Maternal risk factors for neonatal acidosis in women with type 1 diabetes

Authors: Pawel Gutaj, Urszula Mantaj, Agnieszka Zawiejska, Łukasz Adamczak, Sylvie Lagodka, Ewa Wender-Ożegowska

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Paweł Gutaj¹, Urszula Mantaj¹, Agnieszka Zawiejska¹, Łukasz Adamczak¹, Sylvie Lagodka², Ewa Wender-Ożegowska¹
Division of Reproduction, Poznan University of Medical Sciences, Poznań, Poland¹
Center for Medical Education in English, Poznan University of Medical Sciences, Poznań, Poland²

Corresponding Author:
Paweł Gutaj, MD, PhD
Department of Obstetrics, Gynecology and Gynecological Oncology, Division of Reproduction, Poznan University of Medical Sciences, 33 Polna St, 60-535, Poznań, Poland.
Email: pgutaj@o2.pl
Tel. 00 48 61 8419 302
Urszula Mantaj, PhD; Email: urszula.mantaj@gmail.com
Agnieszka Zawiejska MD, PhD, associate professor; Email: agazaw@post.pl
Łukasz Adamczak, MD; Email: lukaszadamczak91@gmail.com
Sylvie Lagodka; Email: slagodka@gmail.com
Ewa Wender-Ożegowska MD, PhD, professor; Email: ewaoz@post.pl

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This study is based on the retrospective analysis of routinely collected data and therefore is exempted from formal review by Poznan University of Medical Sciences Ethics Committee.
Abstract

**Introduction:** Type 1 diabetes in the mother is associated with a high risk of adverse neonatal outcomes.

**Objectives:** To identify maternal factors associated with low arterial pH values (pH < 7.10) in infants of type 1 diabetic mothers.

**Patients and methods:** Data from 789 women was included in the analysis. Based on pH values in the umbilical arteries of their infants, women were divided into 2 groups: NORMAL pH - pH ≥ 7.10 and LOW pH - pH < 7.10. Determinants of LOW pH in umbilical artery were identified by logistic regression with data presented as odds ratios and 95% confidence intervals.

**Results:** There was LOW umbilical artery pH in 72 (9.1%) infants. There was an association between maternal HbA1c (glycated hemoglobin) [%] analyzed before delivery and LOW umbilical artery pH - 1.40 [1.11-1.78], P=0.005. A similar association was found for HbA1c analyzed between 20-24 weeks - 1.29 [1.03-1.63], P=0.026. There was no association between the first trimester HbA1c level or lack of preconception care and LOW umbilical artery pH. In logistic regression, there was an association between urgent cesarean sections and LOW umbilical artery pH 1.64 [1.11-2.44], P=0.01 and this association was independent of HbA1c analyzed before delivery.
Conclusions: Lack of sufficient glycemic control in pregnancy is the strongest predictor of neonatal acidosis in women with type 1 diabetes.

Keywords
asphyxia, neonatal acidosis, pregestational diabetes, pregnancy, type 1 diabetes

Introduction
Type 1 diabetes in the mother is associated with a high risk of adverse neonatal outcomes. The most common complications are congenital malformations, premature delivery, fetal macrosomia, and birth injuries [1, 2]. In a study published in 1988, over 25% of infants delivered to diabetic women had perinatal asphyxia [3]. Nowadays, due to significant improvement in diabetic and obstetric care, these numbers seem to have been reduced [4]. Attempts should be made to prevent neonatal acidosis since it is associated with a higher risk of postnatal adverse outcomes including neurological injuries, multi-organ dysfunctions and, increased long-term morbidity and mortality [5, 6]. Analysis of umbilical artery pH values has been widely adopted in clinical practice. This analysis is especially recommended for high-risk populations such as a diabetic pregnant women. Some factors in the general population such as prior cesarean delivery, maternal age 35 years or older, previous neonatal death, general anesthesia, a thick meconium, uterine rupture, and abnormal fetal heart rate have been identified as predispositions to neonatal acidosis [7]. In women with type 1 diabetes,
antepartum hyperglycemia correlates with umbilical erythropoietin levels at birth, which suggests that maternal hyperglycemia induces fetal hyperinsulinemia, hypoxemia and as a consequence—neonatal acidosis. However, there is limited data presenting determinants of neonatal acidosis in pregnancy complicated by type 1 diabetes. We assumed that insufficient control of maternal diabetes might serve as a dominant factor predisposing to neonatal hypoxemia.

Therefore, this aim of this study is to identify maternal factors associated with low cord arterial pH values in newborns of type 1 diabetic mothers.

Patients and Methods

Clinical and laboratory data from 1069 women with type 1 diabetes and their infants from a period between 1993 and 2015 was extracted from the clinical registry of a tertiary care center of the Poznan University of Medical Sciences. The hospital including its outpatient clinic, is the biggest perinatal center for pregnant women with diabetes in Poland. It provides care for patients from the Greater Poland Province (population of approximately 3.4 million). The data of 280 women with diabetes were excluded from the analysis due to: miscarriage (pregnancy loss< 22 weeks), major birth defects, multifetal pregnancy, other than type 1 or unspecified types of diabetes or incomplete information. Finally, data from 789 women with type 1 diabetes were included in the study. All women were treated with intensive insulin therapy during pregnancy. Because a study is based on the retrospective analysis of routinely collected data, it is exempted from formal review by Poznan University of Medical Sciences Ethics Committee.

Registry of Pregnant Women with Diabetes
Clinical and laboratory data of women with type 1 diabetes has been collected and stored in our center continuously since 1993. According to the Polish Diabetes Association recommendations, and our internal standards, every woman with preexisting type 1 diabetes from our region is immediately referred to our department once pregnancy is confirmed. The process of care delivered to diabetic women without complications is based on at least three planned, short-stay hospital admissions during pregnancy: in the first trimester, in mid-pregnancy (20\textsuperscript{th}-24\textsuperscript{th} weeks of gestation), and near delivery (34\textsuperscript{th}-39\textsuperscript{th} weeks of gestation). Patients who require more vigilant surveillance are admitted more frequently. Between hospital admissions, patients are referred every two weeks for regular check-ups in the hospital-based outpatient clinic [8, 9]. We recommend all of our pregnant patients with type 1 diabetes deliver in our center. That way we have direct access to their pregnancy and peripartum data, including the umbilical cord blood gas analysis, which is practiced routinely in our center.

**Umbilical Cord Blood Gas Analysis**

For the purpose of this study, we analyzed pH values in the umbilical artery. Umbilical cord blood was collected separately from both the artery and the vein, soon after birth, from a doubly clamped segment of the cord, and then immediately transported to the laboratory for analysis. During the sampling procedure it is sometimes difficult to differentiate artery from vein, so we assumed that samples with lower pH came from the artery. Based on the pH values of the umbilical arteries of their infants, women were divided into two groups: NORMAL pH- pH ≥7.10 and LOW pH- pH < 7.10.

**Statistical Analyses**
Statistical analyses were performed using MedCalc for Windows, version 12.1.3.0 (MedCalc Software, Mariakerke, Belgium). Testing for normality of data distribution was performed using the D’Agostino–Pearson test. Student’s $t$-test was used to measure the significance of the difference between two continuous variables when data fitted a normal distribution, with results presented as the mean (standard deviation) (SD). In the case of non-normally distributed data, comparisons were made using the Mann-Whitney test, with results presented as the median and interquartile range (IQR). The Chi-square test was used for the comparison of categorical variables. Determinants of LOW pH in umbilical artery were identified by logistic regression with data presented as odds ratios and 95% confidence intervals. Both univariate and multivariate models were built to search for possible interactions between variables. Statistical significance was defined as $P < 0.05$ (two-sided). The presence of vasculopathy was defined as being diagnosed with at least one of the following: retinopathy, nephropathy, or ischemic heart disease. Small for gestational age (SGA) was defined as birth weight lower than the 10th percentile, and large for gestational age (LGA) was defined as a birth weight greater than 90th percentile using age- and sex-specific regional growth charts. The degree of prematurity was described by gestational age as: late to moderate preterm- 32-37 weeks, very preterm 32-28 weeks, and extremely preterm- less than 28 weeks).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study is based on the retrospective analysis of routinely collected data and therefore is exempted from formal review by Poznan University of Medical Sciences Ethics Committee.
Results

The characteristics of the study subgroups are shown in Table 1. Among the study subgroups, there were no differences in maternal age, age at onset of diabetes, diabetes duration, the proportion of women receiving preconception care, the proportion of women with vasculopathy, gestational week at delivery, and body mass index (BMI).

In 72 (9.1%) infants there was LOW pH in the umbilical artery. LOW pH values were associated with decreased Apgar score at 1 minute (0.76 [0.70-0.82], P<0.001) and 5 minutes (0.77 [0.69-0.85], P<0.001) after birth. Maternal age (0.99 [0.94-1.04], P=0.72), age at diagnosis of diabetes (1.01 [0.97-1.04], P=0.75) and diabetes duration (0.99 [0.95-1.04], P=0.78) had no association with LOW umbilical artery pH. Maternal pre-pregnancy BMI (0.98 [0.94-1.02], p=0.40), the presence of diabetic vascular complications (1.23 [0.73-2.01], P=0.44), chronic hypertension (1.32 [0.65-2.70], P=0.44), and gestational hypertension/preeclampsia (0.73 [0.32-1.65], P=0.44) had no impact on LOW umbilical artery pH.

LOW pH values were not associated with gestational age at delivery (0.95 [0.86-1.05], P=0.34) and the degrees of prematurity: late to moderate preterm- 32-37 weeks (1.32 [0.76-2.31], P=0.33), very preterm 32-28 weeks (1.55 [0.45-5.36], P=0.49), and extremely preterm-less than 28 weeks (there was only one extremely preterm infant with NORMAL pH in the umbilical artery of 7.29). There was an association between maternal HbA1c (glycated hemoglobin) [%] analyzed before delivery and LOW pH in the umbilical artery (1.40 [1.11-1.78], P<0.01). A similar association was found for HbA1c analyzed between 20-24 weeks (1.29 [1.03-1.63], P=0.03). There was no association between the first-trimester HbA1c level (as well as lack of preconception care and LOW pH in the umbilical artery.
Of the 107 newborns delivered via urgent cesarean section, 14 (13.1%) of them had LOW pH in the umbilical artery. There were 27 vacuum-assisted deliveries, and 3 (11.1%) of them had LOW pH in the umbilical artery. There were 4 forceps deliveries, in 2 (50%) we found LOW pH in the umbilical artery. In logistic regression, there was an association between the urgent cesarean sections and LOW pH in the umbilical artery (1.64 [1.11-2.44], P=0.01) and this association was independent of HbA1c analyzed before delivery.

Throughout the whole group, there was no association between either neonatal LGA (birthweight > 90 percentile) or SGA (birthweight < 10 percentile) and LOW pH in the umbilical artery.

To address the possible influence of typical obstetric factors on umbilical artery pH results we performed a separate analysis excluding the women who delivered via urgent cesarean sections and operative vaginal deliveries. The association between HbA1c analyzed between 20-24 weeks and before delivery remained significant as follows (1.36 [1.04 to 1.77], P=0.02) and (1.41 [1.07-1.87], P=0.01). Similarly to the previous analysis of the whole group, no association was found between the first trimester HbA1c and umbilical artery pH (1.16 [0.99-1.36], P=0.07). There was still no association between LOW umbilical artery pH and maternal age, age at diagnosis of diabetes, diabetes duration, maternal pre-pregnancy BMI, the presence of diabetic vascular complications, chronic hypertension, gestational hypertension/preeclampsia, and neonatal LGA/SGA.

Discussion

This study is among the first to evaluate determinants of neonatal acidosis in women with type 1 diabetes using such a large cohort.

In all women, we analyzed multiple factors that might have potentially influenced the development of neonatal acidosis. However, we demonstrated that only maternal HbA1c in
the second and third trimesters of pregnancy and urgent cesarean sections were associated with LOW pH in the umbilical artery. In a population-based study of pregnant women with type 1 diabetes, Klemetti et al. demonstrated an association between most recent HbA1c values before delivery and several adverse neonatal outcomes including asphyxia, which is in line with our results. However, these authors did not find a relationship between the first and second trimester HbA1c values and neonatal asphyxia [10]. In our study, there was also no association between first trimester HbA1c and LOW pH in the umbilical artery. This might be explained by the fact that in general, patients significantly improved their metabolic control during pregnancy due to the intensification of their treatment once they were admitted to our center. Similarly, Striakov RS et al. revealed that in patients with preexisting diabetes mellitus, increased levels of HbA1c during early pregnancy are not useful in predicting most adverse outcomes [11]. Cahill AG et al. investigated the impact of glycemic control on neonatal morbidity in pregnancies complicated by gestational and pre-gestational diabetes. The authors showed that late third-trimester HbA1c is the most useful predictive value for neonatal risks in women with diabetes, which is in line with our findings [12]. They focused mainly on Apgar scores <7 at 5 minutes, but Locatelli et al. demonstrated that, as expected, Apgar scores correlate with neonatal acidemia [5].

Elevated BMI predisposes women to many complications during pregnancy and labor. Cnattingius et al. in their study showed that a BMI value > 25 in diabetic pregnant patients is associated with an increased risk of low Apgar scores and severe asphyxia [13]. In our patient group, we did not observe a significant association between maternal BMI and LOW pH value in the umbilical artery, but we focused only on type 1 diabetic pregnant patients and these are rarely obese or overweight.

Diabetic vasculopathy is a well-known risk factor for unfavorable pregnancy outcomes. Type 1 diabetic women with vasculopathy are at a higher risk of pre-eclampsia and pathological
fetal growth as shown by Howarth et al. [14]. However, the authors did not investigate the influence of pH value in the umbilical artery. In our study, maternal vasculopathy was not associated with LOW pH in the umbilical artery. One reason for that may be that the majority of the women with vasculopathy delivered via elective cesarean section for maternal indications including but not limited to vasculopathy.

It is essential that women with diabetes plan their pregnancies and achieve adequate metabolic control from the very beginning of pregnancy. Previous studies showed that patients with pre-gestational diabetes mellitus who plan their pregnancies achieve better obstetric outcomes [15, 16]. In our cohort one-third of women attended preconception counseling, and these proportions were similar in both NORMAL pH and LOW pH groups. This suggests that even in women with poorly controlled diabetes, intensification of treatment and normalization of glycemic control may have beneficial effects on the neonatal condition at birth.

Vascular complications of diabetes such as nephropathy and retinopathy are associated with greater durations of diabetes mellitus and with a lack of adequate metabolic disease control. In 1949 Priscilla White made a classification system of diabetes in pregnancy according to such factors as the age at onset of the disease, duration, and the presence of diabetic complications [17]. Based on this classification Klemetti MM et al. investigated the pregnancy outcomes in women with type 1 diabetes. The authors found that first trimester HbA1c, pre-eclampsia rates, cesarean sections, deliveries before 37 weeks and neonatal intensive care unit admissions increased from class B to F. It seems that the duration of diabetes can influence these outcomes [18]. In our study, the duration of diabetes or the presence of maternal vasculopathy were not associated with an increased risk of LOW pH in the umbilical artery.
Miailhe et al. demonstrated that HbA1c at delivery of 6.4% or higher was associated with pre-labor urgent cesarean sections for abnormal non-stress tests (NST) [19]. Although the false-positive rate for abnormal NST is relatively high and can reach 55%, in many cases, it can be a manifestation of varying degrees of fetal acidosis [20]. In our study, we used a direct method of the evaluation of neonatal condition at birth, but our results seem to confirm the findings of Miailhe et al. Nonetheless, many urgent cesarean sections in our cohort could not be explained by maternal HbA1c, and they were associated with typical obstetric indications. Our study has both strengths and limitations. The study group consisted of a large cohort of consecutively recruited women with type 1 diabetes. These women were managed according to the same protocols in a single obstetric center for women with diabetes. However, because we collected data over a long time-period, we were not able to access all data concerning the course of the delivery, such as total duration, and time from decision-to-delivery in the cases of urgent cesarean sections and operative vaginal deliveries. Because all of these factors may influence umbilical artery pH, we conducted a sub-analysis excluding women who delivered via urgent cesareans and operative vaginal (Vacuum, forceps) procedures. This left us with a subgroup of women who delivered naturally and via elective cesarean sections with no signs of fetal distress. In this subgroup, the determinants of LOW umbilical artery pH remained unchanged. This suggests that the majority of women who delivered newborns with LOW umbilical artery pH were not presenting any signs of fetal distress. This is a significant clinical finding because fetal metabolic alterations, including acidosis, as an effect of maternal hyperglycemia may precede intrauterine fetal death [21-23]. Another limitation of the study is that our records included only early neonatal data, and we were not able to analyze long-term development of the neonates. Umbilical artery pH is an easily obtainable and useful parameter expressing neonatal asphyxia. However, it may not always correlate with the long-term neonatal development.
Conclusions

Among modifiable factors, lack of sufficient glycemic control in pregnancy is the strongest predictor of neonatal acidosis in women with type 1 diabetes. Therefore, improved glycemic control throughout pregnancy may reduce the risk of neonatal distress postpartum. However, a significant number of cesarean sections performed for acute signs of fetal distress resulting in the delivery of an infant with LOW umbilical artery pH values cannot be explained by maternal hyperglycemia, and these are probably related to classic obstetric factors.

Author contribution:

U Mantaj- Data collection or management. Data analysis.
A Zawiejska- Data collection or management. Data analysis. Manuscript writing/editing.
Ł Adamczak- Manuscript writing/editing
S Lagodka- Manuscript writing/editing
E Wender-Ożegowska- Protocol/project development. Data collection or management. Data analysis. Manuscript writing/editing


Table 1 Characteristics of the groups

<table>
<thead>
<tr>
<th></th>
<th>NORMAL pH- pH ≥ 7.10 N=717</th>
<th>LOW pH- pH&lt;7.10 N=72</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age-years, Mean (SD)</td>
<td>28 (5)</td>
<td>28 (5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Maternal age at diagnosis of type 1 diabetes-years, Mean (SD)</td>
<td>15 (8)</td>
<td>15 (9)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes duration, years Mean (SD)</td>
<td>11 (7)</td>
<td>11 (8)</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI, kg/m2 Mean (SD)</td>
<td>23.2 (7.2)</td>
<td>23.9 (5.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>HbA1c I trimester, %; Mean (SD)</td>
<td>7.3 (1.7)</td>
<td>7.7 (1.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>HbA1c II trimester, %; Mean (SD)</td>
<td>6.1 (1.1)</td>
<td>6.4 (1.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c III trimester, %; Mean (SD)</td>
<td>6.3 (0.9)</td>
<td>6.6 (1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pregnancy planning, %</td>
<td>31.5%</td>
<td>30.4%</td>
<td>0.9</td>
</tr>
<tr>
<td>Vasculopathy, %</td>
<td>26.3%</td>
<td>30.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks Mean (SD)</td>
<td>37 (2)</td>
<td>37 (3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Birthweight, grams Mean (SD)</td>
<td>3298 (777)</td>
<td>3231 (853)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

SD (standard deviation)
### Table 2: Predictors of LOW pH in the umbilical artery based on logistic regression models

<table>
<thead>
<tr>
<th>Significant predictors of LOW pH</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c II trimester, % (univariate logistic regression)</td>
<td>1.29 (1.03-1.63)</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c III trimester, % (univariate logistic regression)</td>
<td>1.40 (1.11-1.78)</td>
<td>0.03</td>
</tr>
<tr>
<td>Urgent cesarean section, yes/no (model adjusted for III trimester HbA1c)</td>
<td>1.64 (1.11-2.44)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**HbA1c (glycated haemoglobin)**