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Maternal and Cord Blood Acylcarnitine Levels and Preterm Birth

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Abstract

The objective of the present study is to determine the relationship between maternal and cord blood acylcarnitine levels and preterm birth. A retrospective cohort study was completed in Tucuman province, Argentina, consisting of 150 preterm (23 to 36 weeks) and 150 term (39 to 40 weeks) mother/infant dyads. Free carnitine and acylcarnitines were measured by tandem mass spectrometry. The relationship between preterm birth and acylcarnitine profile was assessed by univariate and multiple logistic regressions. Maternal and cord blood metabolites were compared using linear regression. Relationship between maternal and cord blood metabolite levels, as well as the ability of metabolite levels to discriminate between preterm and term birth, were analyzed. Univariate logistic regression performed on maternal and cord blood metabolite levels revealed marginally significant changes in acylcarnitines, with distinct patterns in term vs preterm infants. Linear regression revealed correlation between maternal and cord blood metabolite levels within the cohort as a whole, as well as the infants stratified by term and preterm status. Logistic regression was used to model preterm birth status by maternal, cord blood and a combination of maternal/cord metabolite levels. The combination model discriminated between preterm and term birth with an area under the curve of 0.751. Acylcarnitine values vary significantly between the term and preterm infant. Preterm birth status was modeled successfully by a combination of maternal and infant metabolite values. Specific maternal metabolites may stratify preterm vs term status. The ability of maternal whole blood metabolite data to delineate term vs preterm status bears further investigation.

Keywords: Preterm Birth; Acylcarnitine values; maternal/cord metabolite levels

Introduction

In the United States, early ultrasound dating coupled with last menstrual period remains gold standard for gestational age (GA) estimation[1]. In countries with limited access to prenatal care, birthweight and/or examinations of physical characteristics are commonly used to determine GA[2]. Imprecision in estimates of GA and difficulty in differentiating preterm status from small for gestational age infants are particularly burdensome in low and middle income countries (LMIC), where ultrasound services are often unavailable for accurate gestational dating of pregnancies[3]. In order to appropriately allocate resources, it is important to delineate the burden of preterm birth in candidate LMIC. Recently, our group and others have provided models for estimating GA at birth by evaluating newborn metabolic profiles[4-7]. We have shown that newborn metabolic profile, as detected by routine newborn screening, accurately predicted GA to the same degree as birth weight alone and to a better degree than birth weight alone in small for GA neonates[5]. Identified metabolic differences between term and preterm infants may be attributed in

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part to their differential degree of illness[8], renal[9] and hepatic[10] maturity, and use of parenteral nutrition[11,12], all of which may contribute to differential uptake and detoxification of nutrients. As newborn metabolite profile can be readily obtained from cord blood, urine, serum, dried blood spot, and even blood from the infant's mother, it may be of use in low-resource settings. Utilizing banked blood specimens may be particularly relevant for accurately estimating the burden of preterm birth in LMIC.

Previous studies of GA estimation with metabolites have focused on large populations in developed countries using metabolites measured at 24-72 hours of life[4,5,7]. Few studies have assessed the association between maternal and cord blood metabolite levels and preterm birth status within a low-resource setting. This study was conducted to determine the relationship between maternal and cord blood acylcarnitine levels and preterm birth within a cohort of Argentinian women.

Material and methods

We conducted a retrospective analysis of mother-infant dyads delivered at Maternity Institute *Nuestra Senora de las Mercedes* in Tucuman province, northwestern Argentina, between 2005 and 2015. All mothers who presented in labor were approached for study entry. Blood samples were collected at delivery from consenting individuals and paired with infant cord blood samples. Paired maternal and cord blood samples were selected for 150 preterm deliveries (<37 completed weeks gestation) and 150 term deliveries (39-40 weeks). All selected mother-infant dyads were singleton pregnancies not affected by maternal diabetes. When available, GA was determined by prenatal ultrasound (n=31). GA was otherwise determined by postnatal physical examination (n=269).

Maternal blood was drawn in the delivery room, following delivery of the infant. Banked frozen maternal and cord blood stored at -80C was thawed at room temperature and spotted on Whatman 903 filter paper and dried at room temperature. Free carnitine and 31 acylcarnitines were measured by tandem mass spectrometry at the State Hygienic Laboratory (University of Iowa). Tandem mass spectrometry is performed with Waters Quattro Micro triple quadrupole tandem mass spectrometers, equipped with an electrospray ionization source operated in the positive ion mode. Screening procedures in Iowa are based on previously established methodology[13,14]. All cord blood carnitine and acylcarnitine levels were within the ranges previously shown within an Iowa cohort (data not shown), using the same procedures as described above. Amino acids were also measured; however, levels of these metabolites were 11 times higher, on average, for the Argentina samples than previously measured Iowa samples. This could be due to sample storage and handling procedure differences. It is well established that some metabolites can be sensitive to storage and handling procedures[15,16]. All amino acids were therefore excluded from analysis.

Statistical Analysis: Demographic and clinical characteristics of the study population were compared between preterm and term deliveries using Fisher's exact tests for dichotomous and categorical exposures and Wilcoxon-Mann-Whitney non-parametric tests for continuous exposures. All metabolite values were natural log transformed to account for the non-normality. Normality of the transformed variables was assessed visually using histograms and QQ-plots.

Maternal and cord blood metabolite measurements were compared between preterm and term deliveries using univariate logistic regression. Related odds ratios were computed along with their 95% confidence intervals.

We performed multiple logistic regressions modeling with preterm birth status as the outcome measure, using log-transformed metabolites that were significant in the univariate analysis. Three separate models were built using maternal metabolite measurements only, cord blood metabolite measurements only, and a combination of maternal and cord blood metabolite measurements. We evaluated the performance of our models using Receiver Operator Characteristic (ROC) curves and corresponding Area under the curve (AUC). ROC curves were compared using the DeLong, DeLong, and Clarke-Pearson method[17]. Sensitivity and specificity were calculated for each model.

The association between maternal and cord blood metabolite measurements were evaluated using general linear regression. P-values and coefficients of determination (R^2) were presented for each regression model within the total population and preterm/term subgroups separately. Bonferroni correction was applied to correct for number of analyses performed. Statistical analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC). Methods and protocols for this study were approved by the University of Iowa Institutional Review Board.

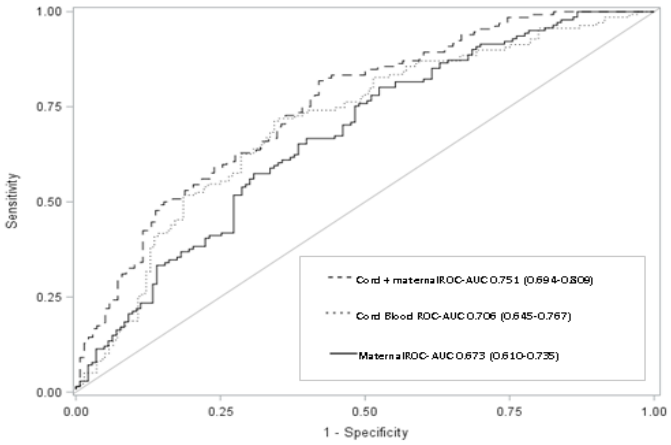

Figure 1: Preterm birth predicted best by model employing both maternal and cord blood metabolite levels

Results

Cord blood and maternal samples were analyzed for 150 preterm and 150 term mother-infant dyads. Demographic information for the cohort is presented in table 1. Preterm infant GA ranged from 23-36 weeks (median 34 weeks), while term infant GA ranged from 39-40 weeks (median 40 weeks). Median birthweight in the preterm group was 1900 g, and 3478 g in the term group. Preterm infants were more often born via vaginal delivery than their term counterparts.

Table 1: Demographic and clinical characteristics of study population.

Characteristic	Total Population (n=300)	Preterm (n=150)	Term (n=150)	p-value
Gestational age (weeks)	36.3 ± 3.9	33.1 ± 2.9	39.6 ± 0.5	<0.001*
Sex‡				0.382
Male	167 (55.7)	88 (58.7)	79 (52.7)	
Female	131 (43.7)	62 (41.3)	69 (46.0)	
Unknown	1 (0.3)	0 (0)	1 (0.7)	
Birth Weight (g)	2691. ± 9478	1903 ± 594	3507 ± 388	<0.001*
Delivery mode‡				1.000
Cesarean Section	12 (4.0)	8 (5.3)	4 (2.7)	
Vaginal	162 (54.0)	109 (72.7)	53 (35.3)	
PPROM‡				<0.001*
Yes	83 (27.7)	83 (55.3)	0 (0)	
No	47 (15.7)	15 (10.0)	32 (21.3)	

g= grams; cm= centimeters; PPROM= preterm premature rupture of membranes
‡Data are expressed as N (%). All other data are expressed as mean ± SD.
*Statistically significant at $\alpha<0.05$.

Maternal and cord blood metabolite measurements were compared by univariate logistic regression in term and preterm infants (Table 2). No significant differences were found based upon the Bonferroni corrected alpha level of 0.0016. However, marginally significant differences ($0.0016 < \alpha < 0.05$) in maternal blood metabolite levels were observed for free carnitine, the short chain acylcarnitine C3, the medium chain acylcarnitines C6-DC and C8:1, and the long chain acylcarnitine C12. Marginally significant differences were observed in cord blood levels of the short chain acylcarnitines C4, C4-DC, C4-OH, C5, and C5:1, C5-DC, and the medium chain acylcarnitine C6-DC.

Table 2: Comparison of term and preterm metabolite levels within maternal and cord blood samples.

Metabolite (µmol/L)	Maternal			Cord		
	Term Median (IQR)	Preterm Median (IQR)	OR (95% CI)	Term Median (IQR)	Preterm Median (IQR)	OR (95% CI)
C0	19.435 (16.270-22.320)	21.010 (17.090-26.830)	3.22 (1.49-6.99)*	19.865 (6.300-29.530)	21.700 (12.260-32.050)	1.09 (0.94-1.26)
C2	4.185 (2.400-6.440)	3.930 (2.340-5.880)	0.96 (0.71-1.29)	17.920 (6.990-33.420)	15.565 (4.950-26.540)	0.85 (0.69-1.06)
C3	0.320 (0.210-0.450)	0.380 (0.250-0.520)	1.52 (1.04-2.21)*	0.325 (0.080-0.580)	0.280 (0.080-0.760)	1.03 (0.88-1.20)
C3-DC	0.020 (0.020-0.030)	0.020 (0.010-0.030)	0.63 (0.39-1.01)	0.020 (0.020-0.030)	0.030 (0.020-0.030)	1.06 (0.72-1.55)
C4	0.090 (0.070-0.120)	0.100 (0.080-0.130)	1.61 (0.97-2.68)	0.135 (0.090-0.210)	0.185 (0.090-0.270)	1.35 (1.02-1.79)*
C4-DC	0.100 (0.060-0.140)	0.120 (0.070-0.180)	1.31 (0.91-1.87)	0.080 (0.060-0.130)	0.070 (0.050-0.110)	0.60 (0.40-0.89)*
C4-OH	0.040 (0.030-0.050)	0.040 (0.030-0.050)	1.05 (0.63-1.76)	0.070 (0.040-0.120)	0.090 (0.050-0.190)	1.36 (1.06-1.75)*
C5	0.060 (0.040-0.080)	0.060 (0.050-0.090)	1.29 (0.79-2.09)	0.110 (0.070-0.160)	0.145 (0.080-0.230)	1.48 (1.12-1.96)*
C5:1	0.020 (0.020-0.030)	0.020 (0.020-0.030)	0.78 (0.50-1.23)	0.030 (0.020-0.040)	0.030 (0.020-0.040)	1.64 (1.02-2.65)*
C5-DC	0.020 (0.010-0.020)	0.020 (0.010-0.020)	0.89 (0.53-1.50)	0.010 (0.010-0.020)	0.020 (0.010-0.020)	1.89 (1.12-3.21)*
C5-OH	0.110 (0.080-0.150)	0.130 (0.100-0.160)	1.19 (0.73-1.95)	0.120 (0.090-0.160)	0.140 (0.100-0.190)	1.39 (0.89-2.15)
C6	0.020 (0.020-0.030)	0.020 (0.020-0.030)	1.05 (0.67-1.66)	0.030 (0.020-0.040)	0.030 (0.020-0.040)	1.22 (0.82-1.81)
C6-DC	0.020 (0.010-0.030)	0.020 (0.01-0.020)	0.45 (0.28-0.75)*	0.020 (0.010-0.020)	0.010 (0.010-0.020)	0.42 (0.23-0.77)*
C8	0.020 (0.020-0.030)	0.020 (0.010-0.030)	0.83 (0.57-1.21)	0.010 (0.010-0.020)	0.015 (0.010-0.020)	1.37 (0.89-2.10)
C8:1	0.030 (0.020-0.040)	0.030 (0.020-0.040)	0.53 (0.32-0.87)*	0.020 (0.020-0.030)	0.020 (0.010-0.030)	0.94 (0.60-1.48)
C10	0.020 (0.020-0.030)	0.020 (0.010-0.030)	0.83 (0.57-1.21)	0.020 (0.010-0.020)	0.010 (0.010-0.020)	0.89 (0.59-1.36)
C10:1	0.030 (0.020-0.030)	0.020 (0.020-0.030)	0.91 (0.53-1.55)	0.010 (0.010-0.020)	0.010 (0.010-0.020)	1.15 (0.69-1.91)
C12	0.020 (0.010-0.030)	0.020 (0.010-0.020)	0.56 (0.36-0.85)*	0.010 (0.010-0.010)	0.010 (0.010-0.020)	1.17 (0.84-1.63)
C12:1	0.020 (0.010-0.020)	0.020 (0.010-0.020)	0.73 (0.45-1.20)	0.010 (0.010-0.010)	0.010 (0.010-0.010)	1.08 (0.54-2.14)
C14	0.030 (0.020-0.040)	0.030 (0.020-0.040)	0.72 (0.48-1.07)	0.010 (0.010-0.030)	0.010 (0.010-0.030)	1.07 (0.82-1.40)
C14-OH	0.010 (0.010-0.010)	0.010 (0.010-0.010)	0.12 (0.01-1.03)	0.010 (0.010-0.010)	0.010 (0.010-0.010)	1.89 (0.66-5.44)

C14:1	0.020 (0.010-0.030)	0.020 (0.010-0.030)	0.78 (0.52-1.15)	0.010 (0.010-0.010)	0.010 (0.010-0.010)	1.32 (0.81-2.16)
C14:2	0.010 (0.010-0.010)	0.010 (0.010-0.010)	0.73 (0.36-1.48)	0.010 (0.000-0.010)	0.010 (0.000-0.010)	0.64 (0.11-3.56)
C16	0.220 (0.160-0.330)	0.200 (0.140-0.300)	0.74 (0.53-1.04)	0.030 (0.020-0.140)	0.040 (0.020-0.240)	1.08 (0.94-1.25)
C16-OH	0.010 (0.010-0.010)	0.010 (0.010-0.010)	0.58 (0.19-1.78)	0.000 (0.000-0.010)	0.010 (0.000-0.010)	2.42 (0.68-8.65)
C16:1	0.020 (0.010-0.030)	0.020 (0.010-0.020)	0.72 (0.47-1.10)	0.005 (0.000-0.010)	0.010 (0.000-0.010)	0.90 (0.55-1.48)
C16:1-OH	0.020 (0.020-0.030)	0.020 (0.010-0.030)	0.70 (0.46-1.08)	0.000 (0.000-0.010)	0.010 (0.000-0.010)	0.89 (0.57-1.40)
C18	0.170 (0.110-0.230)	0.165 (0.110-0.250)	0.95 (0.67-1.34)	0.045 (0.020-0.240)	0.105 (0.030-0.270)	1.17 (0.99-1.37)
C18-OH	0.010 (0.000-0.010)	0.000 (0.000-0.010)	0.32 (0.30-3.39)	0.000 (0.000-0.010)	0.010 (0.000-0.010)	1.65 (0.26-10.28)
C18:1	0.140 (0.090-0.210)	0.145 (0.080-0.210)	0.94 (0.71-1.26)	0.010 (0.010-0.030)	0.010 (0.010-0.050)	1.12 (0.93-1.36)
C18:1-OH	0.010 (0.010-0.010)	0.010 (0.010-0.010)	0.94 (0.71-1.26)	0.000 (0.000-0.010)	0.000 (0.000-0.010)	0.41 (0.05-3.18)
C18:2	0.040 (0.030-0.060)	0.040 (0.030-0.060)	0.90 (0.64-1.28)	0.000 (0.000-0.010)	0.000 (0.000-0.010)	0.87 (0.55-1.36)

IQR= Interquartile range

Note: Median (IQR) was calculated using non-transformed variables. Univariate logistic regression was performed using log-transformed variables. *Marginally significant ($0.0016 < \alpha < 0.05$); **Significant (Bonferroni correction <0.0016)

Correlation was assessed for maternal and cord blood metabolite measurements (Table 3). Within the full study population, significant correlation between maternal and cord blood measurements was found for a variety of short, medium, and long chain acylcarnitines. When examined separately, term infants within the cohort displayed significant correlation for 14 acylcarnitines, including short, medium, and long chain acylcarnitines. Likewise, preterm infants displayed significant correlation for 10 acylcarnitines across the spectrum of chain lengths.

Table 3: Association between maternal and cord metabolite measurements.

Metabolite	Total Population		Term		Preterm	
	p-value	R2	p-value	R2	p-value	R2
C0	0.125	0.008	0.688	0.001	0.155	0.014
C2	$<1.00\times10^{-11**}$	0.364	$<1.00\times10^{-11**}$	0.439	$<1.00\times10^{-11**}$	0.292
C3	0.003*	0.029	0.096	0.019	0.016*	0.038
C3-DC	$2.04\times10^{-6**}$	0.073	0.003*	0.059	$1.39\times10^{-4**}$	0.094
C4	$7.80\times10^{-4**}$	0.037	0.052	0.025	0.010*	0.044
C4-DC	$4.20\times10^{-10**}$	0.123	$9.74\times10^{-7**}$	0.150	$9.56\times10^{-6**}$	0.124
C4-OH	0.054	0.012	0.847	<0.001	0.009*	0.045
C5	$7.27\times10^{-6**}$	0.065	$7.00\times10^{-4**}$	0.075	0.003*	0.059
C5:1	$9.68\times10^{-8**}$	0.091	$7.47\times10^{-5**}$	0.101	$1.41\times10^{-4**}$	0.094
C5-DC	0.030*	0.016	0.046*	0.027	0.248	0.009
C5-OH	$3.02\times10^{-7**}$	0.084	$7.79\times10^{-4**}$	0.074	$1.36\times10^{-4**}$	0.094
C6	$4.42\times10^{-9**}$	0.109	$3.42\times10^{-5**}$	0.110	$9.40\times10^{-6**}$	0.125
C6-DC	$<1.00\times10^{-11**}$	0.377	$<1.00\times10^{-11**}$	0.378	$<1.00\times10^{-11**}$	0.338
C8	$8.53\times10^{-4**}$	0.038	0.009*	0.047	0.022*	0.036
C8:1	$1.00\times10^{-11**}$	0.144	$6.53\times10^{-7**}$	0.154	$2.70\times10^{-6**}$	0.139
C10	$1.96\times10^{-4**}$	0.046	0.001**	0.070	0.041*	0.029
C10:1	$2.15\times10^{-4**}$	0.045	0.002**	0.066	0.032*	0.031
C12	0.045	0.016	0.089	0.023	0.209	0.127
C12:1	$1.96\times10^{-5**}$	0.060	$3.01\times10^{-4**}$	0.086	0.011*	0.043
C14	0.003*	0.030	0.022*	0.037	0.053	0.026
C14-OH	0.675	<0.001	0.820	<0.001	0.140	0.020
C14:1	$1.49\times10^{-4**}$	0.032	$3.82\times10^{-4**}$	0.101	0.044*	0.035
C14:2	0.791	<0.001	0.461	0.006	0.669	0.002
C16	$2.26\times10^{-4**}$	0.045	$9.92\times10^{-4**}$	0.071	0.036*	0.029
C16-OH	0.069	0.023	0.523	0.006	$1.82\times10^{-4**}$	0.174
C16:1	$3.22\times10^{-4**}$	0.079	0.003*	0.116	0.050	0.045
C16:1-OH	0.026*	0.032	0.494	0.007	0.014*	0.073

C18	$1.93x10^{-4**}$	0.046	0.002*	0.064	0.025	0.033
C18-OH	0.053	0.046	0.780	0.002	0.005*	0.180
C18:1	$6.80x10^{-10**}$	0.132	$1.01x10^{-6**}$	0.162	$9.80x10^{-5**}$	0.110
C18:1-OH	0.161	0.015	0.985	<0.001	0.039*	0.059
C18:2	0.003*	0.068	0.020*	0.085	0.090	0.042

Note: General linear regression was performed using log-transformed variables.
*Marginally significant ($0.0016 < \alpha < 0.05$); **Significant (Bonferroni correction <0.0016)

Preterm birth status was modeled by the level of each acylcarnitine found to be significant upon univariate logistic regression. Separate models were created for maternal metabolite levels, infant metabolite levels, and the combination of maternal and infant levels. Models were compared employing ROC and the corresponding AUC, with the model employing both maternal and infant metabolite levels yielding the greatest AUC (Figure 1). The combination model performed significantly better than the maternal model alone (p-value 0.007); no further significant differences were observed between ROC values. Sensitivity and specificity of the combined model were 0.826 and 0.572, respectively (Table 4).

Table 4: Optimal cut-off points for maternal metabolites only, cord metabolites only, and maternal and cord metabolites models.

Model	Maximum Youden's J Statistic	Sensitivity	Specificity
Maternal metabolites	0.277	0.476	0.801
Cord metabolites	0.369	0.719	0.65
Maternal and cord metabolites	0.398	0.826	0.572

Discussion

Our group has previously shown that metabolites measured from dried blood spots collected in the United States between 24 and 72 hours of life vary significantly based upon GA and birth weight[18]. Furthermore, a combination of these metabolite values reliably predicted GA in this same Iowa population[5]; this finding was shown in parallel study populations in California[4] and Canada[7]. Separately, Alexandre et al[6] demonstrated the ability to stratify term infants from infants born less than 32 weeks based upon metabolite profiles of 15 mother-infant dyads using umbilical cord blood, umbilical arterial blood, and maternal venous blood drawn at delivery. In a study of the urinary profile of neonates by nuclear magnetic resonance spectroscopy, Diaz et al[19] revealed significant differences in preterm infants, with the ability to segregate preterm neonates from other stressed states, indicating a signature profile in the preterm infant. A variety of metabolic adaptations are required during pregnancy in order to support the developing fetus, with specific adaptions shifting as gestational age advances. The body must first support organogenesis, followed by growth and maturation of the fetus[17]; this continuum of change over gestation makes it biologically plausible that metabolite profile may assist with gestational dating. Amidst the differential metabolic background of the gestating fetus, previous work has linked an increase in oxidative stress to preterm premature rupture of membranes[20] and preterm delivery[21]. In the setting of the preterm neonate, maternal infection often compounds the oxidative stress that is generated by transition of the fetus from the uterine environment of low oxygen to the high-oxygen ex-utero environment[21]. In addition to a greater degree of insult than their term counterparts, preterm infants have impaired ability to detoxify oxidative stress due to liver immaturity[10] and pulmonary antioxidant system immaturity[21]. Furthermore, premature separation from placental glucose infusion, in the setting of deficient glycogen stores, results in postnatal use of alternative energy-generating pathways in the preterm neonate; these alternative mechanisms result in differences in ketone and fatty acid concentrations between term and preterm infants. Thus, premature infants have a differential metabolic foundation, increased oxidative stress, decreased ability to detoxify oxidative insults, and differential use / generation of glucose and fatty acids. It is therefore reasonable to suspect that the metabolic profile may be used to stratify infant-mother dyads by GA.

The present study of 300 mother-infant dyads increases the body of work to suggest that metabolite data can be used in order to stratify term and preterm infants. A variety of acylcarnitine values were found to vary between the populations, consistent with previous work to this effect[4-7,19]. Interestingly, while most maternal blood metabolites were strongly correlated with cord blood metabolites, the specific metabolites that delineated term from preterm status differed between cord and maternal samples. In fact, only a single small chain acylcarnitine (C6-DC) was significantly different between preterm vs term infants in both maternal and cord blood samples. This differential underscores the fact that, while highly correlated, the metabolite utilization is disparate between mother and infant[22], consistent with both passive diffusion across the placenta, as well as active transport mechanisms directed by fetal requirements[23]. In addition to correlation between mother and infant metabolite levels, preterm birth status was stratified successfully in our cohort by a combination of maternal and infant metabolite values. While many of the differences observed in metabolite level are unlikely to have a strong biological impact, their aggregated values form a signature to differentiate between term and preterm status. This method of analysis may be useful in determining the burden of preterm birth in LMIC, where traditional estimates of GA are challenging to obtain.

This study is strengthened by its relatively robust numbers, with both preterm and term infants represented. The exclusion of diabetic mothers from the cohort reduces the potential confounding effect of metabolic disease, shown elsewhere to be linked to

metabolic profile in preterm birth[24,25]. One notable limitation is the use of retrospective banked samples that were not primarily collected for metabolite analysis. While this did not appear to affect our results for acylcarnitines, amino acid values were vastly different from previouslyobserved values. While prospective collection would be ideal, that is not always realistic; therefore, it is encouraging that samples collected retrospectively still demonstrate value when examining metabolite differences.

Infant and maternal metabolite levels are highly correlated and may reliably stratify term vs preterm birth status. The ability of maternal metabolite data to delineate term vs preterm status bears further investigation and validation. As DBS spotting and storage are feasible in the setting of LMIC, this may prove a useful mechanism for delineating the burden of preterm birth in this setting.

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