The influence of pregnancy-induced hypertension syndrome on the metabolism of newborns

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Background: Pregnancy-induced hypertension (PIH) is associated with an increased number of neonatal complications, but its impact on neonatal metabolism remains unclear. This study aimed to investigate the differential metabolomics of infants born to mothers with and without PIH.

Methods: Blood samples of a total of 115 infants born to mothers with (n=56) and without (n=59) PIH were collected and assigned to two groups, respectively, from the neonatal department of Sixth Affiliated Hospital of Sun Yat-Sen University. A tandem mass spectrometer was used to generate metabolic profiling of amino acid, free carnitine, and acyl-carnitines. The resulting data were analyzed using orthogonal partial least squares discriminant analysis based on the difference between infants born to mothers with or without PIH.

Results: A significant relationship was observed between the two groups (with and without PIH) in the metabolic fingerprint. According to the pattern recognition analysis combined with variance importance, 25 metabolites with high importance were found. The top ten substances were selected for analysis. Compared with infants born to mothers without PIH, glycine levels increased, and C14DC, C22, C4DC, C5:1, C6DC, C5-OH, proline, C14-OH, and C20 decreased in infants born to mothers with PIH.

Conclusions: Using liquid chromatography (LC)-MS/MS metabolomics, a significant relationship was detected between neonatal metabolism and maternal hypertension. It is important to correct the subsequent infantile metabolic disorder by balancing the biomarker metabolites and suppling adequate nutrition to improve the health and growth of newborns of PIH mothers.

Keywords: Pregnancy-induced hypertension (PIH); neonatal metabolism; metabolomics; tandem mass spectrometer; nutrition

Introduction

Pregnancy-induced hypertension (PIH) is characterized by the de novo development of blood pressure above the normal level that arises ≥20 weeks of gestation, accompanied by physiological and pathological changes, such as convulsion, coma, and heart and kidney disease/ failure in severe cases (1-5). The incidence rate is about 5–12%, and the mortality rate is as high as 11–16% (6). In recent years, the incidence of PIH has grown, in parallel with an increase in mothers of advanced maternal age,

increased incidence of female obesity and rheumatoid immune diseases, the demand for assisted reproductive technology, and other high-risk factors (7). At present, this disease's pathogenesis is not clearly understood, which brings great challenges for its treatment and prevention (8). Various maternal and neonatal complications can be caused by PIH and/or chronic hypertension, including acute liver and kidney failure, placental abruption, hemorrhage, growth restriction, small size for gestational age, asphyxia, or hypoxic ischemic encephalopathy, among others (9,10).

Since the introduction of tandem mass spectrometry to newborn screening in 1990, its high sensitivity, high specificity, and rapid detection have propelled its development to become the ideal analytic technology for newborn screening in the past 20 years (11,12). There are many reports in the literature that recommend using this technique to detect metabolites such as amino acids, organic acids, fatty acids, and steroid hormones in samples such as urine, blood, amniotic fluid, and cells to detect genetic metabolic diseases (13,14). Metabolomics, as a discipline that was developed in the mid-1990s, is an emerging omics approach following transcriptomics and proteomics, and is an important part of systems biology (15-17). It can be used not only for disease diagnosis and prognosis assessment, but also for a multi-parameter judgment index of the body's metabolic homeostasis (18).

To our knowledge, the findings of metabolomics of PIH have been reasonably consistent between studies, with lipids and carnitines among the most commonly highlighted metabolites. These results have supported the existence of a PIH metabolome that is predominantly characterized by dysregulated fatty acid metabolism, which can be measured in a variety of biological samples, including blood, urine, placental tissue, and breast milk (19). Some studies have shown that PIH impacted the metabolism of bilirubin and lipid in newborns.

However, to date, research on the effects of PIH on newborns' postnatal metabolism has been scarce. Therefore, the mass spectrometry (MS)/MS-based metabolomics platform in this study used the mothers of newborns with normal pregnancies as controls, and the metabolites were analyzed to study the differences in blood metabolites among them in order to evaluate the impact of maternal hypertension during pregnancy on the blood metabolic status of the newborn and to provide reasonable nutritional supplement recommendations for further correction of metabolic disorders.

We present the following article in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/tp-20-211).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (2017ZSLYEC-105). The blood samples of newborns were obtained after their parents had provided written informed consent.

Data collection

The participant inclusion criteria were as follows: (I) there were no complications during pregnancy, except PIH for mothers with PIH, and no complications during pregnancy for normal mothers; (II) no history of unexplained death or premature death in the family; (III) no previous maternal dietary carnitine deficiency or genetic causes, and no history of alcohol, drug, tobacco, or substance abuse;

The exclusion criteria were as follows: (I) Refusal by family members for the newborn to undergo metabolism testing; (II) Severe complications (such as neonatal sepsis, congenital genetic metabolic disease, neonatal necrotizing enterocolitis, and severe metabolic disorder, among others) or death; (III) Congenital malformations and genetic metabolic diseases; (IV) Other perinatal complications, such as gestational diabetes mellitus, intrahepatic cholestasis during pregnancy, heart disease, hepatitis b virus infection, and hyperthyroidism or hypothyroidism, among others.

A total of 56 patients with PIH (average age 23–35) who were admitted between September 2010 and August 2012 to the Sixth Affiliated Hospital of Sun Yat-sen University were selected as the case group, and 59 normal pregnant women who were hospitalized or delivered in the hospital during the same period were selected as the control group. The heel Blood samples from the infants' heels were collected the 3 days after birth and 30 minutes after feeding.

Diagnostic criteria

We employed PIH's diagnostic criteria as listed in the 9th edition of 2019 Obstetrics and Gynecology: Hypertension during pregnancy refers to hypertension (≥140/90 mmHg) on two occasions, ≥4 hours apart, after 20 weeks of gestation.

Samples collection

After the parents had understood and signed the informed consent to screen neonatal genetic and metabolic diseases, the newborn blood samples were collected. After disinfection, heel blood was collected using a blood collection needle on the inside or outside of the heel near the 1/3 of the heel. Blood droplets naturally penetrated the filter paper. Three blood spots were continuously collected, each blood spot diameter was >8 mm, and the front and back sides of the filter paper were fully infiltrated to ensure that the blood concentration was uniform and that there was no blood ring. After the blood collection, the blood tablets were placed in a cool and clean place for natural drying, while avoiding ultraviolet rays, sunlight, and external pollution. After passing inspection, the dried blood tablets were placed in sealed bags and stored in a 2–8 ℃ refrigerator.

Test methods

The blood tandem mass spectrometer was a Waters ultra-performance liquid chromatography MS (I-class) tandem (Xevo-TQD, Waters Corp., Milford, MA, USA). It used non-derivatized succinylacetone and various amino acid and carnitine assay kits. After punching, an extraction solution containing 100 μL of internal standard (8: 2 methanol: ultrapure water) was added, it was placed in a microplate shaker at 700 rpm and 45 ℃ for 45 minutes, and then centrifuged in a centrifuge at 4,000 rpm for 5 minutes. A 75 μL sample of the supernatant was placed in a 96-well heat-resistant V bottom plate, and the aluminum film was used for testing.

Data analysis

Qualitative analysis was performed according to the m/z of the mass spectrum peaks. The concentration values of amino acids and fatty acids of the 115 samples were automatically calculated by quantitative analysis software, and analyzed by SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA). We used the Kolmogorov-Smirnov and Shapiro-Wilk tests to test the normality of the data. Accord with normal distribution and variance of the quantitative data with mean ± SD ($\bar{x}$±SD) was described, and inter-group comparison was performed by t-test. The quantitative data not conforming to normal distribution were described by median (M) (P25, P75), and the rank-sum test was used for comparison between groups. The qualitative data were

described by frequency, and the chi-square (χ^2) test was used for comparison between groups. Orthogonal partial least squares discriminant analysis (OPLS-DA) was performed using the SIMCA14.0 data processing software. The OPLS-DA analyzed the blood metabolism of the two groups of newborns and looked for key differential metabolites. Two key indicators for evaluating the matching degree of the OPLS-DA model (R^2X represented the interpretation rate of the X matrix; R^2Y represented the interpretation rate of the Y matrix, both of which reflected the stability of the model, each of the two were >0.5, indicating that the model matches well; the closer to 1, the higher the matching degree of the model). According to the OPLS-DA model, the more the substances at both ends were biased, the greater their covariance and correlation was, and the blood metabolites with variable important plots (VIPs) weighted >1 were screened out from them, and the scatters of different individual substances were plotted. Differences were considered to be significant when P<0.01.

Results

Basic clinical data

The maternal age, weight, height, prenatal weight with and without PIH, the gestational age, gender, birth weight, length, and circumference of the above participants were recorded respectively, as shown in *Table 1* and *Table 2*.

There were no significant differences between mothers with or without PIH regarding age and height (P>0.05). However, the weight and body mass index (BMI) of mothers between the two groups were significantly different (P<0.001). The PIH women were more likely to be overweight. Overweight and obese women are at higher risk of developing PIH.

There were no significant differences between the infants born to mothers with and without PIH in terms of gender and head circumference (P>0.05). However, the gestational age, birth weight, and body length between the two groups were significantly different (P<0.001). The average gestational age, weight, and body length of newborns of mothers with PIH were lower than those of newborns of mothers with normal pregnancies.

Results of blood metabolism analysis of neonatal group with pregnancy-induced hypertension and neonatal group with normal pregnancy

In order to eliminate the effects of non-essential factors,

Table 1 Comparison of the basic clinical data of pregnant mothers in the two groups

Variable	PIH ($\bar{x} \pm$ SD)	Normal ($\bar{x} \pm$ SD)	t-value	P value
Age (year)	28.8±5.1	27.2±4.3	−1.78	0.079
Weight (kg)	72.5±8.8	65.6±8.0	−3.58	<0.001
Height (cm)	159.7±4.4	159.9±4.5	0.25	0.803
BMI (kg/m^2)	28.4±0.5	25.6±0.4	−4.65	<0.001

PIH, pregnancy-induced hypertension; BMI, body mass index; SD, standard deviation.

Table 2 Comparison of basic clinical data of neonatal in the two groups

Variable	PIH ($\bar{x} \pm$ SD)	Normal ($\bar{x} \pm$ SD)	χ^2/t-value	P value
Gestational age (day)	261.9±15.2	275.3±6.6	6.145	<0.001
Gender (male)	50%	84%	0.207	0.711
Weight (g)	2,564.8±630.8	3,220.3±275.3	7.156	<0.001
Height (cm)	47.1±3.0	49.6±1.4	4.053	<0.001
Head circumference (cm)	32.4±1.5	32.90±1.3	1.648	0.103

PIH, pregnancy-induced hypertension; SD, standard deviation.

complete the maximum separation between the two groups, and find the differential metabolites with larger weights, we used the supervised OPLS-DA method to remove information that was irrelevant to the sample grouping. We analyzed the mothers with PIH full spectrum of neonatal blood metabolism compared to the normal pregnancy mothers. The OPLS-DA score chart of the full spectrum of blood metabolism data is shown in *Figure 1*. The model contained two principal components, R^2Xcum =0.508 and R^2Ycum =0.805, indicating that the model had a better interpretation ability. The prediction rate was high, which supported the model's reliability, and there was no overfitting phenomenon. It can be seen from *Figure 1* that the PIH mother's pregnancy neonatal group and the mother's normal-pregnancy newborn group were each distributed in two regions, indicating that there were significant differences in blood metabolome between the two groups.

Analysis of differential substances in mothers with pregnancy-induced hypertension and mothers with normal pregnancy

The variable importance score chart was the most commonly used method to evaluate the contribution of variables in the supervised analysis method using the

OPLS-DA model. Screening for substances with significant differences was based on VIPs >1.0. After analysis by the OPLS-DA model, we identified myristyl carnitine (C14DC) and docosa carnitine (C22), succinyl carnitine (C4DC), glycine (Gly), prenyl carnitine (C5: 1), adipoyl carnitine (C6DC), 3-hydroxyisovaleryl carnitine (C5-OH), proline (Pro), 3-hydroxymyristoyl carnitine (C14-OH), eicosyl carnitine (C20), ornithine (Orn), myristyl dienoyl carnitine (C14:2), cycladienoyl carnitine (C10: 2), 3-hydroxypalmitoyl carnitine (C16: 1-OH), cyclinoyl carnitine (C10: 1), threonine (Thr), tryptophan (Trp), leucine (Leu), asparagine (Asn), hexacosyl carnitine (C26), glutamic acid (Glu), octadecadienoyl carnitine (C18: 2), hexanoyl carnitine (C6), malonyl carnitine (C3DC), and valine (Val); a total of 25 different metabolites with weights >1 (*Figure 2*). The differential substances ranked in the top 10 in weight were selected for analysis. The levels of these 10 amino acids and/or acyl carnitine are shown in *Table 3*.

Scatter plot of differential metabolites

Metabolomics analysis was performed on the PIH mothers and the normal pregnancy mothers, and a total of 25 differential metabolites were obtained. From the scatter plot analysis (*Figure 3*), it could be seen that compared with the normal pregnancy mothers, Gly showed an increasing
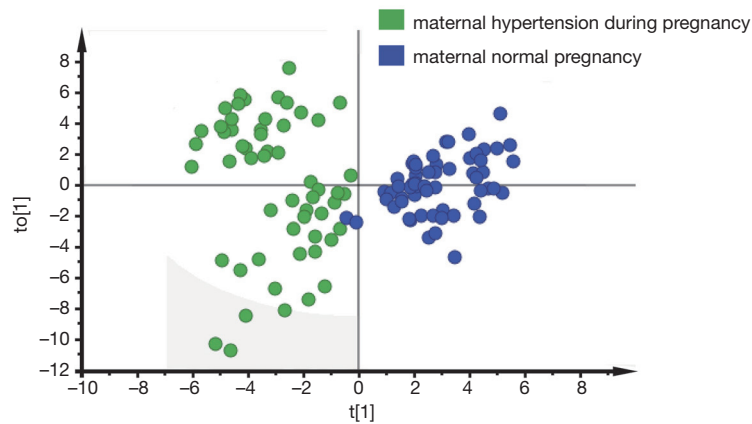
Note: the abscissa t[1] represents the predicted component, showing the difference between the groups; The vertical coordinate to[1] represents the orthogonal component and represents the degree of intra-group dispersion. The green dots indicate 56 maternal hypertension cases during pregnancy, and the blue dots indicate 59 cases of normal maternal pregnancy.

Figure 1 The OPLS-DA score plot of the neonatal group with maternal PIH and with normal pregnancy. OPLS-DA, orthogonal partial least squares discriminant analysis; PIH, pregnancy-induced hypertension.
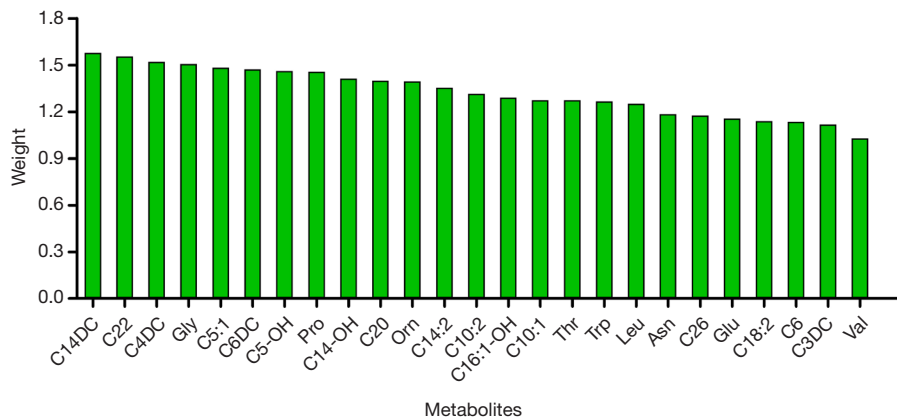
Figure 2 The variable important plot (VIP >1).

trend; C14DC, C22, C4DC, C5:1, C6DC, C5-OH, Pro, C14-OH, and C20 showed a decreasing trend in the maternal PIH neonatal group.

Our research cohort included 59 cases of normal pregnancy, 11 cases of gestational hypertension, 18 cases of mild preeclampsia, 26 cases of severe preeclampsia, and 1 case of eclampsia. To understand the influence of PIH's severity on the newborn, we compared the different groups (as shown in *Figure 4*), but because of too small a number of eclampsia cases, here did not include it in the comparison.

As shown in *Figure 4*, the changes of blood metabolites

in neonates between different degrees of PIH with normal pregnancy were statistically significant (P<0.001), while no statistical difference was detected between different degrees of PIH (P>0.05).

According to the scatter plot, the level of Gly tended to increase with the increase of PIH degree, while the levels of Pro, C4DC, C14-OH, C14DC, and C20 tended to decrease. There was a trend of change but no statistical difference. Considering this study involved a small number and imbalance of samples, enlargement of the sample size in future research will help to verify these findings.

Table 3 Levels of different substances in blood amino acid and fatty acid

Material (µmol/L)	PIH (x ± SD)/M (P$_{25}$, P$_{75}$)	Normal (x ± SD)/M (P$_{25}$, P$_{75}$)	t/Z-value	P value
C14DC[b]	0.01 (0, 0.05)	0.06 (0.05, 0.07)	6.25	<0.001
C22[b]	0.02 (0.01, 0.04)	0.06 (0.04, 0.07)	6.62	<0.001
C4DC[a]	0.18±0.09	0.32±0.12	7.46	<0.001
Gly[a]	274.43±122.75	163.20±35.49	−6.53	<0.001
C5:1[b]	0.03 (0.01, 0.10)	0.10 (0.09, 0.13)	5.16	<0.001
C6DC[b]	0.02 (0.01, 0.38)	0.38 (0.33, 0.50)	5.93	<0.001
C5-OH[a]	0.13±0.06	0.20±0.05	6.63	<0.001
Pro[b]	181.32 (100.33, 619.23)	628.49 (531.11, 792.38)	5.83	<0.001
C14-OH[b]	0.02 (0.01, 0.04)	0.05 (0.04, 0.06)	5.49	<0.001
C20[b]	0.03 (0.01, 0.05)	0.05 (0.04, 0.07)	6.13	<0.001

[a]data were normally distributed, and a *t*-test was used for comparison between the two groups; [b]data did not conform to the normal distribution, and the rank-sum test was used for comparison between the two groups. PIH, pregnancy-induced hypertension; SD, standard deviation; M, median.
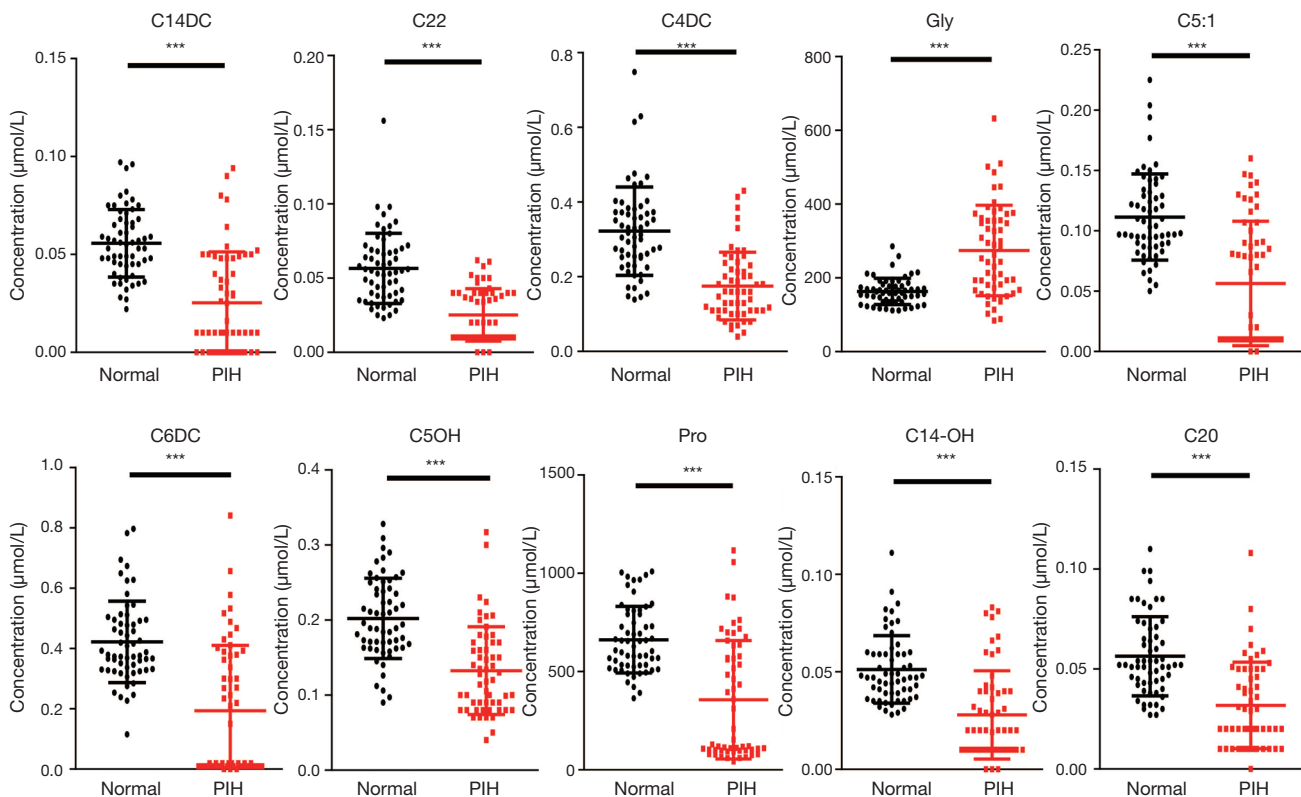

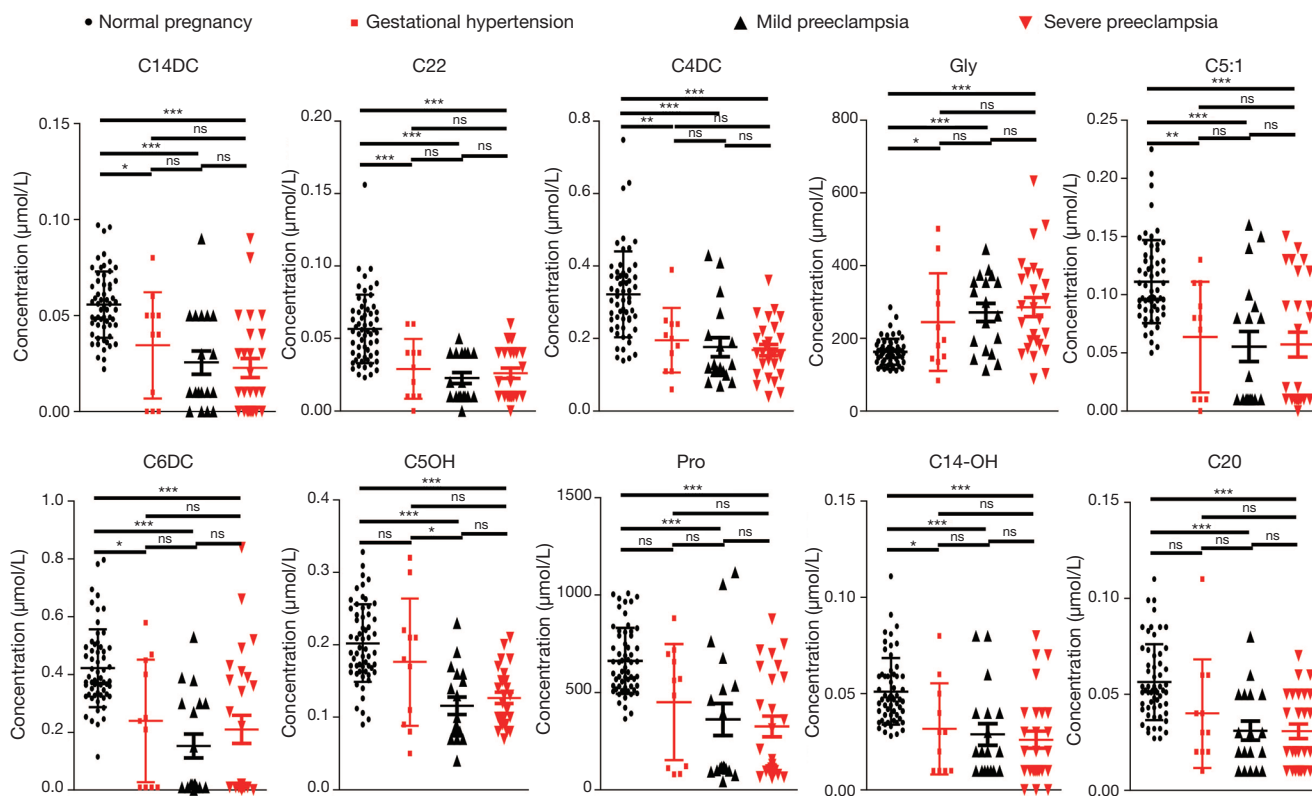**Figure 3** Scores plots for different metabolites in two groups. ***P<0.001.

Figure 4 Scores plots for different metabolites in four groups. ***P<0.001; **P<0.01; *P<0.05; ns, P>0.05.

Discussion

In this study, based on the metabolomics platform, the blood metabolites of newborns of PIH mothers were analyzed by tandem mass spectrometry. The differences between these blood metabolites were studied to help evaluate the influence of gestational hypertension from mothers on newborns' blood metabolic status. All of the mothers were healthy except for PIH during their pregnancy. This study found a significant difference in blood metabolism between newborns with maternal PIH and those of mothers with normal pregnancy, which showed different metabolic characteristics.

Among 85 blood metabolites, 10 differential metabolites were found, which were different from those of normal pregnancy mothers. Compared with the normal pregnancy infant group, Gly showed an increasing trend in the neonatal group of mothers with PIH, while C14DC, C22, C4DC, C5:1, C6DC, C5-OH, Pro, C14-OH, and C20 showed a decreasing trend. This result was similar to the study of Wu *et al.* (20), who used tandem mass spectrometry

to study the differences in blood metabolomes of preterm infants and term infants. They found 12 biomarkers such as free carnitine and succinyl carnitine, which decreased the preterm infant group. Li *et al.* (21) conducted a urine metabolomics study on very low weight births and found that stearic acid, palmitic acid, and myristic acid, among others, were significantly reduced in the very low birth weight group. At present, the side effects of PIH on newborns remain unclear. Studies have shown that the complication of hypertension in pregnancy accounted for 5% of all pregnancies, and was generally related to preterm labor (22). Our results also showed that PIH women are likely to experience preterm birth; there was a certain correlation between prematurely delivered fetuses and maternal PIH. Davies, Bell, and Bhattacharya (23) found that there was a positive correlation between PIH and premature delivery. Research by Omu, Othman, Al-Qattan, Al-Falah, and Sharma (24) also showed that compared with normal pregnant women, preterm birth incidence, caesarean birth, low birth weight, and perinatal mortality in women with PIH was significantly increased. Any of the

symptoms caused by high blood pressure during pregnancy could be associated with many complications. Preterm birth is the main cause of perinatal morbidity, death, and long-term neurological sequelae. There are various complications such as bleeding, postpartum sepsis, bladder injury, and visceral trauma, which can be very serious, and low birth weight neonates are the leading division of neonatal death and morbidity. Saadat, Nejad, Habibi, and Sheikhvatan (25) considered that hypertension during pregnancy could cause complications such as respiratory distress, low birth weight, gestational diabetes, and maternal death. Wang *et al.* (26) showed that preeclampsia's clinical characteristics were similar in different hospitals in China, but the cesarean section rate was higher. Fallahian and Emahidosadati (27) found that pregnant women with gestational hypertension had a 7.5-fold higher neonatal mortality rate than healthy pregnant women, and a premature birth rate that was 3.5 times that of healthy pregnant women. Odell *et al.* (28) recruited African women as participants to observe the impact of PIH on maternal and infant complications, and found that pregnant women with hypertension were a high-risk group for gestational diabetes, and 10% of these women gave birth to low-birthweight newborns. Considering the above discussion, this study's results may be applied to premature delivery, cesarean section, low birth weight, neonatal complications, and even death caused by PIH.

Effects of amino acid changes on tissue and organ functions

Glycine

Glycine is one of the non-essential amino acids and plays a very important physiological role in the anabolism of various substances in the body. Glycine is a precursor for various important metabolites such as glutathione, porphyrins, purines, haem, and creatine. These processes are mainly performed through the glycine cleavage system (GCS) and serine hydroxyl methyl transferase (SHMT) (29). Our study found that the increased glycine level of newborns in the PIH group may be related to the low GCS or SHMT enzyme activity in premature infants and low birth weight infants. What is more, glycine acts as a neurotransmitter in the central nervous system, and it has many roles such as antioxidant, anti-inflammatory, cryoprotective, and immunomodulatory in peripheral and nervous tissues. There were only 3 cases of neonatal asphyxia (3/56=5%) in the PIH group, and all of them were mild asphyxia, which might be related to the compensatory protective mechanism of glycine in the body cells.

Proline

Proline is also one of the non-essential amino acids. Studies (30) have shown that proline content in the blood is positively correlated with newborns' birth weight, and the higher the content, the higher the incidence of macrosomia. Zhiqiang *et al.* (31) found that proline is the most critical biomarker in the process of interleukin (IL)-1-mediated chondrocyte metabolism, which can alleviate the metabolic disorder of osteoarthritis. Our study found that the decreased proline level was considered to be a risk factor for low birth weight of newborns with PIH mothers compared with those with normal maternal pregnancy. Moreover, we should avoid using drugs to affect the development of neonatal cartilage and monitor the newborn's cartilage development closely.

Effects of fatty acid changes on tissue and organ functions

Acyl carnitine is essential for intracellular energy metabolism, and characteristic changes in one or more acyl carnitines indicate the presence of a fatty acid-oxidative metabolism disorder. Kido *et al.* (32) found that an increased level of acyl carnitine in the blood promoted fatty acids' metabolism, affected the metabolism of amino acids, and facilitated the production of energy of the heart and skeletal muscles. Scalais *et al.* (33) found that reduced levels of long-chain acyl carnitine led to cardiomyopathy, hepatic encephalopathy, severe hypoglycemia with low ketone, or sudden death. Makarova *et al.* (34) found that reduced levels of long-chain acyl carnitine were associated with insulin resistance in the muscles and heart. Our study detected decreased levels of different chain lengths of acyl carnitine in the PIH group, which showed us that the energy metabolism of the PIH group was weaker than in normal pregnancy, and that hypothermia, hypoglycemia, neonatal hypoxic ischemic encephalopathy, neonatal hyperbilirubinemia, and other complications are more likely to occur. It is important to provide sufficient energy during the early postnatal period to prevent the occurrence of fatty acid metabolic disorders in newborns of mothers with PIH.

Many current studies have shown that PIH could increase newborns' complications, but the mechanism is unclear (35). It has not been elucidated whether the neonatal outcome is more affected by the gestational age or the severity of hypertension during pregnancy. This study supports that PIH impacts neonatal metabolism, and screening of target metabolites can provide reasonable nutritional supplement recommendations for further correction of metabolic

disorders.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-211

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-20-211

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-211). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of this work in ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (2017ZSLYEC-105). All infant participants included in this study were recruited with the provision of written informed consent from their guardians.

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