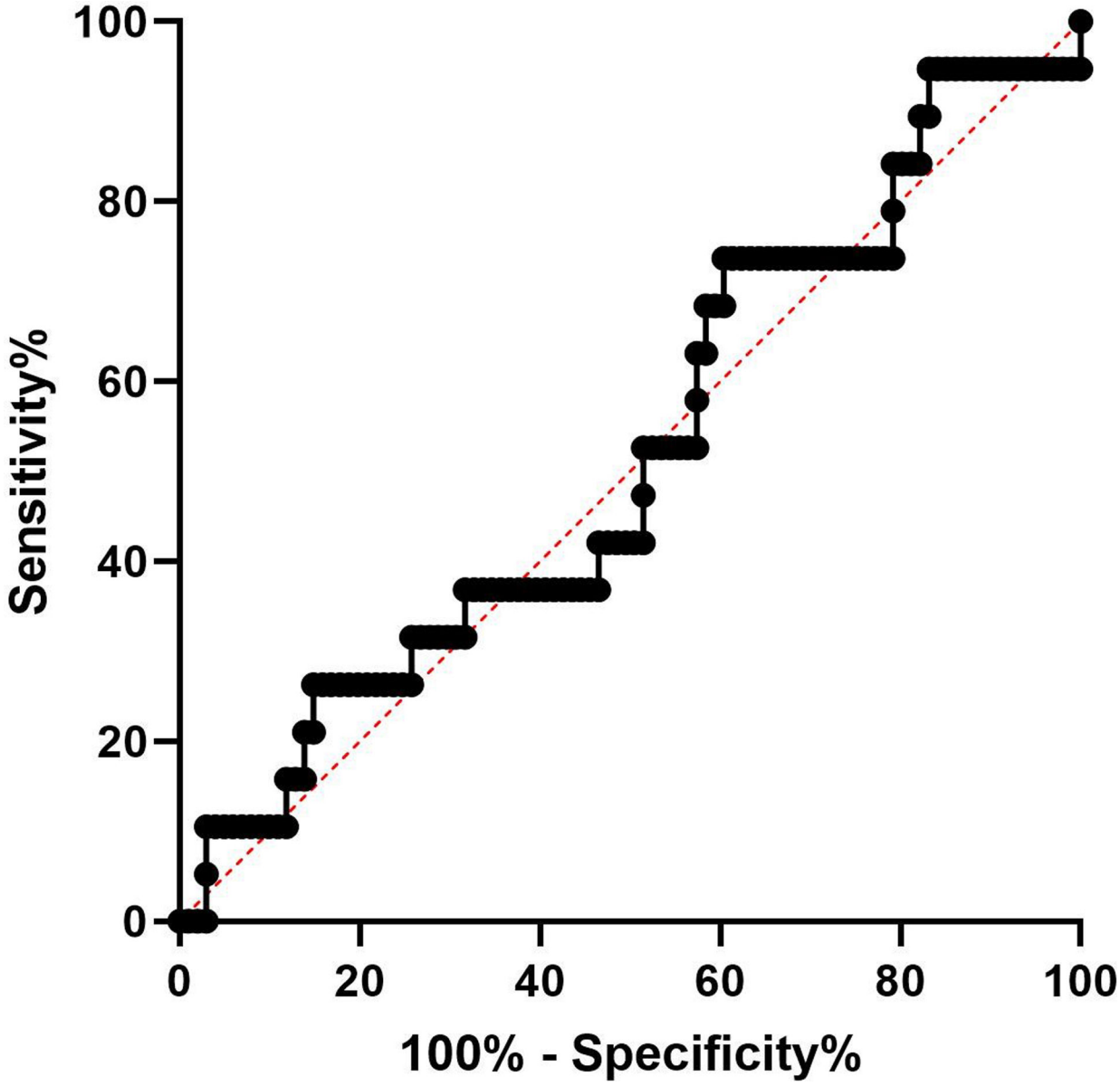


Figure 4 : Receiver-operator characteristics curve for cTAA to identify fetuses with FGR at risk of perinatal morbidity.

AUC = 0.52, 95% CI 38–67. The diagonal dashed line, or *line of equivalence*, represents an AUC of 0.5, or tests that are no better than chance at identifying the index condition. ROC, receiver-operator characteristics; cTAA, corrected transverse adrenal area; FGR, fetal growth restriction; AUC, area under the curve.

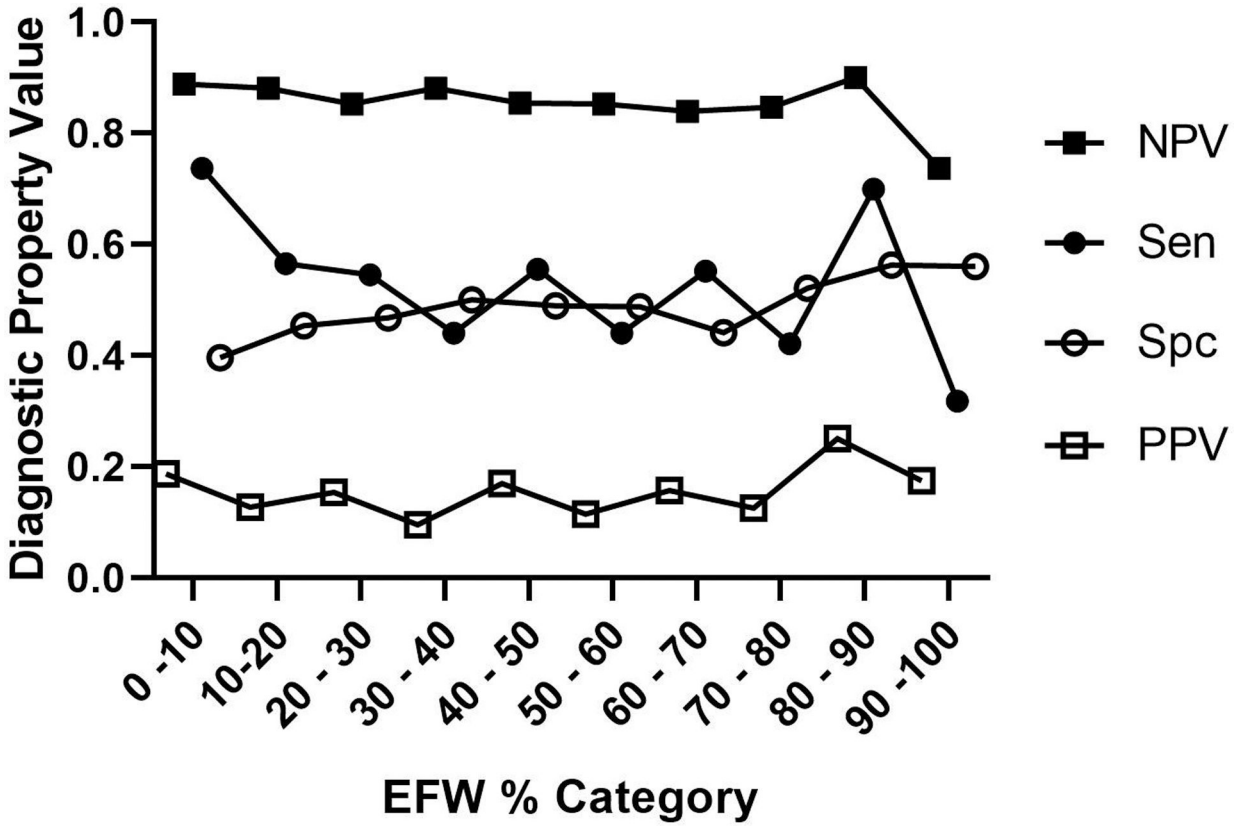


Figure 5 : Performance of the cTAA* to identify fetuses at risk of neonatal morbidity across EFW percentile deciles.

cTAA, corrected transverse adrenal area; EFW, estimated fetal weight; NPV, negative predictive value; Sen, sensitivity; Spc, specificity; PPV, positive predictive value; %, percentile. All point estimates and CIs can be provided as supplemental material.

*Using a cutoff of cTAA=44.3

Table 1.

Characteristics of participants who were excluded due to inability to complete adrenal measurements and those in whom adrenal measurements were successfully completed

Characteristic	Value	Unable to complete adrenal measurements	Adrenal measurements successfully completed	
		n = 288	< 10th percentile n = 120	≥10th percentile n = 1589
Race/ethnicity	Non-Hispanic White	156 (54.2)	55 (45.8)	918 (57.8)
	Non-Hispanic Black	30 (10.4)	22 (18.3)	188 (11.8)
	Hispanic	76 (26.4)	31 (25.8)	350 (22.0)
	Asian	5 (1.7)	8 (6.7)	79 (5.0)
	Other	21 (7.3)	4 (3.3)	54 (3.4)
Age category at Visit 1	13–17 years	2 0.7)	4 (3.3)	42 (2.6)
	18–34 years	255 (88.5)	109 (90.8)	1416 (89.1)
	35+ years	31 (10.8)	7 (5.8)	131 (8.2)
BMI at Visit 1	Geometric mean (95% CI)	27.3 (26.56, 28.05)	24.1 (23.3, 25.0)	25.2 (24.9, 25.5)
BMI category at Visit 1	Underweight: BMI< 18.5	2 (0.7)	7 (5.9)	57 (3.6)
	Normal wt: 18.5≤ BMI< 25	120 (41.8)	77 (64.7)	819 (51.9)
	Overweight: 25≤ BMI< 30	68 (23.7)	18 (15.1)	398 (25.2)
	Obese: 30≤ BMI< 35	51 (17.8)	12 (10.1)	177 (11.2)
	Morbidly obese: BMI≥ 35	46 (16.0)	5 (4.2)	128 (8.1)
Education status	Less than HS grad	19 (6.6)	15 (12.5)	135 (8.5)
	HS grad or GED	40 (13.9)	16 (13.3)	208 (13.1)
	Some college	55 (19.1)	28 (23.3)	306 (19.3)
	Assoc/Tech degree	37 (12.8)	20 (16.7)	161 (10.1)
	Completed college	75 (26.0)	22 (18.3)	427 (26.9)
	Degree work after college	62 (21.5)	19 (15.8)	352 (22.2)
Tobacco Smoke	Never	170 (59.0)	67 (55.8)	922 (58.0)
	Prior to pregnancy	94 (32.6)	39 (32.5)	569 (35.8)
	During pregnancy	24 (8.3)	14 (11.7)	98 (6.2)
Nicotine Exposure	Never	108 (37.5)	42 (35.0)	558 (35.1)
	Prior to pregnancy	66 (22.9)	17 (14.2)	359 (22.6)
	During pregnancy	114 (39.6)	61 (50.8)	672 (42.3)
Poverty category	> 200%	170 (76.9)	47 (58.0)	887 (70.1)
	100–200%	29 (13.1)	15 (18.5)	180 (14.2)
	<100%	22 (10.0)	19 (23.5)	198 (15.7)
GA at delivery	< 37 weeks	24 (8.3)	14 (11.7)	115 (7.2)
	≥ 37 weeks	264 (91.7)	106 (88.3)	1474 (92.8)
Estimated Fetal Weight	Mean (SD)	1178 (241)	952 (175)	1195 (236)
US – delivery interval (weeks)	Mean (SD)	11.3 (3.9)	11.4 (2.5)	11.5 (2.0)

Characteristic	Value	Unable to complete adrenal measurements	Adrenal measurements successfully completed	
		n = 288	< 10th percentile n = 120	≥10th percentile n = 1589
Sex of baby or fetus	Male	160 (55.6)	45 (37.5)	827 (52.2)
	Female	128 (44.4)	75 (62.5)	757 (47.8)
	Ambiguous	0 (0.0)	0 (0.0)	1 (0.1)
Eclampsia or Preeclampsia	Eclampsia or Severe PreE	16 (5.6)	4 (3.3)	55 (3.5)
	Otherwise	272 (94.4)	116 (96.7)	1531 (96.5)

NuMoM2b adrenal sub-study baseline characteristics according to inclusion in the study and FGR status. Categorical data are listed as n(%) and continuous data are listed as the (geometric) mean with 95% confidence intervals, unless otherwise specified. V1, visit 1; BMI, body mass index; HS, high school; GED, general education development; GA, gestational age; US, ultrasound; SD, standard deviation; preE, preeclampsia.

Table 2:

Mean adrenal measure by neonatal morbidity among fetuses with FGR.

Adrenal Measure	Composite neonatal morbidity = yes n=19	Composite neonatal morbidity = no n=101	P*
cTAA	46.4 (35.2, 61.3)	43.4 (38.6, 48.8)	0.649
TAA	446 (334.0, 594.2)	403 (359, 452)	0.507
cFZA	12.6 (9.4, 16.9)	13.8 (12.0, 15.9)	0.556
FZA	121 (88.1, 166.0)	128 (112, 147)	0.721
FZR	2.61 (2.2, 3.1)	2.96 (2.7, 3.2)	0.19

Comparison of adrenal measurements among neonates who did and did not experience morbidity. Data are presented as geometric means with 95% confidence intervals. cTAA, corrected transverse adrenal area; TAA, transverse adrenal area; cFZA, corrected fetal zone area; FZA, fetal zone area; FZR, fetal zone ratio.

*two-sample t-test on log-scale adrenal measure.

Table 3:

Area under the receiver-operator curve for the use of adrenal measures to identify fetuses at risk for neonatal morbidity

Adrenal Measure	AUC (95% CI)
cTAA	0.52 (0.38, 0.67)
TAA	0.54 (0.39, 0.69)
cFZA	0.58 (0.46, 0.71)
FZA	0.55 (0.41, 0.68)
FZR	0.59 (0.45, 0.72)

AUC, area under the curve; CI, confidence interval; cTAA, corrected transverse adrenal area; TAA, transverse adrenal area; cFZA, corrected fetal zone area; FZA, fetal zone area; FZR, fetal zone ratio.

An AUC > 0.5 indicates a test performs better than chance to identify the index condition. 95% CIs that include 0.5 indicate the measure does not perform better than chance.