Assessment of lactate production as a response to sustained intrapartum hypoxia in large-for-gestational-age newborns

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Abstract

Introduction: Lactate concentration in umbilical cord blood is an important measure of intrapartum anaerobic metabolism. The aim of the study was to compare lactate production of large-for-gestational-age (LGA) fetuses against appropriate-for-gestational-age (AGA) fetuses during hypoxia, in diabetic and non-diabetic mothers.

Material and methods: A total of 17 358 validated paired arterial and venous umbilical cord blood samples taken at birth with a full panel of pH, glucose, and lactate were analyzed relative to LGA (n = 2789) and AGA (n = 14 569). Umbilical cord blood acidemia (pH < mean minus 2 SD) was identified in 518 cases.

Results: Diabetes, but not acidemia, was more common among LGA (5.4%) than AGA cases (2.9%) (respectively P < .0001 and P < .69). At normal pH, glucose was lower in non-diabetes LGA cases, but not in diabetes LGA compared with corresponding AGA cases (respectively P < .0001 and P < .067). Glucose levels were higher in all groups during acidemia (P ≤ .0005), with lower values in non-diabetes LGA but not in diabetes LGA compared with corresponding AGA cases (respectively P = .005 and P < .58). At normal pH, lactate was lower in non-diabetes LGA but not in diabetes LGA compared with corresponding AGA cases (respectively P < .0001 and P < .98), during acidemia, lactate levels were higher in all groups (P < .0001), resulting in no significant difference between LGA and AGA in diabetes as well as in non-diabetes cases (respectively P = .29 and P < .084).

Conclusions: Considering cord acidemia a proxy for intrapartum hypoxia, LGA fetuses showed no impaired ability to produce lactate during hypoxia. Maternal diabetes did not hamper the ability of LGA fetuses to produce lactate during hypoxia.

KEYWORDS
acidemia, cord blood, delivery, diabetes, glucose, hypoxia, lactate

1 | INTRODUCTION

The human fetus has been described as a “glucose-dependent parasite” because the major source of fetal energy comes from the oxidation of glucose.1 Anaerobic conditions during birth force the fetus to oxidize glucose to lactic acid (lactate) for energy. A high umbilical cord lactate concentration at birth is thus an indicator of sustained intrapartum exposure to strenuous hypoxic stress,2-5 resulting in metabolic acidosis with low pH and high base deficit (BD).6

Abbreviations: AGA, appropriate-for-gestational-age; BD, base deficit; BDex, base deficit in extracellular fluid; FPGS, fractional placental glucose supply; GDM, gestational diabetes mellitus; LGA, large-for-gestational-age; SVD, spontaneous vaginal delivery; WD%, weight deviation in percent from the gestational age-adjusted mean weight.

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Based on observations made already during the 1920s, Pedersen launched his well-known hypothesis in the 1960s, highlighting the effect of maternal hyperglycemia in diabetic pregnancies leading to fetal hyperglycemia, which in turn causes fetal hyperinsulinism and subsequent “fetal gigantism” and metabolic dysfunction. This correlation between maternal hyperglycemia, fetal hyperglycemia, and resultant fetal hyperinsulinism is well established and is not limited to diabetes only but covers the whole range of maternal glycemia. Large-for-gestational-age (LGA) fetuses in general show hyperinsulinism resulting in increased deposits of adipose tissue and overweight.

Chronic hyperglycemia and hyperinsulinemia independently and additively affect aerobic and anaerobic metabolism with subsequent increase in oxygen consumption, hypoxemia, acidemia, and lactacidemia, as experimentally demonstrated in fetal sheep. The link between hyperinsulinemia, macromasia, and chronic hypoxemia is recognized in human fetuses as well, which could explain the higher umbilical cord blood lactate found in LGA newborns. However, in fetuses exposed to labor, it cannot be determined to what degree lacticemia is due to antenatal chronic hypoxemia and to intrapartum-fetal oxygen consumption, hypoxemia, acidemia, and lactacidemia, as experimentally demonstrated in fetal sheep. The link between hyperinsulinemia, macromasia, and chronic hypoxemia is recognized in human fetuses as well, which could explain the higher umbilical cord blood lactate found in LGA newborns. However, in fetuses exposed to labor, it cannot be determined to what degree lacticemia is due to antenatal chronic hypoxemia and to intrapartum-sustained oxygen deficit. Holzmann et al found lower scalp blood lactate levels in LGA fetuses as compared with appropriately-gestational-age (AGA) fetuses in a series where non-reassuring cardiotocograms indicated fetal scalp blood sampling. This raises the question of whether LGA fetuses have an impaired ability to produce lactate when exposed to hypoxia. Holzmann and co-workers concluded that hypoxic LGA fetuses had no impaired ability to produce lactate compared with hypoxic AGA fetuses, but because they used lacticemia as a proxy for hypoxia involving comparison of fetuses with scalp lactate >4.8 mmol/L, selection bias was introduced and a difference could thus not be expected.

In this study, we addressed this issue using cord blood acidemia as a proxy for intrapartum hypoxia. We compared umbilical cord blood glucose and lactate concentrations relative to AGA and LGA birthweight cohorts in diabetic and non-diabetic pregnancies during aerobic and anaerobic conditions. We hypothesized that LGA fetuses would have higher glucose and lactate levels than AGA fetuses during non-acidemic conditions, but that during acidemia they would show lower lactate values. Since insulin inhibits glycogenolysis of glycogen to glucose, endogenous glucose might be abated and we therefore also wanted to estimate the maternal glucose supply across the placenta.

## 2 | MATERIAL AND METHODS

Umbilical cord blood gases have for decades been routinely determined at birth at the maternity units of Malmö and Lund, Skåne University Hospital, Sweden. Arterial and venous umbilical cord blood was sampled immediately after birth in separate pre-heparinized 2-mL syringes and analyzed within 15 minutes in ABL 735 Radiometer blood gas analyzers (Radiometer A/S, Copenhagen, Denmark). The analyzers were calibrated daily by an expert biomedical analyst. The Radiometer 735 analyzer determines not only blood gases but optionally also analyzes lactate, glucose, hemoglobin, electrolytes, etc. pH and pCO₂ are determined by potentiometry and l-lactate and o-glucose in plasma by amperimetry.

All analyte results were electronically transferred from the analyzers’ hard drives to a computerized statistical program (STATVIEW® version 5.0.1, SAS Institute, Cary, NC, USA). Samples that did not include a complete panel of values from the umbilical cord artery and vein for pH, lactate, and glucose data were excluded. Another prerequisite was that all blood samples could be identified without doubt in the analyzers’ hard drive data storage by their unique maternal personal identification number, site of sampling (arterial, venous), place of origin (labor and delivery ward), and time and date of analysis. All samples where the analyzer quality check system reported error, for example, poor calibration, temperature error, electrode instability, and air bubbles at the electrode, were also excluded from the study. This rigid criteria ensured a high data quality in our database.

The study material was collected from March 2001 to July 2010, when a total of 28,727 newborns had a complete panel of analyses with pH, lactate, and glucose from both vessels. The final cohort comprised a total of 17,358 cases with complete and validated data, after exclusion of cases with poor analysis quality, cases not fulfilling the validation criteria of a venous-to-arterial pH gradient of ≥0.020, no match in our electronic obstetric database, delivery before 37 weeks or by elective cesarean section, multiple gestations, small-for-gestational-age newborns, and cases without information about birthweight.

A normal pH was defined as a value equal or greater than the gestational age-adjusted mean value minus 2 SD and neonatal acidemia as pH less than the mean minus 2 SD.

BD in extracellular fluid (BD_ecf) was calculated post hoc with the algorithm BD_ecf = −0.9149 × (0.23 × pCO₂ × 10^(0.6276)) – 24.1 + 16.21 × [pH – 7.4]). There is no established reference curve for BD relative to gestational age, but the gestational age-dependency can be adjusted for by the regression equation BD = 4.288 + 0.0319 × (GA – 280.0905), where GA denotes gestational age in days. Using the regression equation, all individual values were adjusted to a fictive gestational age of 280 completed days (40 weeks). Metabolic acidosis was defined as an arterial pH less than the mean minus 2 SD combined with BD_ecf less than 12.0 mmol/L when adjusted to 280 days. Lacticemia was defined as an arterial lactate value above the gestational age-adjusted mean value plus 2 SD according to Wiberg et al.
To estimate the transplacental supply of glucose to the fetus, the fractional placental glucose supply (FPGS) to venous cord blood was calculated as $FPGS = (\text{[glucose vein]} - \text{[glucose artery]})/\text{[glucose artery]}$ concentration per kg placental weight.

AGA was defined as a birthweight within the 10th to the 90th percentile interval, LGA as above the 90th percentile, and small-for-gestational-age as below the 10th percentile relative to our fetal weight reference curve.21

In Southern Sweden, a 75-g oral glucose tolerance test is routinely performed at all maternal healthcare service centers at gestational week 28 in normal pregnancies. Gestational diabetes mellitus (GDM) was defined as a 2-hour capillary blood glucose value $\geq$9.0 mmol/L tested with a HemoCue blood glucose analyzer (HemoCue AB, Ängelholm, Sweden) in 2 consecutive blood samples.22 Women with a 2-hour value between 7.8 and 8.9 mmol/L were retested after 1 week. Women diagnosed with GDM were followed at a specialist antenatal care clinic until delivery, as were women with type 1 or type 2 pre-gestational diabetes mellitus.

### 2.1 Statistical analyses

The Mann-Whitney $U$ test was used for group comparison of continuous variables, simple and multiple linear regression analysis and Kendall’s rank correlation coefficient (tau) for correlation between variables, and the Chi-square test and Fisher’s exact test for comparisons of categorical variables. Multiple logistic regression analysis was used to estimate influences of dependent variables. A two-tailed $P < .05$ was considered statistically significant. Statistics were performed with aid of the STATVIEW® computer software (SAS Institute, version 5.0.1, Cary, NC, USA). Values are reported as mean ± SD and median with range.

### 2.2 Ethical approval

The study was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnr 2009/222 and 2012/5).

### 3 RESULTS

Demographic data of the study population is shown in Table 1. Significant differences between AGA and LGA cohorts were found for nulliparity, diabetes, spontaneous vaginal delivery (SVD), and gestational age. There was a negative association between gestational age and weight deviation in percent from the gestational age-adjusted mean weight (WD%) ($r^2 = .004, P < .0001$) and SVD occurred less often among nulliparous (79%) than among multiparous (93%) ($P < .0001$). The possible influences of demographic factors on glucose and lactate values were estimated using multiple logistic regression analyses (see below).

The umbilical cord arterial plasma glucose concentration was positively associated with gestational age ($r^2 = .015, P < 0.0001$) and negatively associated with WD% ($r^2 = .006, P < .0001$), but not with birthweight ($P = .89$). Using multiple linear regression analysis,
glucose concentration was found to be independently associated with both gestational age ($P < .0001$) and WD% ($P < .0001$).

Similarly, the umbilical cord arterial plasma lactate concentration was positively associated with gestational age ($r^2 = .094$ and $.62$, respectively, $P < .0001$) and negatively associated with WD% ($r^2 = .007$, $P < .0001$), but not with birthweight ($P = .97$). Multiple linear regression analysis showed that lactate concentration was independently associated with both gestational age ($P < .0001$) and WD% ($P < .0001$).

Cord artery concentrations of glucose and lactate were linearly correlated ($r^2 = .21$, $P < .0001$) and both variables were negatively correlated with umbilical cord arterial pH ($r^2 = .020$, $P < .0001$) and negatively associated with WD% ($r^2 = .007$, $P < .0001$), but not with birthweight ($P = .97$).

Acidemia occurred as often in the AGA group (438/14 569, 3.0%) as in the LGA group (80/2789, 2.9%) ($P = .69$). When calculated for acidemic newborns, the positive significant associations between glucose and lactate remained in both the AGA group (n = 438; $r^2 = .053$, $P < .0001$) and the LGA group (n = 80, simple linear regression analysis, $r^2 = .048$, $P = .050$; Kendall’s tau 0.23, $P = .002$) (Figure 1).

In all, 141 women had pre-gestational diabetes and 433 had GDM, resulting in a total of 574 women with diabetes. Diabetes was significantly more common among LGA cases (5.4%) than AGA cases (2.9%) (Table 1). Comparing pre-gestational diabetes and GDM for demographic characteristics presented in Table 1, significant differences were found for SVD (94/141 vs 363/433, $P < .0001$), gestational age (275 ± 8 days vs 277 ± 8 days, $P = .009$), and birthweight (3876 ± 498 g vs 3646 ± 437 g, $P < .0001$), but not for other variables ($P ≥ .08$). There were no significant differences in cord arterial glucose ($P = .32$) and lactate ($P = .49$) concentrations, or rates of acidemia ($P = .21$), BD $\text{ecf}$ ($P = .30$), metabolic acidosis ($P = 1.0$).

**TABLE 2** Umbilical cord arterial plasma glucose concentration (mmol/L) relative to birthweight cohorts, diabetes, and arterial pH in 17 358 singleton deliveries at 37 or more gestational weeks. Values are mean ± SD and median (range).

|                | AGA n = 14 569 | LGA n = 2789 |
|----------------|----------------|--------------|
| Normal pH $a$  | 4.8 ± 1.3      | 4.7 ± 1.5    |
| Acidemia $a$   | 6.4 ± 1.6      | 6.5 ± 1.9    |

*Statistics were performed with the Mann-Whitney U test. The table should be read horizontally for comparisons of AGA vs LGA and diabetes vs non-diabetes, and vertically for comparisons of normal pH vs acidemia. Normal pH was defined as cord artery pH equal or greater than the gestational age-adjusted mean value minus 2 SD, and acidemia as pH less than the mean minus 2 SD.*

**FIGURE 1** Plot of umbilical cord blood arterial glucose-to-lactate values in 80 large-for-gestational-age (LGA) and 438 appropriate-for-gestational-age (AGA) acidemic newborns. Acidemia was defined as a cord artery pH below the gestational age-adjusted mean value minus 2 standard deviations.
Table 3: Umbilical cord arterial plasma lactate concentration (mmol/L) relative to birthweight cohorts, diabetes, and arterial pH in 17,358 singleton deliveries at 37 or more gestational weeks. Values are mean ± SD or median (range).

|            | AGA     | LGA     |
|------------|---------|---------|
|            | Non-diabetes | Diabetes | Non-diabetes | Diabetes | Non-diabetes | Diabetes | AGA vs LGA |
|            | n = 14,569 | n = 2,789 | n = 14,569 | n = 2,789 | n = 14,569 | n = 2,789 |            |
| Normal pH  | n = 13,723 | n = 2,565 | n = 17,023 | n = 2,789 | n = 17,023 | n = 2,789 |            |
|            | 5.0 ± 2.0 | 4.6 ± 1.9 | 5.0 ± 2.3 | 4.6 ± 1.9 | 5.0 ± 2.3 | 4.6 ± 1.9 |            |
|            | (1.2-16.0) | (1.2-15.0) | (1.2-15.0) | (1.2-15.0) | (1.2-15.0) | (1.2-15.0) |            |
| Acidemia   | n = 424  | n = 72  | n = 424  | n = 72  | n = 424  | n = 72  |            |
|            | 10.9 ± 2.4 | 10.4 ± 2.9 | 10.9 ± 2.4 | 10.4 ± 2.9 | 10.9 ± 2.4 | 10.4 ± 2.9 |            |
|            | (6.1-23.0) | (5.7-25.0) | (6.1-23.0) | (5.7-25.0) | (6.1-23.0) | (5.7-25.0) |            |

Statistics were performed with the Mann-Whitney U test. The table should be read horizontally for comparisons of AGA vs LGA and diabetes vs non-diabetes, and vertically for comparisons of normal pH and acidemia.

*Normal pH was defined as cord artery pH greater than or equal to the gestational age-adjusted mean value minus 2 SD, and acidemia as pH less than the mean minus 2 SD.
FIGURE 2 Umbilical cord blood lactate concentration at birth in non-acidemic and acidemic appropriate-for-gestational-age (AGA) and large-for-gestational-age (LGA) birthweight groups of newborns compared between mothers with and without diabetes. At paired comparisons, a significant difference was found only between non-acidemic non-diabetes AGA and LGA. With acidemia, lactate increased in all birthweight groups compared to normal pH ($P < .0001$). For details, see Table 3.

3.3 | $B_{\text{ecf}}$ and metabolic acidosis relative to birthweight groups

Arterial $B_{\text{ecf}}$ could be calculated in 17 243 cases (pCO$_2$ values were missing in 115 cases). Metabolic acidosis status could be determined in 17 354 cases ($111$ of 115 cases with missing pCO$_2$ had a pH greater than the mean minus 2 SD, ie no metabolic acidosis by definition).

Umbilical cord artery $B_{\text{ecf}}$ was significantly lower in non-diabetes LGA cases compared with non-diabetes AGA cases ($P < .0001$), but for diabetes LGA vs diabetes AGA there was no significant difference ($P = .70$) (table not shown). The prevalence of metabolic acidosis was 0.45% (65/14 566) in the AGA group and 0.25% (7/2788) in the LGA group ($P = .20$). There were no significant differences in glucose and lactate concentrations in comparisons between AGA and LGA groups with metabolic acidosis ($P = .087$ and $P = .25$, respectively).

3.4 | Fractional placental glucose supply

Data for FPGS calculation were available in 16 647 cases (placental weight missing in 711 cases). Among non-acidemic cases, FPGS was higher in non-diabetes AGA than non-diabetes LGA cases ($P < .015$); for diabetes cases, the difference was not significant ($P = .58$). When comparing non-acidemic and acidemic cases, FPGS decreased significantly in all groups ($P < .040$) except among diabetes AGA cases ($P = .10$).

Among acidemic cases, non-diabetes LGA cases had a higher FPGS than non-diabetes AGA cases ($P = .027$), but there was no difference for diabetes cases ($P = .61$). In comparisons between diabetes and non-diabetes cases, there were no significant differences within the categories AGA and LGA, respectively, with or without acidemia ($P > .11$).

4 | DISCUSSION

This study showed that despite having lower cord arterial glucose levels relative to AGA fetuses during aerobic conditions, LGA fetuses had similar lactate production capabilities when exposed to sustained intrapartum hypoxia leading to acidemia. This was found in LGA fetuses of both non-diabetic and diabetic mothers. In all birthweight groups, during anaerobic metabolism, glucose was mobilized concomitantly with increased production of lactate. Furthermore, when estimating the “fractional glucose supply” by the placenta, we found that the supply in general decreased during anaerobic metabolism, but it was not impaired in LGA compared with AGA cases.

Considering the association between LGA and hyperinsulism, a simultaneous occurrence of fetal hyperinsulinemia and hyperglycemia was not supported by this study. During both aerobic and anaerobic conditions, the cord glucose concentration was lower in non-diabetes LGA cases than non-diabetes AGA cases. This trend was similar but not significant during aerobic conditions in diabetes LGA. Furthermore, there was a weak but significant negative correlation between the cord glucose concentration and WD%, though the 0.6% impact of WD% on glucose values is negligible.

It thus appears that fetal hyperglycemia is much more a “fetal glucose hypermetabolism” rather than chronic hyperglycemia, with postprandial pulsatile hyperglycemia stimulating fetal insulin secretion. Chronic hyperinsulinemia in LGA fetuses could explain the lower glucose concentration observed during aerobic conditions, enhancing glucose uptake by peripheral tissues and accelerating fetal growth; however, this did not prevent a sufficient mobilization of glucose reserves and lactate production during hypoxic stress.

A major strength of our study was that more than 17 000 complete and strictly validated paired samples of arterial and venous cord blood were analyzed. The series was unselected, meaning that all cord samples were included aside from those of suboptimal quality. However, despite the large sample size, there were only 8 LGA cases with cord blood acidemia in the group of maternal diabetes. According to Mundry and Fisher, this was a large enough number to perform the non-parametric Mann-Whitney U test, but it can still be noted as a limitation when evaluating hypoxic LGA fetuses of diabetic mothers. Another strength was that we performed separate analyses for aerobic and anaerobic conditions, as designated by cord pH values, and estimated the placental glucose supply from the mother. None of our statistical calculations indicated any impaired capacity of the LGA fetus to produce lactate during hypoxic conditions.

We merged pre-gestational and gestational diabetes in the statistical analyses, which we believe was of minor relevance to our hypothesis, since the glycemic control might vary just as much within one of the groups as between the two groups. Several GDM cases might in fact have been previously undetected pre-pregnancy type 2 diabetes. We found no significant differences between the types of diabetes as regards cord glucose or lactate concentrations, or in rates of acidemia, metabolic acidosis or lacticemia.

We did not consider factors such as epidural analgesia and length of labor, which are factors that are known to influence acid-base
status at birth. However, using multiple logistic regression analyses, we evaluated the influence of demographic differences between the AGA and LGA cases, finding no confounding influences. We performed numerous statistical tests, being aware of the risk of type 1 error, but all our findings were consistent and pointed to an intact lactate-producing capacity of LGA fetuses during hypoxia.

5 | CONCLUSION

Considering cord blood acidemia at birth a proxy for intrapartum hypoxia, this population-based comparative study showed that, compared with AGA fetuses, LGA fetuses had an intact ability to produce lactate in response to sustained intrapartum hypoxia. Maternal diabetes did not hamper the ability of LGA fetuses to mobilize glycogen stores for the production of glucose and lactate in strenuous situations during labor.

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CONFLICT OF INTEREST

The authors have stated explicitly that they have no actual or potential conflicts of interest in connection with this article.

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