Metabolomic Pathways Predicting Labor Dystocia by Maternal Body Mass Index

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Abstract

Objectives   The purpose of this study was to evaluate the metabolic pathways activated in the serum of African-American women during late pregnancy that predicted term labor dystocia.

Study Design   Matched case–control study ($n = 97$; 48 cases of term labor dystocia and 49 normal labor progression controls) with selection based on body mass index (BMI) at hospital admission and maternal age. Late pregnancy serum samples were analyzed using ultra-high-resolution metabolomics. Differentially expressed metabolic features and pathways between cases experiencing term labor dystocia and normal labor controls were evaluated in the total sample, among women who were obese at the time of labor (BMI ≥ 30 kg/m2), and among women who were not obese.

Results   Labor dystocia was predicted by different metabolic pathways in late pregnancy serum among obese (androgen/estrogen biosynthesis) versus nonobese African-American women (fatty acid activation, steroid hormone biosynthesis, bile acid biosynthesis, glycosphingolipid metabolism). After adjusting for maternal BMI and age in the total sample, labor dystocia was predicted by tryptophan metabolic pathways in addition to C21 steroid hormone, glycosphingolipid, and androgen/estrogen metabolism.

Conclusion   Metabolic pathways consistent with lipotoxicity, steroid hormone production, and tryptophan metabolism in late pregnancy serum were significantly associated with term labor dystocia in African-American women.

Keywords
► labor dystocia
► obesity
► mechanisms
► metabolomics
► parturition

Cesarean birth increased steadily in the United States over the past several decades across all gestational ages, maternal ages, and racial groups.[1–3] After a brief plateau from 2009 to 2016, the cesarean delivery rate rose again in 2017 to reach 32.0%.[4] Morbidity after primary cesarean and in subsequent pregnancies is increased due to wound complications, deep vein thrombosis and pulmonary embolism, bladder injury, obstet-rical hemorrhage, placenta previa/accreta, and cesarean hysterectomy.[5–7] For this reason, a key strategy identified by the Centers for Disease Control and Prevention to decrease pregnancy-related deaths is to avoid the use of cesarean delivery unless medically indicated.[8]

Cesarean deliveries are most often performed for abnormally slow labor progression, a complication known as labor

dystocia.[9,10] Expectations for labor progress are based on findings from large studies showing the median time required for changes in the uterine cervix during labor.[11,12] Secondary analyses of these studies showed that there is a dose-dependent slowing of labor with elevations in maternal body mass index (BMI); for example, a woman having her first baby who has a BMI ≥ 40 kg/m^2 may take up to 7 hours longer than a normal weight women to progress from 4 to 10 cm of cervical dilation.[13] Largely due to labor dystocia,[14] women with higher BMI ranges are at increased risk of cesarean delivery, even after accounting for the influence of parity, pregnancy complications, and hospital characteristics.[15–18]

Basic science studies examining mechanisms for slow labor progress suggest that in obese pregnant women, myometrial cells contract with reduced efficiency.[19–21] A theoretical cause of myometrial inefficiency in settings of maternal obesity is lipotoxicity, whereby storage of excess free fatty acids in nonadipose tissues and use of fatty acids instead of glucose for cellular energy requirements causes widespread cellular damage and dysfunction.[22–24] High-throughput metabolomics, the comprehensive study of the end products and pathways of metabolism, offer a new capacity for the study of labor dystocia by allowing for the simultaneous measurement of trace biomarkers from several different mechanistic pathways.[25–29] Thus, we conducted a case–control study to identify the metabolic profiles activated in the late second trimester/early third trimester serum of pregnant, African-American women who would go on to experience labor dystocia at term gestation. African-American women are nearly twice as likely as white women to be obese,[30] and 15 to 30% are more likely to have cesarean delivery.[31,32] We hypothesized that African-American women with labor dystocia would have distinct metabolic profiles in late pregnancy compared with similar women who experienced normal active labor progression, and that metabolic changes consistent with lipotoxicity would predict labor dystocia in women with obesity.

Methods

Study Design and Ethical Approvals
Women from an ongoing prospective investigation (parent study) were included in this project. We obtained IRB approval from Emory University for this work. We conducted a matched case–control study, with a planned enrollment of 62 women (31 cases, 31 controls) based on an a priori power analysis. We used the MD Anderson Microarray Sample Size tool, appropriate for metabolomics data, to estimate power. Given that metabolomics data after log transformation are observed to follow an approximately normal distribution, 27 samples per group are required to reach 90% power (assuming a standard deviation of 0.7, controlling for a fold change of 2 and false positive under 1, which is consistent with prior analyses).[33–37]

Study Participants
To select cases and comparison controls for these analyses, all participants from the parent study[38] (African-American women, age 18–45 years) were first assessed for eligibility. Women meeting inclusion criteria (term delivery [gestational age ≥ 37 0/7 weeks], nondiabetic (no gestational diabetes mellitus nor pre-existing diabetes], who completed active phase labor [4–10 cm of cervical dilation with regular contractions] with a nonanomalous singleton fetus in vertex presentation) had their medical records abstracted. Next, cases of labor dystocia and controls with normal labor progress were selected, matching individually on BMI at hospital admission (± 3 kg/m^2) and maternal age (± 5 years).

Medical chart abstractions were conducted by two experienced clinicians using a standardized chart abstraction tool to ascertain maternal demographic factors, prenatal complications, gestational age at time of delivery, and details of delivery. Maternal delivery BMI was calculated from height at first prenatal visit and weight at the time of hospital admission for term labor (or at last prenatal visit occurring at 36 weeks gestation or later, if hospital admission weight was not available). Information on cervical progress was collected from each examination during labor. Repeat rater reliability testing was performed to confirm chart abstraction accuracy, showing greater than 98.0% accuracy on 10% of the abstracted charts. Clinical data was entered into REDCap and downloaded into R Statistical Software 3.5.2 (R Foundation Vienna, Austria) for data cleaning and statistical analyses.

Active phase labor durations were calculated for each woman who had regular, progressive contractions from 4 to 10 cm dilation. The slowest labors were chosen as cases, with controls selected from among the fastest labors while matching for maternal hospital admission BMI and age. Both BMI and age were also included as covariates in multivariate analyses to control for possible confounding caused these matching factors.[39] Investigators using metabolomics have shown that obesity causes profound changes in pregnant women that are distinguishable in a variety of body fluids and tissue samples and suggest multiple ways in which obesity changes metabolism.[40,41] For this reason, we examined the within-group influence of maternal delivery BMI by creating obese and nonobese groups (BMI at hospital admission < or ≥ 30 kg/m^2) of cases and controls for metabolomics analyses. Independent risk factors for labor dystocia were either used as exclusion criteria, balanced in case–control groups, used as covariates in multivariate analyses, or not controlled in analyses if they occurred during active phase labor as part of the causal pathway (►Supplementary Table 1).[42,43]

Frequencies and percentages were calculated for categorical variables describing maternal demographic, pregnancy, and labor characteristics across case–control groups; continuous data were assessed using median and interquartile range (non-normal distribution) or mean and standard deviation (normal distributions). Mann–Whitney U test or t-tests were used for continuous data and likelihood ratio tests for categorical data. A 2-tailed α of 0.05 was used for determining statistical significance.

High-Resolution Untargeted Metabolomics
Serum samples (26–30 weeks gestation) from participants were transported on dry ice and maintained at –80°C until

analysis. Thawed samples were analyzed using high-resolution metabolomics platform, as described.[35,37,44–46] Briefly, the samples were treated with acetonitrile (2:1, v/v), spiked with internal standard mix, and centrifuged at $14{,}000\times$ g for 5 minutes at 4°C to remove proteins. Samples were maintained at 4°C in an autosampler until injection. A Thermo Scientific Q Exactive HF Quadruple-Orbitrap mass spectrometer (Thermo Fisher, San Diego, CA) was used, while an Orbitrap Fusion Tribrid mass spectrometer and an LTQ-Velos Orbitrap were used as backup as necessary. Dual chromatography (anion exchange and C18 reverse-phage columns) was used, and the coverage was enhanced by allowing positive and negative electrospray analysis of the same samples. Samples were analyzed in triplicate to improve reliable detection of low abundance metabolites. Samples were batch randomized, with case–control pairs randomized and analyzed within a single batch. For quality control purposes, six technical replicates were run at the beginning, middle, and end of each batch of 40 samples. Raw data files were extracted and aligned using apLCMS[47] and xMSanalyzer.[48] ComBat[49] was used prior to data analysis to correct for batch effects.

Metabolomics Data Extraction

The liquid chromatography mass-spectrometry (LC-MS/MS) data were processed by computational methods designed for high-resolution mass spectrometry[47,48] to extract and quantify metabolite features. The resulting data contained 16,481 ions (defined by mass to charge ratio [m/z] and retention time), which were filtered by detection quality metrics. For categorical variables, we checked for sparse cells and regrouped categories if necessary. For missing data, sensitivity analyses were performed to evaluate the impact of missing data on results, with consideration for implementing multiple imputation of missing values. All differential analyses were performed using xmsPANDA package v. 1.0.7.5.[50] The comparison between groups with or without labor dystocia produced a statistic score to rank metabolic features, according to how likely they differentiated between the two groups. Features were filtered if they were present in less than 80% across all samples or were present in less than 80% in one group, log2 transformed, and quantile normalized. Missing features were replaced with median values. We selected different metabolite features from the comparison groups using linear regression with a p-value < 0.05. Multiple hypothesis correction was performed using the Benjamini–Hochberg false discovery rate (FDR) correction method with threshold q-value of 0.20.[51] Because the goal of this study was to explore metabolic differences among women with and without labor dystocia in pregnancy for future hypothesis-testing, we also used raw p-values for visualization methods and metabolic pathway enrichment analysis.

Analyses were also conducted after adjustment for maternal BMI and age. In building multivariable models, we checked linearity assumptions for continuous predictors and considered higher-order terms as appropriate. Type 1 (-log10p vs m/z) and Type 2 (-log10p vs. retention time) Manhattan plots were created to visualize patterns of differentially expressed metabolites across all features with respect to molecular mass and chemical properties. Two-way hierarchical clustering analysis (HCA) was used to visualize relationship between women with and without labor dystocia in each group.

Metabolic Pathway Analysis

Metabolic pathways analysis was conducted with the top-ranked ($p < 0.05$) metabolite features using Mummichog 2.0 (http://mummichog.org/).[44] Mummichog combines metabolite identification and metabolic pathway/network analysis. Significant metabolic patterns, even if not represented by conventional pathways, can be identified by Mummichog as clustered metabolic reactions. Pathway enrichment analysis thereby provides a two-step approach, which protects against both type I and type II errors.[52] By this analysis, we identified distinct metabolic profiles/networks that were associated with labor dystocia at raw $p < 0.05$.[29,53–55] Metabolic pathway enrichment analyses were conducted on all samples with adjustment for maternal BMI and age, then again within obese and nonobese groups. Significant metabolic pathways with a minimum overlap size of 4 (e.g., number of metabolites with significant discrimination between cases and controls within a particular metabolic pathway) were evaluated for further analyses.

Results

A total of 287 medical record abstractions were completed. After excluding women who did not meet inclusion criteria or were missing key information on delivery BMI or cervical progress, a total of 165 labors remained. From these, 48 cases of labor dystocia and 49 normal labor progression controls were selected, matching on BMI at hospital admission and maternal age. Maternal demographic, pregnancy/labor characteristics, and labor outcome variables were similar between cases and controls ($p > 0.05$) within the obese and nonobese groups, with the exception of epidural anesthesia (higher in nonobese cases) (►**Table 1**). Median active phase labor duration (4–10 cm) was 10.9 hours in cases and 1.9 hours in controls across all maternal BMIs.

After quality filtering, a total of 8,792/16,481 (53.3%) of detected ions (defined by m/z and retention time) were identified in mass spectral data from LC-MS/MS analysis of serum from participants for further analyses. Metabolic features that differentiated between labor dystocia cases and controls were selected in subgroups of obese women (140 features) and nonobese women (109 features) from the total sample. Using two-way HCA with these features, we observed separation between cases and controls that was also visible among significant features using principal components analysis (►**Fig. 1**, Ai-ii and Bi-ii). No individual metabolites were significant by FDR q-value of 0.20.

Next, we examined metabolic pathways enriched in cases of labor dystocia within (a) the entire sample, (b) obese women, and (c) nonobese women (►**Fig. 1**, A-iii and B-iii and ►**Table 2**). Using the pathway enrichment program Mummichog, we determined which of the m/z ions differing at raw $p < 0.05$ were also enriched in specific metabolic pathways after adjusting for the influence of maternal BMI

Table 1 Maternal demographic, pregnancy and labor characteristics, and labor outcomes by comparison groups

	Total sample (n = 97)	Labor dystocia case		Normal labor progression control		p-Value difference between cases and controls	
		BMI < 30 kg/m² (n = 19)	BMI ≥ 30 kg/m² (n = 29)	BMI < 30 kg/m² (n = 20)	BMI ≥ 30 kg/m² (n = 29)	Nonobese[a]	Obese[b]
Maternal demographic							
Race: African-American (n, %)	97 (100)	19 (100)		20 (100)		1	1
Insurance status (n, %)						0.49	0.17
Private	19 (19.6)	2 (10.5)	8 (27.6)	4 (20.0)	5 (17.2)		
Medicaid	78 (80.4)	17 (89.5)	21 (72.4)	16 (80.0)	24 (82.8)		
Maternal age (years, median ± IQR)	24.0 (7)	22.0 (3)	25.0 (10)	24.0 (6)	25.0 (8)	0.27	0.43
Pregnancy characteristics							
Prepregnancy BMI (kg/m², median ± IQR)	28.3 (11.4)	21.9 (5.2)	31.7 (11.7)	22.7 (2.9)	33.7 (8.6)	0.80	0.93
Gestational weight gain (kg, median ± IQR)	11.3 (8.8)	10.4 (7.7)	14.0 (14.0)	10.5 (6.3)	9.5 (9.6)	0.71	0.70
Delivery BMI (kg/m², median ± IQR)	32.6 (10.3)	26.9 (4.7)	36.7 (10.1)	26.7 (2.6)	37.0 (7.5)	0.95	0.35
Parity (n, %)						0.62	0.43
Nulliparous	47 (48.5)	8 (42.1)	16 (55.2)	10 (50.0)	13 (44.8)		
Multiparous	50 (51.5)	11 (57.9)	13 (44.8)	10 (50.0)	16 (55.2)		
Labor characteristics							
Gestational age at labor admission (weeks, days, median ± IQR)	39.2 (1.9)	38.6 (2.0)	39.4 (1.4)	38.6 (1.6)	39.3 (2.0)	0.67	0.59
Mode of labor onset (n, %)						0.64	1
Induced labor	42 (43.3)	5 (26.3)	16 (55.2)	5 (25.0)	16 (55.2)		
Spontaneous labor	55 (56.7)	14 (78.7)	13 (44.8)	15 (75.0)	13 (44.8)		
Cervical ripening in labor (n, %)	29 (29.9)	2 (10.5)	12 (41.4)	5 (25.0)	10 (34.5)	0.23	0.59
Synthetic oxytocin in labor (n, %)	59 (60.8)	11 (57.9)	23 (82.1)	9 (45.0)	16 (55.2)	0.42	**0.03**
Type of membrane rupture (n, %)[c]						0.27	0.16
Spontaneous	47 (48.5)	9 (47.4)	9 (31.0)	14 (70.0)	15 (51.7)		
Artificial	49 (50.5)	10 (52.6)	19 (65.5)	6 (30.0)	14 (48.3)		
Epidural in labor (n, %)	73 (75.3)	16 (84.2)	25 (86.2)	11 (55.0)	21 (72.4)	**0.04**	0.19
Active labor duration (hours, median ± IQR)	6.5 (8.9)	8.25 (6.8)	11.4 (4.9)	1.35 (2.0)	2.5 (2.3)	**<0.001**	**<0.001**
Labor outcomes							
Type of delivery (n, %)						0.08	0.09
Spontaneous vaginal	84 (86.6)	17 (89.5)	23 (79.3)	20 (100)	24 (82.8)		
Vacuum-assisted vaginal	11 (11.3)	2 (10.5)	4 (13.8)	0	5 (17.2)		
Cesarean	2 (2.1)	0	2 (6.9)	0	0		
Postpartum hemorrhage (>500 mL, n %)	6 (6.2)	0	4 (13.8)	0	2 (6.9)	–	0.38
Newborn gender (n, %)						0.87	1
Male	50 (51.5)	10 (52.6)	15 (51.7)	10 (50)	15 (51.7)		
Female	47 (48.5)	9 (47.4)	14 (48.3)	10 (50)	14 (48.3)		
Newborn NICU admission (n, %)	5 (5.3)	0	2 (6.9)	2 (10.5)	1 (3.6)	0.09	0.57
Neonatal birthweight (grams, mean ± SD)	3119.3 (394.4)	2965 (571.0)	3060.0 (533.0)	3070.0 (446.5)	3175.0 (465.0)	0.83	0.42

Abbreviations: BMI, body mass index; IQR, interquartile range; NICU, neonatal intensive care unit; SD, standard deviation.

[a,b]p-Value for comparison of cases and controls within nonobese[a] and obese[b] groups. Likelihood ratio significance testing for categorical variables and Mann–Whitney U test used for continuous variables. p-Values < 0.05 are shown in bold font.

[c]One case of "uncertain" method for rupture of membranes in labor dystocia case in obese group.

Obese Women

Non-Obese Women
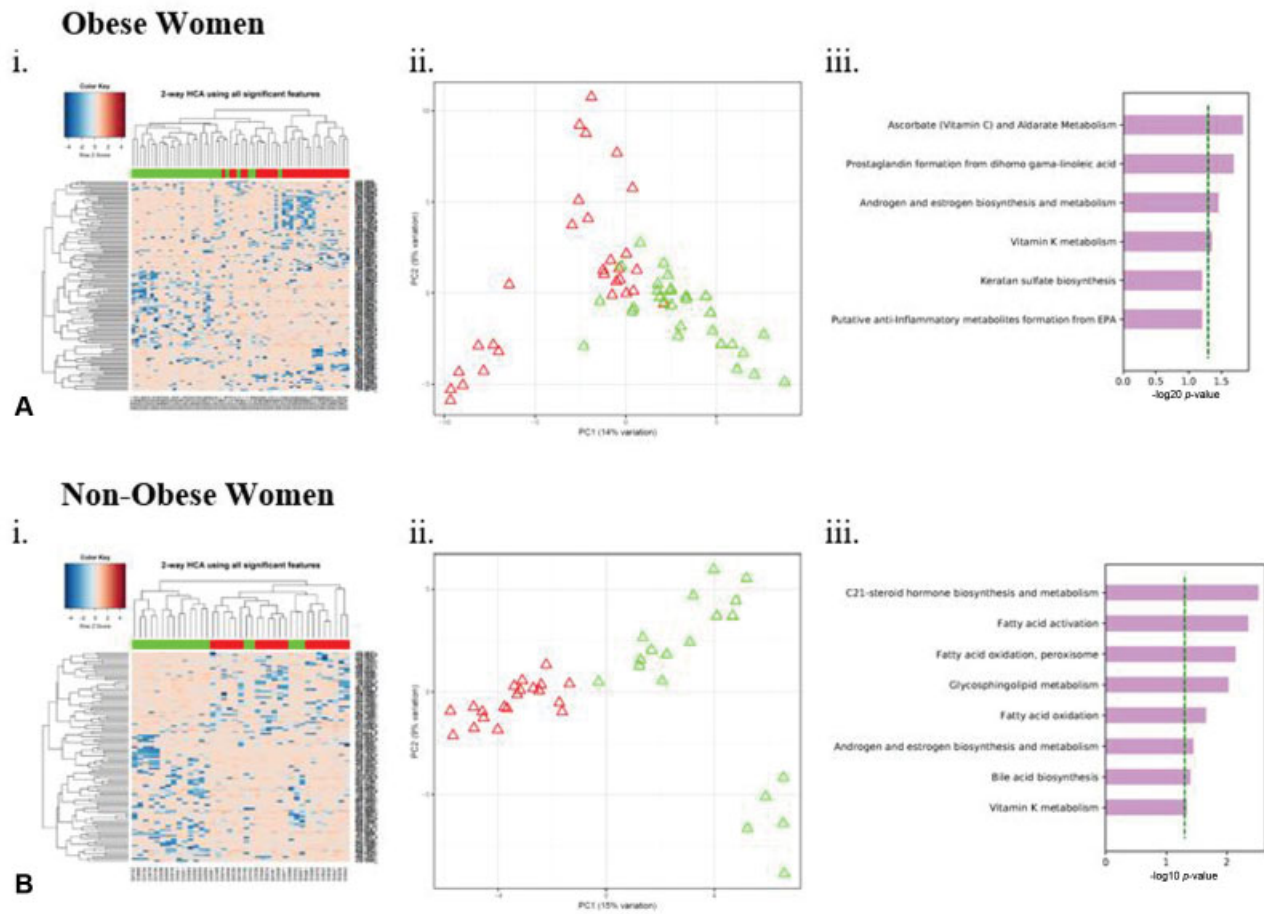
Fig. 1 Two-way hierarchical cluster analysis (HCA) (i), principal components analysis (PCA) (ii), and metabolic pathway analysis (iii) showing metabolites and metabolic pathways differentially expressed between women with labor dystocia and normal labor controls among (A) obese and (B) nonobese women caption: Each column in HCA represents a participant and each row represents a metabolite feature. Red hues indicate metabolites with enhanced levels, and blue hues represent metabolites with lower metabolite concentrations. Labor dystocia is represented in green and normal labor in red across x-axis. Red triangles in PCA represent normal labor and green triangles represent labor dystocia. (A) Obese women, (i) HCA with top 140/8813 metabolites with a raw $p < 0.05$ is shown and (ii) PCA and (iii) Mummichog enriched metabolic pathways differentiating labor dystocia in matched groups (B) Nonobese women, (i) HCA with top 109/8704 metabolites with a raw $p < 0.05$ is shown and (ii) PCA and (iii) Mummichog enriched metabolic pathways differentiating labor dystocia in matched groups of (A) obese and (B) nonobese women shown with dotted green line represents pathways significant at $p < 0.05$. Metabolic pathway analyses include adjustment within each group for maternal body mass index (continuous, at hospital admission for labor) and maternal age.

Table 2 Metabolite pathways significantly dysregulated in labor dystocia in multivariate analyses

Pathways	Total sample			BMI < 30 kg/m^2			BMI ≥ 30 kg/m^2		
	Overlap size	Pathway size	*p*-Value	Overlap Size	Pathway size	*p*-Value	Overlap Size	Pathways size	*p*-Value
C21-steroid hormone biosynthesis and metabolism	11	64	0.001	9	60	0.003			
Glycosphingolipid metabolism	5	30	0.017	5	30	0.010			
Tryptophan metabolism	7	53	0.021						
Fatty acid activation				6	33	0.005			
Androgen and estrogen biosynthesis and metabolism	6	45	0.028	5	42	0.036	5	45	0.035
Bile acid biosynthesis				4	31	0.041			

Abbreviations: BMI, body mass index; C21, 21 carbon.
Significant metabolite pathways predicting labor dystocia shown for total sample and in subgroups defined by maternal obesity using raw *p*-value multivariate analysis with adjustment within each group for maternal BMI (continuous, at hospital admission for labor) and maternal age. Pathways with an overlap size of at least 4 are shown (i.e., pathway included at least 4 metabolites that significantly differentiated the case–control groups).

and age. Across all three comparison groups, cases of labor dystocia differed from normal labor controls in androgen and estrogen biosynthesis pathway metabolites (total sample, $p = 0.028$, overlap size 6 of 45; nonobese women, $p = 0.036$, overlap size 5 of 42; obese women, $p = 0.035$, overlap size 5 of 45).

Among women in the nonobese group, C21-steroid hormone biosynthesis and metabolism pathway metabolites significantly differentiated labor dystocia cases and controls. This metabolic pathway also differentiated women with labor dystocia in the total sample after adjusting for the influence of maternal BMI and age, but did not differentiate women in the obese group who experienced labor dystocia. As measured in the untargeted LC-MS/MS, serum levels of metabolites in the C21-steroid pathway were lower among women who went on to experience labor dystocia compared with control samples.

Similar to the C21-steroid pathway findings, glycosphingolipid pathway metabolites were also overrepresented among the features discriminating women with labor dystocia from controls in both the total sample and nonobese group, but not the obese group (►Table 2). By contrast, only women in the nonobese group with labor dystocia were differentiated from normal labor controls by metabolites mapped to the bile acid biosynthesis and fatty acid activation pathways. Among m/z features linked to the bile acid biosynthesis and fatty acid activation pathways, all were relatively higher in serum from women with normal labor progression, compared with nonobese women who experienced labor dystocia (0.23–3.59-fold increase in controls vs. cases, $p = 0.04$–0.47). Neither of these pathways differentiated labor dystocia case–controls in the obese group nor in the total sample once maternal BMI and age were included in multivariate models.

When the influence of maternal BMI and age was held constant, tryptophan metabolism significantly differentiated labor dystocia cases and controls across all women (►Table 2). Among metabolites tentatively matched from this pathway to untargeted LC-MS/MS ions, women with normal labor progression had relatively higher circulating serum levels than women with labor dystocia (1.32–2.28-fold increase in controls vs. cases, $p = 0.03$–0.004).

Discussion

In this case–control study, we present evidence that labor dystocia was predicted by different metabolic pathways in late second/early third trimester serum among obese versus nonobese African-American women, and only androgen and estrogen biosynthesis pathway metabolites predicted labor dystocia across both obese and nonobese groups. A range of factors can slow labor progress, thereby increasing women's risk for unplanned cesarean birth. However, there is growing recognition that in some women, there is a phenotype of labor dystocia that complicates the labor process and can worsen labor outcomes.[17,24] Maternal BMI above normal ranges appears to be one part of this labor dystocia phenotype, as evidenced by clinical investigations showing increases in labor length[13,56] and risk for cesarean delivery[57] among women

with higher BMIs. However, labor dystocia is not confined to obese women.[21,38,39] Additionally, not all pregnant women with obesity go on to experience labor dystocia and cesarean birth.[58] Thus, there is a need to identify biomarkers of labor dystocia.[12]

Sex hormone metabolism was associated in this study with labor dystocia in both the obese and nonobese groups, and in the total sample after adjustment for maternal age and BMI. We repeated metabolomics analyses while adjusting for fetal gender, but saw no difference in associations between labor dystocia and sex hormone metabolism pathways (analyses not shown). In other investigations, women with obesity were noted to have increased levels of estrogen and testosterone both within[59] and outside of pregnancy.[60] In addition, lower serum levels of estrogen and progesterone[61] and single nucleotide polymorphisms of sex hormone-related genes[62] were associated with preeclampsia in two recent investigations. We did not locate published studies reporting links between sex hormone metabolites and labor dystocia. However, given close links between maternal obesity and both hypercholesterolemia[63] and preeclampsia,[64] further research with targeted measures of specific sex and steroid hormones in women with active labor slowing is warranted.

Contrary to our prediction that metabolic changes consistent with lipotoxicity would predict labor dystocia in women with obesity, we found more evidence for associations between lipotoxicity and labor dystocia among *nonobese* women in our sample. Both fatty acid activation and glycosphingolipid metabolism pathways were increased in nonobese women who had fast active labor progression (controls). These observations hint that more efficient mobilization of lipids from the diet and adipose tissue for use by energy-requiring tissues may protect pregnant women from cellular damage and dysregulation associated with lipotoxicity, thereby leading to faster labor progression. We also observed decreases in C21-steroid hormone metabolites among nonobese women who went on to experience labor dystocia. The C21 steroid hormone metabolic pathway involves production of both progestins and adrenal corticosteroids, and is closely related to the C-19 and C-18 pathways, which produce androgens and estrogens, respectively.[65]

There is evidence from mouse and human models that increased fatty acid oxidation decreases systemic free fatty acid and dyslipidemia[66,67]—both landmarks of lipotoxicity. In addition, glycosphingolipid metabolism—the other pathway associated with labor dystocia among nonobese women in this study—is also related to lipotoxicity. Glycosphingolipids are a group of bioactive glycolipids that are involved in signal transduction, cholesterol lipid rafts, and cellular communication.[68] Our observation of relatively lower levels of metabolites tentatively mapped to glycosphingolipid metabolism in nonobese women with labor dystocia is interesting, given evidence that cholesterol lipid rafts may be involved with an unstable, asynchronous uterine contractile pattern in a mouse model.[69] Myometrial lipotoxicity involving accumulation of lipids and reduction in muscle mass in uterine tissue from obese pregnant women were recently demonstrated by Gam et al.[22] Building on these findings, we theorize that labor dystocia

cases among nonobese women in our investigation were more likely than normal-labor comparison subjects to have lipotoxicity-related changes in their uterus that ultimately slowed their labor progression. For example, as a result of problems with fatty acid oxidation, their myometrial tissue may have accumulated lipid deposits, thereby reducing contractile force and frequency during labor and slowing cervical dilation. In addition, glycosphingolipid metabolite alterations may have decreased these women's capacity to maintain a stable, synchronous uterine contractile pattern—thereby further impeding labor progress.

As mentioned above, we did not find evidence for associations between lipotoxicity and labor dystocia among *obese* women in our sample. It is possible that lipotoxicity may be a more important differentiator of the labor dystocia phenotype among women who are not yet obese, but show evidence of less effective metabolism of fats. It is not known how circulating levels of metabolites from the glycosphingolipid or fatty acid activation pathways in obese women compared with nonobese women in our sample, as no *m/z* features from these pathways were also annotated at a high confidence level. However, lower fatty acid oxidation and lipid accumulation have been correlated with higher maternal BMIs in umbilical stem cells of neonates born to obese versus normal weight women.[70] These data suggest that reduced lipid oxidation during pregnancy is an important facet of obesity-related changes in the maternal–fetal pair. It is possible that perturbed fatty acid activation and glycosphingolipid pathways were therefore present in most or all of the women from our sample of obese women, thereby reducing heterogeneity of these pathways for the purposes of our metabolic pathway analysis. Future targeted metabolomics investigations are needed to quantify levels of metabolites involved in lipotoxicity among women of different BMIs and compare lipotoxicity metabolite exposure to labor durations.

Also supported in the literature was our unexpected finding of relatively higher levels of features linked to the tryptophan metabolism pathway in women with normal labor progress after adjustment for the influence of maternal BMI and age. The tryptophan metabolic pathway is important during pregnancy for fetal development, neuronal protection, and serotonin signaling.[71] Serotonin signaling deficiencies may be linked to depression or anxiety in pregnancy, and both maternal trauma history[72] and prenatal depression and anxiety[73–75] were associated with labor dysfunction in previous clinical investigations. In addition, serotonin stimulates uterine smooth muscle contractions in pregnant women.[76] Thus, relative upregulation of tryptophan metabolism in women with normal labor progress could suggest possible links between maternal mood, uterine contractility, and labor duration. However, further investigation is needed to target metabolites of the tryptophan metabolic pathway, including serotonin, in pregnant women who experience labor dystocia and other difficulties of parturition.

The application of metabolomics to understand pregnancy risks is still a young field. In 2009, the first review on this topic was published based on limited data.[77] Since then, emerging studies demonstrate the promising possibilities of this technology in the complex field of pregnancy where a mother–baby pair are interacting for mutual benefit.[78–82] Most recently, metabolomics was used to identify specific metabolites that were predictive of women's eventual development of preeclampsia[83,84] and of their neonate's level of adiposity.[85]

Metabolomics is also useful for understanding labor processes. Several teams of investigators differentiated between women in different phases of labor using metabolomics.[86,87] As mentioned, metabolic profiles can be generated from a variety of biological fluids; this methodologic advantage was recently utilized to demonstrate biomarkers present in amniotic fluid and maternal serum collected during women's second trimester that predicted later preterm delivery.[88] Metabolomics has also been used to identify biomarkers produced in mice uterine tissue following pharmacologic stimulation versus inhibition of contractions, revealing new detail on the mechanisms of uterine contractility in rodents.[89]

Our study has several strengths. First, potential differences in labor duration that could potentially be caused by differences in labor management were offset in this study by our focus on participants who were managed by the same team of physicians and midwives following the same protocols across two hospitals.[42] Another strength of this study is our careful consideration of variables known to associate with the duration of labor in our choice of inclusion/exclusion criteria, case–control group assignment, and statistical covariates. A range of factors can affect labor progress, including maternal age,[90] BMI,[13] maternal parity,[11] and mode of labor onset.[91] In this study, we adjusted for the influence of maternal age, and matched cases with controls on mode of labor onset and BMI. In bivariate comparisons, we saw no difference after controlling for the above-mentioned factors in maternal parity. An additional strength was our use of high-resolution LC-MS/MS combined with powerful analytic tools to provide broad coverage of both low- and high-abundance metabolites that are potentially relevant to labor dystocia pathophysiology.

Our study also has several limitations. First, the retrospective nature of this analysis means that we cannot differentiate between cause and effect, but only on associations between metabolic pathways present in late pregnancy serum and term labor dystocia. Second, although our sample size exceeded a priori calculations, larger numbers of participants—especially in the nonobese group—would strengthen these analyses. In addition, our metabolomics samples were collected in the late second/early third trimester of pregnancy. Future investigations might better capture the metabolic signature of a labor dystocia phenotype by also including a first trimester sample and a late third trimester sample. With these repeated measures, a longitudinal analysis might be conducted where intraindividual might be filtered out, leaving a clearer signal for significant *m/z* features and metabolic pathways distinguishing women with labor progression difficulty. We were also not able to consider whether the timing of late-pregnancy serum influenced the strength of metabolic signals in this analysis due to small sample size. Future longitudinal analysis with larger groups of samples would allow us to consider how metabolic levels in these critical pathways might vary across pregnancy. In our analyses of individual metabolites, we were unable to correct for multiple comparisons, as no metabolite

reached the FDR *q*-value < 0.20. Possibly, in a future analysis involving longitudinal measures or standardization in sample collection by time of day and dietary intake, this threshold would be reached. However, our use of metabolic pathway analysis using features significant at raw *p*-value provides a 2 step approach that protects against both type I and type II errors while revealing networks of perturbed metabolites.[52] This approach allowed us to explore metabolic differences among women with and without labor dystocia in pregnancy for future hypothesis-testing using targeted metabolomics approaches while employing orthogonal methods to confirm findings. Finally, our study is limited by our inclusion of only one race of women for all analyses. However, given the disparities experienced by African-American women in rates of cesarean delivery[92] and maternal morbidity/mortality[93,94] and the benefits of looking intrarace for differences in high-throughput methodologies like metabolomics,[95] this study's focus on one race is a logical choice. Metabolic pathways associated with labor dystocia in African-American women from this study should be further investigated in future studies that might include samples with a range of maternal races, standardization in sample collection by time of day and dietary intake, and targeted analysis of associated metabolites.

We need new approaches to improve birth outcomes in women with a labor dystocia phenotype.[58,96,97] As a methodology that covers the spectrum from hypothesis development to hypothesis testing, metabolomics offers investigators the ability to quantify multiple metabolites in a single sample and flexibility in the type and amount of sample required for analyses. Thus, metabolomics offers considerable promise in the investigation of mechanisms contributing to labor dystocia among women of different race/ethnicities, with or without obesity. With a fuller understanding of the unique metabolic mechanisms contributing to labor dystocia, we step closer to breaking the cascade of health complications resulting from poor labor outcomes.

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