Umbilical Cord Blood Acidosis in Term Pregnancies With Gestational Diabetes Mellitus and Its Relations to Maternal Factors and Neonatal Outcomes

Soroush Aalipour[1], Sedigheh Hantoushzadeh[1,2], Mamak Shariat[2], Sadaf Sahraian[1] and Mahdi Sheikh[1,2,*]

[1]Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, IR Iran
[2]Breastfeeding Research Center, Tehran University of Medical Sciences, Tehran, IR Iran

[*]*Corresponding author*: M.D, Ph.D, Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-9128481663, Fax: +98-2122834332, E-mail: mahdisheikh@gmail.com

Abstract

Background: Umbilical cord blood (UCB) gas analysis is recommended in high-risk pregnancies. However, in chronic medical conditions, cord blood acidosis might not indicate acute fetal stress, rather it might be due to fetal adaptation to the chronic stress.
Objectives: Evaluating the association between UCB acidosis with maternal factors and adverse neonatal outcomes in term pregnancies with gestational diabetes mellitus.
Methods: This prospective cohort evaluated 673 pregnant women who had term pregnancies and were admitted for elective cesarean delivery. A total of 80 women had gestational diabetes. After delivery, a blood sample was obtained from the umbilical artery for arterial blood gas analysis. The neonates were then followed.
Results: Term pregnancies with gestational diabetes had significantly higher UCB acidosis rates compared to the healthy controls (26.2% vs. 6%, P < 0.001). In mothers with gestational diabetes, UCB acidosis was independently associated with higher maternal body mass index (P = 0.04) and HbA1C levels (P = 0.01). In the term neonates born to gestational diabetes mothers, after adjustment for gestational age, birth weight and pre-delivery blood glucose, UCB acidosis remained significantly associated with macrosomia (47.6% vs. 23.7%, P = 0.04), neonatal hypoglycemia (76.1% vs. 25.4%, P = 0.002), and moderate-severe jaundice (71.4% vs. 27.1%, p0.01).
Conclusions: In our study term, pregnancies with gestational diabetes had a higher rate of UCB acidosis, which was associated with poor maternal glycemic and weight control during the last gestational trimester. UCB acidosis in these pregnancies seems to be independently associated with adverse neonatal outcomes.

Keywords: Acidemia, Hypoglycemia, Hyperbilirubinemia, Macrosomia, Weight

1. Background

The burden of neonatal mortality and morbidity is very high in developing countries (1); therefore, evidence based strategies are required for early prediction and management of adverse neonatal outcomes. One of the oldest tools to predict adverse neonatal outcomes is umbilical cord arterial blood gas (UC-ABG) analysis (2), which is still recommended by the American Colleges of Obstetricians and Gynecologists (ACOG) in all high risk deliveries (3, 4). In a recent meta-analysis of 481753 infants, umbilical cord blood (UCB) acidosis was significantly associated with neonatal mortality and morbidities (5). Although the value of UC-ABG analysis for prediction of adverse neonatal outcomes in high risk and pre-term deliveries is documented

(3-6), the predictive value of UC-ABG analysis in term deliveries is still controversial; in a study of 51519 term neonates, UCB acidosis was weakly associated with adverse neonatal outcomes (7).

UCB acidosis is not always suggestive of acute neonatal stress, rather it can happen in chronic conditions with placental dysfunction including gestational diabetes mellitus (GDM) and preeclampsia (8-10), in which impairment of placental blood flow can affect trans-placental gas exchange, placing the fetus at risk for chronic hypoxia and acidosis (11-13). The high rate of chronic fetal acidosis, placental insufficiency in chronic conditions like preeclampsia and GDM (10, 14, 15), and fetal adaptation to these conditions through changes in fetal circulation might affect the value of UC-ABG analysis in the prediction of adverse

neonatal outcomes in these special populations ([10]); previously, we showed that UCB acidosis might not be a good predictive of adverse neonatal outcomes in pregnancies with preeclampsia, probably due to fetal adaptation to chronic acidosis and placental dysfunction ([10]).

The use and value of UC-ABG analysis in GDM seems to be even more complicated than other chronic conditions, due to the fact that in addition to placental dysfunction and impairment of utero-placental blood flow that can result in fetal acidosis, impaired maternal glucose metabolism might be another mechanism that induce fetal acidosis; it is shown that excessive glucose in GDM can cross the placenta and induce fetal hyperinsulinemia, accelerated fetal metabolisms, oxygen consumption, and subsequent acidosis ([8]). Therefore, in GDM fetal acidosis might not only be due to fetal and placental conditions, rather maternal metabolic factors such as glucose and weight control during gestation and during the 24 hours before delivery might also affect UC-ABG parameters. Therefore, it is not clear if UC-ABG analysis can still be used to predict adverse outcomes in these patients.

2. Objectives

We conducted a prospective cohort study to assess the effect of GDM on UC-ABG parameters and to address the maternal factors associated with UCB acidosis in term neonates born to GDM mothers. Additionally, we tried to evaluate if UCB acidosis in term neonates born to GDM mothers is associated with adverse neonatal outcomes in this population.

3. Methods

3.1. Study Population and Design

This prospective cohort study was conducted on pregnant women with term pregnancies who were admitted for elective cesarean delivery to a governmental referral hospital with an annual 2200 birth rate, from January 2015 through January 2016. The inclusion criteria included: birth within the study center at a gestational age of $\geq$ 37 weeks, delivery through elective cesarean section from a singleton pregnancy, absence of any hypertensive disorder including preexisting hypertension, gestational hypertension, preeclampsia or eclampsia, absence of prepregnancy diabetes mellitus and autoimmune diseases, and accepting to participate in the study. The exclusion criteria were: the presence of intrauterine fetal growth restriction (IUGR), major congenital anomalies, history of maternal smoking, and consumption of opiates or alcohol

during pregnancy. A total of 673 women accepted to participate in this prospective cohort study and gave a written informed consent before delivery. This study was reviewed and approved by the Research Deputy and Ethics Committee of our institute on 03/10/2014.

3.2. Data and Specimen Collection

Upon enrollment, a standardized questionnaire was completed for every mother and every neonate through medical records and physical examinations. Gestational age was calculated using the first gestational trimester's ultrasound imaging. The participant vital signs, weights, heights, and body mass index (BMI) were calculated and recorded. GDM was diagnosed based on the documented glucose challenge test (GCT) and glucose tolerance test (GTT) performed during the 28-32 gestational weeks. Participants were assigned to the GDM group if they had met the criteria of ACOG for diagnosing GDM ([16]). All the participants had undergone a routine glycemic screening for GDM at 28 - 32 gestational weeks with a non-fasting oral GCT, in which venous blood was sampled 1 hour after a 50-g oral glucose load. If the 1-hour glucose result was $\geq$ 140 mg/dL, the participant was referred for a 100-g fasting glucose 3-hour GTT ([14]). Based on the ACOG ([16]), normal GTT results were a blood glucose level < 95 mg/dL at baseline, < 180 mg/dL at 1 hour, < 155 mg/dL at 2 hours, and < 140 mg/dL at 3 hours. Impaired GCT was defined as failing the GCT (1-hour glucose result of $\geq$ 140 mg/dL). GDM was defined as failing the GCT in addition to exhibiting 2 high glucose values during the 3-hour GTT ([16]).

Indications for performing elective cesarean section were previous caesarean delivery, breech or abnormal fetal presentation, fetal macrosomia, and maternal indications including maternal requests, previous retinal detachment, and previous myomectomy. After an overnight fasting, the surgical procedure was performed with spinal anesthesia, while no hypotension was recorded in any case. Upon enrollment, a blood sample was drawn from GDM mothers to evaluate glycosylated hemoglobin (HbA$_1$C) levels. HbA$_1$C > 6% was considered elevated and having increased HbA1C levels was considered as poorly controlled GDM. Furthermore, capillary blood glucose was serially checked for these mothers and insulin was administered based on standardized protocols to achieve ideal fasting and postprandial blood glucose levels.

In the operating room, after delivery, the umbilical cord was double clamped, and an umbilical artery blood sample was drawn for arterial blood gas analysis, which was performed by a blood gas analyzer (Nova Biomedical, Waltham, MA). The physicians were educated in the operating room before the beginning of the study to avoid possible interpersonal biases of obtaining the UC-ABG. Birth

weights were measured using regularly calibrated scales in the delivery room. A total of 1-3 hours after birth capillary blood samples were obtained from the neonates through heel prick method and blood glucose levels were recorded using chromogen reagent strips and reflectance meter (Accuchek Aviva, Roche Boehringer Mannheim Diagnostics Systems, Inc., NJ). The neonates were then followed and the following information were recorded: having a UCB acidosis, defined as UCB pH < 7.2 (17); having macrosomia, defined as giving birth to a neonate weighing > 4000 grams; the occurrence of hypoglycemia, defined as BS < 46 mg/dl (< 2.5 mmol/L); and the occurrence of moderate-severe neonatal jaundice requiring intensive phototherapy and/or exchange transfusion based on the American Academy of Pediatrics (AAP) guidelines (18).

3.3. Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 22.0, Chicago, IL). Shapiro-Wilk test was used for normality analysis. Independent samples t-test, Mann-Whitney U test, Chi-squared analysis, Fisher's exact test, and multivariate logistic regression were used to analyze the data. Sample size was calculated for a power of 80% and an alpha error of 0.05 in which the least sample size of 79 would be required in each group, assuming a dropout rate of 15%. Estimated odds ratios (ORs) with 95% and confidence intervals (95% CIs) were calculated to assess the statistical significance, while P value < 0.05 was also considered statistically significant.

4. Results

4.1. Descriptive Statistics

A total of 673 women accepted to participate in this prospective cohort study, while 19 women were excluded due to meeting the exclusion criteria. The remaining 654 pregnant women who delivered term neonates through elective cesarean section at gestational ages of 37 - 42 weeks remained in the study and were included in the analyses.

At enrollment, the mean $\pm$ standard deviation (SD) for maternal age was 28.6 $\pm$ 5.6 years, maternal BMI before delivery was 28.7 $\pm$ 4.6, gestational age at birth was 38.6 $\pm$ 1 weeks, birth weight was 3246 $\pm$ 485 grams, and 5 minute Apgar score was 9.7 $\pm$ 0.5. A total of 80 mothers (12.2%) had gestational diabetes, 351 neonates (53.6%) were male, 44 (6.7%) had macrosomia, 56 (8.5%) had UCB acidosis, 41 neonates (6.2%) developed hypoglycemia, and 153 (23.3%) had moderate-severe jaundice requiring phototherapy and/or exchange transfusion. There were no statistically significant differences in the demographics between healthy versus GDM mothers (Table 1).

4.2. GDM and UC-ABG Analysis in Term Neonates

In the term, neonates born to mothers with GDM, the UCB pH was lower compared to those born to healthy mothers (Medians and ranges: 7.29 (6.85 - 7.48) vs. 7.31 (7.15 - 7.5), P = 0.04). UCB acidosis was more detected in the term neonates born to mothers with GDM compared to those born to healthy mothers (26.2% vs. 6%, P < 0.001) (Table 2). In mothers with GDM, UCB acidosis was significantly associated with higher maternal BMI before delivery (29.4 $\pm$ 3.5 vs. 27.3 $\pm$ 4.5, P = 0.01) and poorer diabetic control during the 3rd gestational trimester (HbA$_1$C; 6.1 $\pm$ 0.6 vs. 5.2 $\pm$ 0.3, P = 0.004) (Table 3).

4.3. GDM, UCB Metabolic Acidosis and Adverse Neonatal Outcomes in GDM Mothers

Term neonates born to GDM mothers experienced significantly more adverse outcomes including macrosomia, hypoglycemia, and moderate-severe jaundice (P < 0.001 for all) (Table 2). In the term neonates born to GDM mothers, UCB acidosis was significantly associated with macrosomia (47.6% vs. 23.7%, P = 0.04), neonatal hypoglycemia (76.1% vs. 25.4%, P < 0.001), and severe jaundice (71.4%, P < 0.001) (Table 3).

4.4. Dependency of the Obtained Results

Multivariate logistic regression was used to adjust the obtained results for maternal age, gestational age at delivery, maternal BMI before delivery, HbA$_1$C level, and BS before delivery; UCB acidosis remained significantly associated with higher HbA$_1$C level (B = 0.28, P = 0.01, OR = 1.32, 95%CI = 1.06 - 1.64) and higher maternal BMI (B = 0.09, P = 0.04, OR = 1.1, 95%CI = 1.01 - 1.19) (Table 3).

Among the GDM group, after adjustment for gestational age, birth weight and pre-delivery BS and UCB acidosis remained significantly associated with neonatal hypoglycemia (B = 2.66, P = 0.002, OR = 14.3, 95% CI = 2.71 - 75.38), moderate-severe neonatal jaundice (B = 2, P = 0.01, OR = 7.38, 95% CI = 1.34 - 32.5), and macrosomia (B = 0.79, P = 0.04, OR = 2.2, 95%CI = 1.33 - 3.65), however, macrosomia was only adjusted for gestational age and pre-delivery BS (Table 3).

5. Discussion

In this prospective cohort study of 654 term neonates who were born through elective cesarean, neonates who were born to mothers with GDM had a significantly higher rate of UCB acidosis compared to neonates who were born to healthy mothers that were independently associated with poor glycemic and weight control during the last gestational trimester. We also found higher rates of adverse

Table 1. Comparison of the Demographics Between Mothers With Term Deliveries Who Had GDM Versus the Healthy Controls[a]

Demographics	GDM Group (N = 80)	Control Group (N = 574)	P Value
Maternal age, years	30.6 ± 5.7	28.4 ± 5.7	0.23
Maternal BMI	29.1 ± 3.9	28.5 ± 4.8	0.11
Gestational age at birth, weeks	38.3 ± 0.4	39 ± 1.1	0.08
Birth weight, grams	3322 ± 564	3188 ± 464	0.07
5 minute Apgar score (Median (Ranges))	10 (6 - 10)	10 (8 - 10)	0.98

[a]Data are presented as Mean ± SD

Abbreviations: GDM, gestational diabetes mellitus; SD, standard deviation; BMI, body mass index.

Table 2. Comparison of the Umbilical Cord Blood pH and Study Outcomes Between Term Neonates Who Were Born to Mothers With Gestational Diabetes Mellitus Versus Those Who Were Born to Healthy Mothers

	GDM Mothers N = 80	Healthy Mothers N = 574	OR	95% CI	P Value
UCB pH (Median (Range))	7.29 (6.85 - 7.48)	7.31 (7.15 - 7.5)	-	-	0.04
UCB acidosis, N (%)	21 (26.2%)	35 (6%)	5.48	2.99 - 10.02	< 0.001
Macrosomia, N (%)	24 (30%)	20 (3.5%)	11.87	6.17 - 22.83	< 0.001
Hypoglycemia, N (%)	31 (38.7%)	10 (1.7%)	35.68	16.51 - 77.08	< 0.001
Severe jaundice, N (%)	47 (58.7%)	96 (16.7%)	7.09	4.31 - 11.64	< 0.001

Abbreviations: GDM, gestational diabetes mellitus; N, number; OR, odds ratio; 95%CI, 95% confidence interval; UCB, umbilical cord blood.

Table 3. Comparison of the Maternal Metabolic Factors and Study Outcomes Between Term Neonates Who Were Born to Mothers With Gestational Diabetes Mellitus and Had UCB Acidosis Versus Those Who Did Not Have UCB Acidosis

	GDM mothers		Non-Adjusted OR (95% CI)	Adjusted [a] OR (95% CI)	Adjusted [a] P Value
	UCB Acidosis (N = 21)	UCB Normal (N = 35)			
Maternal BMI, Mean ± SD	29.4 ± 3.5	27.3 ± 4.5	-	-	0.04
HbA1C levels (%), Mean ± SD	6.1 ± 0.6	5.2 ± 0.3	-	-	0.01
Hypoglycemia, N (%)	16 (76.1%)	15 (25.4%)	9.38 (2.93 – 30.02)	14.29 (2.71 – 75.38)	0.002
Jaundice, N (%)	15 (71.4%)	16 (27.1%)	6.71 (2.22 – 20.32)	7.38 (1.34 – 32.5)	0.01
Macrosomia, N (%)	10 (47.6%)	14 (23.7%)	2.92 (1.02 – 8.31)	2.2 (1.33 – 3.65)	0.04

Abbreviations: UCB, umbilical cord blood; GDM, gestational diabetes mellitus; N, number; OR, odds ratio; 95%CI, 95% confidence interval; BMI, body mass index; HbA1C, glycosylated hemoglobin levels.

[a] Adjustment for gestational age, birth weight and pre-delivery serum glucose levels, macrosomia was only adjusted for gestational age and pre-delivery serum glucose levels.

neonatal outcomes including neonatal macrosomia, hypoglycemia and severe jaundice in term neonates born to mothers with GDM, which were independently associated with UCB acidosis.

In this study term neonates who were born to mothers with GDM, had lower UCB pH in their UC-ABG analysis. UCB acidosis was significantly more detected among these neonates, compared to term neonates who were born to healthy mothers; these results are consistent with other studies (8, 15). In the study of Taricco et al., although reduction in oxygen saturation and O_2 content combined with increased lactate concentration were observed in the fetuses of GDM mothers, the rate of UCB acidosis and UCB pH

were not different between the GDM and non-GDM mothers (14). This could be due to the tight control of glucose levels and GDM during the 3rd trimester in the study of Taricco et al., while in our study many women did not have good glucose control.

Fetal acidosis in GDM pregnancies might be hypoxic and/or metabolic in origin; placental insufficiency and poor glucose and weight control might be important underlying mechanisms for the ABG changes in the cord blood of pregnancies complicated by GDM (9, 11, 13, 15); GDM is associated with significant changes in the structure, development, and function of the placenta (13, 19). Studies have shown that in the chronic condition with pla-

cental dysfunction such as GDM and preeclampsia, impairment of feto-placental blood flow, and poor trans-placental gas exchange can cause chronic fetal hypoxemia and subsequent fetal acidosis (9, 11, 13). Our results that poor glycemic control during the 3rd gestational trimester and higher maternal BMI were independently associated with UCB acidosis in mothers with GDM, further confirm the hypothesis of metabolic origin in addition to the hypoxic origin for the fetal acidosis in GDM (15). As we demonstrated in a previous study (20), high maternal pre-pregnancy BMI and excessive weight gain during gestation are associated with increased glucose levels and impaired glucose metabolism probably through inducing β-cell dysfunction and increasing insulin resistance (20). In addition to the aforementioned mechanisms, placental function in GDM could further get impaired by the disturbances in glucose metabolism and control during the course of GDM, which further increases placental inflammation and oxidative stress (19). All these changes accelerate poor fetal oxygenation and chronic fetal hypoxemia leading to more fetal acidosis (9, 11, 13). Additionally in GDM, the increased passage of glucose through the placenta might induce hyperinsulinemia in the fetus, which increases fetal metabolisms and oxygen consumption and causes the accumulation of lactate and a further fall in the pH (8).

In the current study, mothers with term pregnancies and GDM had higher rates of adverse neonatal outcomes, which was in accordance with other studies (21-25), however, this study showed that among term pregnancies with GDM, adverse neonatal outcomes occur significantly more in those who have UCB acidosis at birth; therefore, UC-ABG analysis could be used as a valuable predictive tool in term GDM pregnancies for early detection of high risk term neonates. In our study UCB acidosis was associated with fetal macrosomia. Ballard et al. (26), and Salvesen et al. (15), also showed the association of fetal acidemia and macrosomia in GDM pregnancies. The hyperglycemic state and other metabolic derangements in GDM can cause fetal pancreatic β-cell hyperplasia resulting in fetal hyperinsulinemia that can cause fetal macrosomia and increases fetal oxygen consumption and fetal acidemia (15).

In our study UCB acidosis was significantly associated with neonatal hypoglycemia in term neonates born to mothers with GDM. Similarly, Flores-le Roux et al., in their study, concluded that neonatal hypoglycemia is influenced by umbilical cord pH and hypoglycemic infants had a lower UCB pH in their study (27). Fetal hypoxia, hyperinsulinemia and transient neonatal hyperinsulinemia that can occur in GDM pregnancies, increase fetal metabolic rate via sympathetic nervous system activation and thyroid hormone secretion as well as prevent the normal activation of metabolic pathways at birth that produce glu-

cose and ketone bodies; all these changes can lead to increased glucose consumption by tissues and cause subsequent neonatal hypoglycemia (27, 28).

To our knowledge, our study was the first that showed term neonates of mothers with GDM who had UCB acidosis, experienced significantly more severe jaundice than those who did not have UCB acidosis at birth. This might be due to the more severe and chronic hypoxemia and hyperinsulinemia experienced by neonates who had UCB acidosis; this chronic hypoxemia can increase erythropoietin synthesis and production with subsequent neonatal polycythemia. Later by the hemolysis that occurs after birth, these neonates can be at an increased risk of experiencing severe hyperbilirubinemia requiring intervention (29). In addition the delayed clearance of bilirubin in these neonates due to impaired hepatocyte uptake, conjugation or excretion can exacerbate hyperbilirubinemia, therefore, close follow up is mandatory in these neonates (30).

The large sample size, and also addressing the changes in UC-ABG parameters in term GDM pregnancies without apparent fetal distress in regard to maternal metabolic factors and evaluating the predictive value and independency of UC-ABG in these pregnancies were the strengths of this study. The current study however had some limitations; we did not collect information regarding the diet and physical activity in the studied population, which could affect both maternal metabolic status and pregnancy outcomes in the studied groups. Also, the results require to be confirmed in other studies and populations because of the different dietary, lifestyle, and genetic patterns among women with GDM in different populations.

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