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Maternal and umbilical cord plasma purine concentrations after oral carbohydrate loading prior to elective Cesarean delivery under spinal anesthesia: a randomized controlled trial

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Abstract

Objective To evaluate the effect of preoperative intake of oral carbohydrates versus standard preoperative fasting prior to elective cesarean delivery on plasma purine levels (hypoxanthine, xanthine, and uric acid) and beta-hydroxybutyrate (β-HB) in mother's blood plasma and umbilical cord blood plasma.

Methods Prospective randomized clinical trial, performed according to the Declaration of Helsinki, IRB approval (KB-0012/113/19, 13.05.2019). Patients with at term gestation with singleton uncomplicated pregnancies, scheduled for cesarean delivery under spinal anaesthesia were randomized in a 1:1 ratio to Group I (oral carbohydrate drinks (CHO Group, oral carbohydrate drink – 200 mL – 12.5% dextrose in water) 2 h prior to surgery in addition to standard solid fasting (6 h) or Group II which underwent only standard fasting (6 h - solids, 2 h for – liquids, SF Group). Blood samples were collected at 2 h after carbohydrate consumption (maternal) and at umbilical cord clamping (umbilical cord). The primary outcomes - plasma concentrations of hypoxanthine, xanthine, uric acid, in maternal blood and umbilical cord blood were measured using high-performance liquid chromatography. The secondary outcomes were blood pH, and lactate, and butyrate concentration.

Results The study was conducted between August 2019, and March 2020 with 148 patients enrolled (75 CHO group; 73 SF group). Lower concentrations of hypoxanthine (3.87 (3.13–5.18) vs. 4.85 (3.88–6.53)μmol/l, $p = 0.00050$)

There is a clinically significant relationship between oral carbohydrate loading and maternal and neonatal purinergic pathways (including ATP), which may guide procedures to optimize outcomes.

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and xanthine (0.79 (0.68–0.95) vs. 1.00 (0.88–1.22) µmol/l, < 0.00001) were observed in the maternal blood plasma and umbilical cord blood plasma (10.6 (8.00-16.5) vs. 13.9 (8.53–24.8) µmol/l, $p = 0.035$ and 1.05 (0.82–1.58) vs. 1.45 (0.94–3.17) µmol/l, $p = 0.0035$) in patients supplemented with carbohydrates. No difference in β-hydroxybutyrate concentration was noted.

Conclusions Oral carbohydrate loading prior to cesarean delivery was associated with lower plasma purine levels in maternal and umbilical cord blood. Further work to understand the role of the purinergic pathway and ATP metabolism in maternal and neonatal health may guide interventions such as carbohydrate loading to optimize outcomes.

Trial registration ClinicalTrials.gov identifier NCT04069806 (20190823).

Keywords Purines, Hypoxanthine, Xanthine, Uric acid, Oral carbohydrate, Cesarean delivery

Background

Pregnancy is characterized as a physiologically distinct period that can be associated with oxidative stress, especially during fasting. Every surgery, including cesarean delivery, causes significant changes in metabolic and hormonal processes, which can have negative implications for postoperative recovery [1]. As underscored recently, excessive preoperative fasting can have detrimental effects on patients, including women undergoing cesarean delivery, including insulin resistance with ketosis, dehydration, and increased catabolic response to surgery [2–5].

It has been shown that oral carbohydrate loading (CHO) improves outcomes in surgery and labor, including cesarean delivery, but the cellular energetic pathways are not fully understood [2]. Preoperative CHO significantly reduces the mean fasting time from the last caloric intake and may help prevent metabolic derangements. Limiting fasting to < 4 h with a carbohydrate drink significantly reduces ketonuria [3] and improves insulin sensitivity in patients [1, 5, 6]. In addition, carbohydrate-rich beverages used before cesarean delivery compared with fasting procedure were associated with reduced thirst, hunger, shorter time to flatus [5], and even shorter time to colostrum [7], but not with reduced incidence of postoperative nausea and vomiting (PONV) [5]. In pregnant women, gastric aspiration was also not observed when a carbohydrate drink of different concentration (5.9%, 10%,14%), quantity (150mL or 355mL) and time (1 to 4 h before induction of spinal anesthesia) was administered [8, 9]. In turn, a randomized clinical trial indicated an increase in the neonatal glucose level [6].

With metabolic stress and decreased delivery of glucose, mitochondrial dysfunction during pregnancy and delivery may disrupt the purinergic pathway of the adenosine triphosphate (ATP) cycle [10]. Purine bases and nucleosides are the end-products of cellular conversion in tissues and can be utilized by various cells of the body, including erythrocytes, hepatic and kidney cells, or muscles. This occurs within the purine conversion pathways and influences the cellular energy status [10]. However, when tissue metabolic needs exceed glucose delivery to cells, degradation of ATP occurs, with the production of a series of intermediate products: ATP → ADP (adenosine diphosphate) → AMP (adenosine monophosphate) → adenosine → inosine → hypoxanthine → xanthine → uric acid → excretion of uric acid with urine [10, 11].

In addition, a shift from the utilization of glucose to the utilization of fat may occur during periods of fasting. Prolonged fasting leads to a shift from carbohydrates to fat as the primary energy source, resulting in the production of ketones such as beta-hydroxybutyrate (β-HB) [12]. Beta-hydroxybutyrate serves as an alternative energy source for extrahepatic tissues, such as the brain, heart, and skeletal muscles, when glucose is limited, such as during starvation [13, 14] with hyperketonaemia as a side effect in many patients. According to Bellwood et al. if starvation duration is limited by oral carbohydrate use to under 4 h, then the incidence of ketonuria is 10% [3].

The working hypothesis for this study was that the concentration of purines (hypoxanthine, xanthine, and uric acid) related to cell energy will differ between patients undergoing elective cesarean delivery under spinal anaesthesia and their offspring, depending on the preoperative intake of oral carbohydrate to limit the negative effects of preoperative fasting.

Previous studies demonstrated metabolites of the purine pathway in umbilical cord or term neonates, including uric acid levels and hypoxanthine levels [15–17] or hypoxanthine, xanthine, and uric acid [11] by mode of delivery (elective cesarean delivery, oxytocin-augmented labor), but these metabolites have not been previously compared between mothers fasted before cesarean delivery and those receiving oral carbohydrate supplementation.

Unraveling the details of energy transfer during perioperative fasting with glucose deprivation and oxidative stress seems to be an important and relatively accessible target to improve mother and infant outcomes after cesarean delivery, with information relevant for anesthesiologists, obstetricians, and neonatologists. Therefore, this interdisciplinary study aimed to examine the effect of

preoperative intake of oral carbohydrates versus standard preoperative fasting in elective cesarean deliveries on plasma purine levels (hypoxanthine, xanthine, and uric acid) and β-HB in mothers and healthy term neonates.

Materials and methods

Patients and study design

This was a secondary analysis of a prospective unblinded randomized clinical trial conducted between August 2019, and March 2020. The study was performed following the Declaration of Helsinki after gaining approval of the Bioethical Committee of the Pomeranian Medical University in Szczecin, Poland (KB-0012/113/19, dated 13.05.2019). It was registered prospectively at ClinicalTrials.gov before the inclusion of the first patient (Identifier: NCT04069806). The data used in this analysis has been collected during the initial study (ClinicalTrials.gov identifier: NCT04069806) and were deposited in a publicly available dataset on the Mendeley Data website: "POC-NaVoP", Mendeley Data, V2, doi: https://doi.org/10.17632/fx8394xnh4.2. https://data.mendeley.com/datasets/fx8394xnh4/2 (accessed on 20 September 2022). A full description of the methodology was published previously [18]. Adult patients (> 18 years), with single uncomplicated pregnancies scheduled for an elective cesarean delivery at term gestation (37–42 weeks) under spinal anesthesia were included. Exclusion criteria included diabetes (gestational or type I or II diabetes mellitus, gastroesophageal reflux disease, history of bariatric surgery, obesity (BMI > 40), inability to provide informed consent, contraindications to spinal anesthesia (i.e., coagulopathy) or contraindication to oral carbohydrate loading.

In this study patients scheduled for an elective cesarean delivery were randomized in 1:1 ratio using a randomization table generated for two groups. A member of the research team who was not involved in patient care allocated patients to one of the two study groups. Patients in Group I received an oral carbohydrate drink 2 h before the surgery (CHO Group, oral carbohydrate drink – 200 mL – 12.5% dextrose in water, Pre-op®, N.V. Nutricia, Zoetermeer, The Netherlands) in addition to standard fasting for solids (6 h). Patients in Group II underwent standard fasting (SF Group; 6 h for solids and 2 h for clear liquids).

Sample Preparation

Venous blood from the mothers and arterial umbilical cord blood samples were collected. Venous blood from the mothers was collected directly before surgery, 2 h after consuming a high-carbohydrate drink (CHO group). Arterial blood from the umbilical cord was collected immediately after umbilical cord clamping and removal. The blood was transported in refrigerated conditions to the laboratory and was centrifuged (20,000 g, 10 min, 4°C).

Primary and secondary outcomes

The primary outcome was plasma purine concentrations (hypoxanthine, xanthine, and uric acid) in maternal and umbilical cord blood. The secondary outcomes were blood pH, lactate, and β-HB blood concentration.

Biochemical parameters analysis

β-hydroxybutyrate analysis

The concentration of β-HB was determined in the blood serum of pregnant women and umbilical cord blood using the colorimetric method (505 nm) using β-Hydroxybutyrate Assay Kit H7587-58 (Pointe Scientific, Poland).

Blood pH, and lactate analysis

Lactate concentration and blood pH were measured immediately after collection in the heparinized blood of pregnant women and umbilical cord blood using a blood gas and electrolytes analyzer (GEM Premier 3500, Instrumentation Laboratory, USA).

Plasma purine analysis

The heparinized blood was centrifuged as above and plasma was deproteinized with 300 µl of perchloric acid (1.3 M), mixed, and then stored at -80°C until further testing was performed. The plasma was thawed on ice and centrifuged (20,000 g, 5 min, 4°C). Potassium phosphate was added to 400 µl of the supernatant to obtain a pH of 6–7. The samples were centrifuged again. The concentrations of hypoxanthine, xanthine, and uric acid were determined in the plasma using high-performance liquid chromatography (HPLC).

All buffer chemicals and solvents used as mobile phases were of HPLC grade and were purchased from Sigma Aldrich (St Louis, MO, USA) or Merck. Double-distilled water was obtained from a Milli-Q Water System (Millipore, Billerica, MA, USA). All buffers used for HPLC analysis were filtered through 0.22 µm nylon filters (Agilent). A detailed list of reagents was previously published [19].

The HPLC separations were performed on an Agilent Technologies 1260 liquid chromatograph, consisting of a model G1379B degasser, a model G1312B bin pump, a model G1316A column oven, and a model G1315CDAD VL+. Samples were injected using model G1329B. An Agilent ChemStation software (Agilent Technologies, Cheadle, UK) was used for instrument control and data acquisition and analysis. The separation was completed on a Thermo Scientific Hypersil BDS C18 column 100 × 4.6 mm 3 µm (cat no. 28103–104630). The temperature of the column oven was set at 20^0C.

A dual mobile phase gradient was used to achieve appropriate separation of all analytes of interest. Mobile phase A contained 150mM KH2PO4/K2HPO4, 150mM KCl pH 6.0. Mobile phase B had the same final concentrations as mobile phase A, except for the addition of 15% acetonitrile (v/v). The elution was performed with a linear gradient. The flow rate was 1.0 mL/min. The sample injection volume was 20 mL. The DAD detector monitored peaks by adsorption at 254 nm.

Statistical analysis and sample size calculation

Categorical variables were shown as proportions, with Chi-square test used for comparison between groups. Continuous variables were shown as medians with first quartile and third quartile. To describe the baseline characteristics of the patients the Mann–Whitney U test or Student's t-test were used. Spearman rank correlations were performed to obtain correlation coefficients. Statistical significance is a p-value $p < 0.05$.

This manuscript is a secondary analysis of a randomized controlled trial, so the sample size was calculated for the original trial to detect specified difference between groups in the incidence of selected endpoint (PONV) [18]. Such sample size calculation is not relevant to the aim of the current secondary analysis, so it is not presented in the manuscript. All data were analyzed using software Statistica 13 (StatSoft, Inc., Tulsa, OK, USA).

Results

Baseline characteristics

The blood and umbilical cord blood samples from 148 patients (CHO group – 75; control group – 73) scheduled for cesarean delivery were collected. There were no significant differences between the two groups regarding baseline characteristics, intraoperative or anaesthetic factors (Appendix 1 and Appendix 2).

Neonatal data are presented in Appendix 3. No significant differences in neonatal data were noted in respect of the gestational age, gender, or condition after delivery, with comparable Apgar scores at 1, 5 min and 10 min. The median neonatal birth weight was significantly higher in Group I 3510 g (Q1-Q3 3200–3730 g; $p = 0.033$ compared to Group II 3350 g (Q1-Q3 3080.0–3640.0).

Biochemical parameters

Plasma concentrations of uric acid, hypoxanthine, xanthine, lactate, β-HB, and plasma pH were measured from maternal blood and umbilical cord blood. Significantly lower concentrations of hypoxanthine (3.87 (3.13–5.18) vs. 4.85 (3.88–6.53)μmol/l, $p = 0.00050$) and xanthine (0.79 (0.68–0.95) vs. 1.00 (0.88–1.22) μmol/l, < 0.00001) were observed in the mother's blood plasma and umbilical cord blood plasma (10.6 (8.00-16.5) vs. 13.9 (8.53–24.8) μmol/l, $p = 0.035$ and 1.05 (0.82–1.58) vs. 1.45 (0.94–3.17) μmol/l, $p = 0.0035$) in the CHO group compared to the fasted group (Table 1).

Moreover, significantly higher pH (7.45 (7.43–7.46) vs. 7.43 (7.41–7.44), $p = 0.0013$) and plasma lactate concentration (1.50 (1.30–1.90) vs. 1.10 (0.90–1.30) mmol/l, $p < 0.00001$) were found in the mother's blood in patients supplemented with carbohydrates before the procedure (Table 1).

Correlations between the measured parameters in blood plasma were analyzed. In the CHO group, significant positive correlations were found in the mother's blood between the plasma concentrations of uric acid and xanthine and β-HB, hypoxanthine and xanthine, xanthine, and lactate and β-HB (Table 2). On the other hand, significant negative correlations between blood pH and plasma xanthine and lactate concentrations were identified (Table 2).

In cord blood plasma, significant positive correlations were found between xanthine, hypoxanthine, and lactate concentrations, as well as significant negative correlations between blood pH and xanthine and lactate concentrations (Table 2).

Additionally, in the group of patients who received carbohydrate supplementation, significant positive correlations were observed between uric acid concentrations in maternal blood plasma and umbilical cord blood plasma, as well as between hypoxanthine concentrations in these two compartments. Moreover, a significant positive correlation was observed between the concentration of xanthine in the mother's plasma and the concentration of uric acid in the umbilical cord plasma (Table 2).

In the CHO group, significant positive correlations were found in the mother's blood between plasma concentrations of hypoxanthine and xanthine, lactate, β-HB, as well as between xanthine and lactate concentrations, as well as a significant negative correlation between blood pH and plasma lactate concentration (Table 3).

In cord blood plasma, significant positive correlations were found between the concentrations of uric acid and lactate, hypoxanthine, and xanthine, as well as a significant negative correlation between blood pH and lactate concentration (Table 3).

Additionally, in the CHO group, significant positive correlations were found between plasma uric acid concentrations in the mother's blood and umbilical cord blood. Significant positive correlations were also observed between maternal blood pH and hypoxanthine and xanthine concentrations in umbilical cord blood plasma (Table 3).

The biochemical changes are summarized in Figs. 1 and 2.

Table 1 Purine, blood pH, plasma lactate, and β-hydroxybutyrate concentrations in maternal plasma and umbilical arterial plasma in a group of patients supplemented orally with carbohydrates and fasting patients undergoing spinal anesthesia before planned Cesarean delivery

Parameters		n	Group I - CHO	n	Group II - SF	p*
			Median (IQR)		Median (IQR)	
Mother	UA [µmol/l]	75	447 (394–525)	73	484 (426–539)	0.13
	HYP [µmol/l]	75	3.87 (3.13–5.18)	73	4.85 (3.88–6.53)	0.00050
	XA [µmol/l]	75	0.79 (0.68–0.95)	73	1.00 (0.88–1.22)	< 0.00001
	blood pH	74	7.45 (7.43–7.46)	73	7.43 (7.41–7.44)	0.0013
	LAC [mmol/l]	74	1.50 (1.30–1.90)	73	1.10 (0.90–1.30)	< 0.00001
	β-HB [mmol/l]	75	1.71 (1.58–1.87)	73	1.69 (1.51–1.78)	0.14
Umbilical cord	UA [µmol/l]	75	452 (396–537)	71	478 (425–527)	0.22
	HYP [µmol/l]	75	10.6 (8.00-16.5)	71	13.9 (8.53–24.8)	0.035
	XA [µmol/l]	75	1.05 (0.82–1.58)	71	1.45 (0.94–3.17)	0.0035
	blood pH	71	7.33 (7.30–7.36)	70	7.34 (7.31–7.36)	0.93
	LAC [mmol/l]	70	1.55 (1.20–2.10)	70	1.50 (1.30–1.90)	0.82

CHO group – preoperative oral carbohydrate supplementation; SF group – fasted for 6 h for solids and 2 h for clear liquids; *U Mann-Whitney test; IQR – Interquartile Range; UA – uric acid; HYP – hypoxanthine; XA – xanthine; LA – lactate; β-HB - β-hydroxybutyrate

Discussion

The results of this secondary biochemical analysis of a prospective randomized controlled trial showed that concentrations of hypoxanthine and xanthine in the mother's blood plasma and umbilical cord blood plasma in patients supplemented with carbohydrates were significantly lower compared to patients without carbohydrate supplementation undergoing spinal anesthesia for elective cesarean delivery, with no differences between the level of uric acid between the two groups. These results suggest a clinically important relationship between CHO and maternal and neonatal ATP metabolism and the purinergic pathway. What is important to emphasize is that during metabolic stress (i.e., fasting) with limited glucose access, tissues, and cells utilize a pathway alternative to ATP formation through ADP phosphorylation. In such an event ATP undergoes a different process - degradation in the purinergic pathway with the formation of hypoxanthine and xanthine and later conversion to uric acid. Lower levels of intermediate products (hypoxanthine and xanthine) in the group provided a preoperative CHO suggesting that preoperative glucose delivery limits metabolic stress and is associated with a favorable biochemical response.

Significant positive correlations were observed in the group of patients who received carbohydrate loading (CHO) prior to elective cesarean delivery. In maternal plasma, these included correlations between uric acid and xanthine, uric acid and β-hydroxybutyrate (β-HB), hypoxanthine and xanthine, xanthine and β-HB, and lactate and β-HB.

The authors are unaware of any prior studies comparing CHO loading to no CHO loading in patients undergoing elective cesarean delivery, with maternal and neonatal assessment for purinergic pathway metabolites. Some studies are reporting metabolic data in this aspect of research, including a study by Calderon et al. who compared the effect of modes of delivery on purines and malondialdehyde concentration in the plasma of blood drawn from the umbilical artery of healthy newborns born at term [11], demonstrating that vaginal delivery was associated with higher hypoxanthine and xanthine concentration than elective cesarean delivery [11]. The authors hypothesize that reduction of placental and umbilical flow during uterine contractions, especially when augmented with oxytocin infusion, decreases the blood flow between the mother and her fetus which may preferentially induce the ATP breakdown pathway with increased levels of xanthine and hypoxanthine. However, no direct correlation was demonstrated between purine levels and negative clinical outcomes [11]. Although our study examined the purine pathway in the context of

Table 2 Correlations between purines, blood pH, lactate, and β-hydroxybutyrate in maternal plasma and umbilical arterial plasma in a group of patients supplemented orally with carbohydrates (Group I – CHO) undergoing spinal anesthesia before elective Cesarean delivery

Parameters		Mother						Umbilical cord				
		UA	HYP	XA	blood pH	LA	β-HB	UA	HYP	XA	blood pH	LA
		Rs						Rs				
Mother	UA		-0.04	**0.32**	0.02	-0.03	**0.24**	**0.94**	-0.06	-0.12	0.03	-0.16
	HYP			**0.39**	-0.09	0.22	0.21	-0.01	**0.24**	0.17	-0.04	-0.03
	XA				**-0.34**	**0.30**	**0.24**	**0.35**	-0.16	-0.10	-0.04	0.04
	blood pH					**-0.24**	0.08	0.01	0.19	0.09	0.11	0.10
	LA						0.22	-0.08	0.06	0.07	0.07	0.13
	β-HB							0.19	0.05	0.10	0.22	-0.16
Umbilical cord	UA								-0.13	-0.21	0.06	-0.18
	HYP									**0.83**	-0.06	0.12
	XA										**-0.23**	**0.29**
	blood pH											**-0.45**
	LA											

bolded values - statistically significant; CHO group – preoperative oral carbohydrate supplementation group; SF group – fasted for 6 h for solids and 2 h for clear liquids; Rs – Spearman's rank correlation coefficient; UA – uric acid; HYP – hypoxanthine; XA – xanthine; LA – lactate; β-HB - β-hydroxybutyrate

Table 3 Correlations between purines, blood pH, lactate, and β-hydroxybutyrate in maternal plasma and umbilical arterial plasma in a group of fasting patients (Group II – SF) undergoing spinal anesthesia before elective Cesarean delivery

Parameters		Mother						Umbilical cord				
		UA	HYP	XA	blood pH	LA	β-HB	UA	HYP	XA	blood pH	LA
		Rs						Rs				
Mother	UA		-0.14	0.15	0.10	0.06	-0.01	**0.95**	-0.04	0.03	0.18	0.21
	HYP			**0.43**	-0.03	**0.24**	**0.25**	-0.16	0.17	0.15	0.02	0.11
	XA				-0.14	**0.28**	0.03	0.12	-0.05	0.00	0.04	0.08
	blood pH					**-0.32**	0.14	0.04	**0.29**	**0.31**	0.06	0.09
	LA						-0.09	0.08	0.08	0.16	0.14	0.05
	β-HB							0.03	-0.15	-0.15	-0.03	0.05
Umbilical cord	UA								-0.16	-0.07	0.18	**0.25**
	HYP									**0.91**	-0.03	0.06
	XA										-0.04	0.16
	blood pH											**-0.40**
	LA											

bolded values - statistically significant; CHO group – preoperative oral carbohydrate supplementation group; SF group – fasted for 6 h for solids and 2 h for clear liquids; Rs – Spearman's rank correlation coefficient; UA – uric acid; HYP – hypoxanthine; XA – xanthine; LA – lactate; β-HB - β-hydroxybutyrate

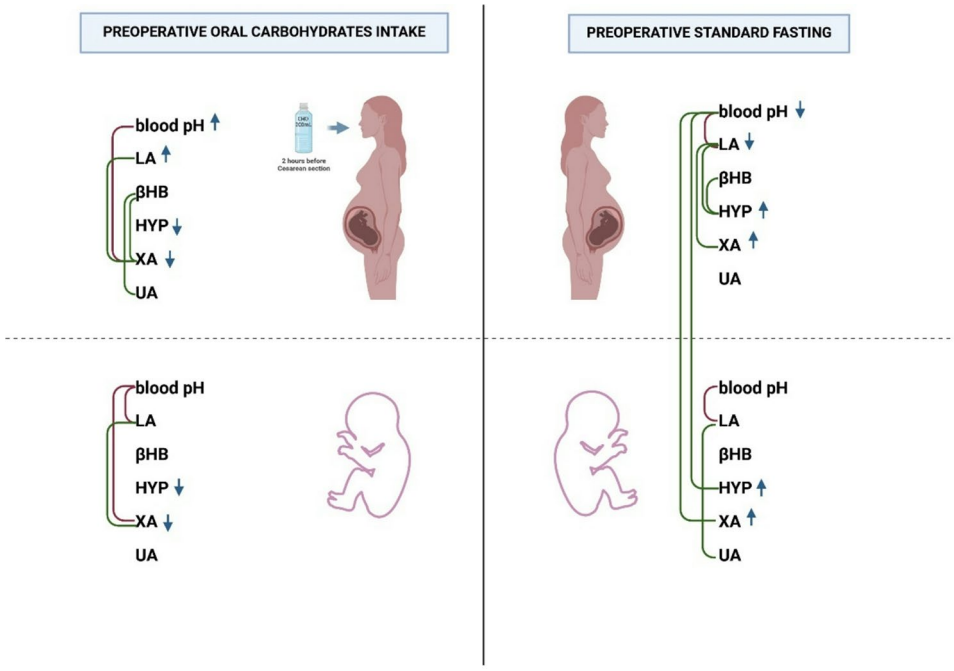

Fig. 1 Correlations (Spearman's rank correlation) and comparison of the analyzed parameters: hypoxanthine (HYP), xanthine (XA), uric acid (UA), lactate (LA), β-hydroxybutyrate (β-HB), blood pH, between the studied groups as follows: preoperative oral carbohydrate group and preoperative standard fasting group ($p < 0.05$). ↑ higher concentration/higher parameter value compared to the second study group; ↓ lower concentration/lower parameter value compared to the second study group; - negative correlation (red line); - positive correlation (green line); (Created with BioRender.com)

maternal and neonatal metabolism, it does not provide evidence for a direct effect of metabolic changes with CHO or SF on neonatal clinical outcomes.

Uric acid is the end-product of the purinergic pathway, usually excreted in urine. Our findings of no difference in uric acid between the two groups suggest that uric acid is either not produced excessively or may be excreted rapidly. Studies regarding this subject are rather scarce. In a quantitative study Manzke et al. measured the excretion of uric acid, hypoxanthine, and xanthine in a group of healthy infants at birth and 12 h later, with measurements of the urinary excretion of uric acid being nearly the same at both time points [15]. Wallenburg et al. quantified uric acid levels in infants born from mothers with vaginal delivery augmented with oxytocin infusion and concluded that uric acid values in umbilical cord plasma do not reflect neonatal levels during labor, with no explanation as to the cause of this observation [16].

β-hydroxybutyrate serves as an alternative energy source for extrahepatic tissues, such as the brain, heart, and skeletal muscles, when glucose is limited, such as during starvation [14]. Fasting shifts the utilization of glucose towards the utilization of fat, where a combination of reduced insulin levels and elevated cortisol and glucagon levels additionally augmented by stress stimulates the release of non-esterified fatty acids by adipocytes [3, 15]. Prolonged fasting causes a change of primary energy sources from carbohydrates to fat, resulting in the production of ketone bodies, including β-HB [15]. The metabolism of β-HB in humans involves its production in the liver through the degradation of fatty acids [20]. Hyperketonaemia and ketoacidosis have been observed in young children fasting for surgery [13].

On the other hand, an observational study including 100 non-diabetic adults presenting for surgery indicated no relationship between fasting times and either blood glucose or ketone levels [13]. Normal ketone levels are defined as β-HB less than 0.5 mmol/l, hyperketonaemia > 1.0 mmol/l, and ketoacidosis - above 3.0 mmol/l. Baseline ketone levels are two to three times normal during pregnancy [20]. In our study of mothers undergoing spinal anesthesia before planned cesarean delivery, there was no difference in concentration of β-HB after supplementation with oral carbohydrates and compared to fasting group. This finding suggests that in this patient population, fasting with or without CHO did not shift the utilization of glucose towards the utilization of fat.

To our knowledge, there are no other studies analyzing the level of β-hydroxybutyrate in patients qualified for cesarean delivery in the context of the use of a carbohydrate drink or standard fasting, with which we could compare our results. So far, only the study by Scheepers et al. has been published, in which the study group consisted of pregnant women during physiological labor, receiving a carbohydrate drink or placebo just before the second stage of labor. Similarly to our study,

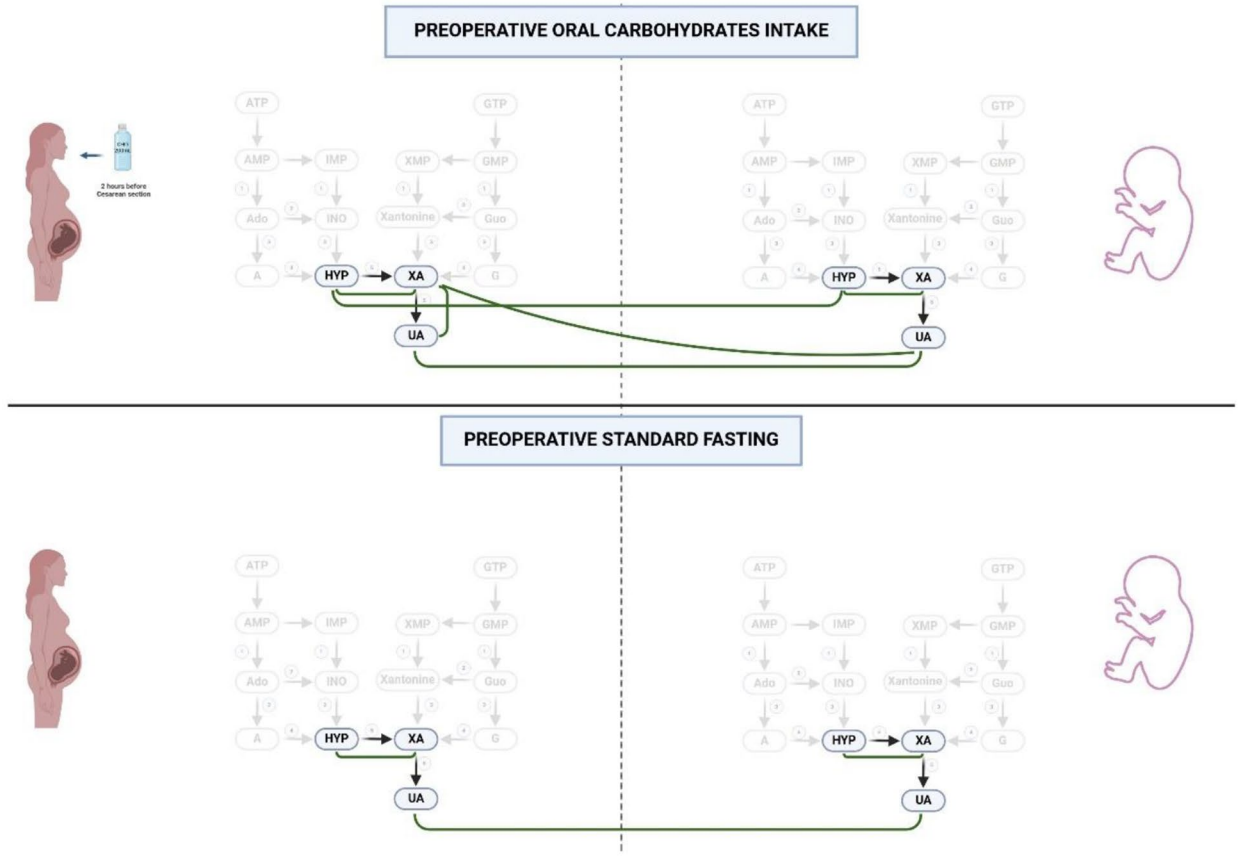

Fig. 2 Correlations (Spearman's rank correlation) between analyzed parameters: hypoxanthine (HYP), xanthine (XA), uric acid (UA), in mothers and neonates among the studied groups as follows: preoperative oral carbohydrate group and preoperative standard fasting group ($p < 0.05$). - negative correlation (red line); - positive correlation (green line); Adenine (A), adenosine (Ado), Adenosine monophosphate (AMP), Adenosine triphosphate (ATP), guanine (G), guanosine (Guo), guanosine monophosphate (GMP), Guanosine-5′-triphosphate (GTP), hypoxanthine (HYP), inosine monophosphate (IMP), inosine (INO), uric acid (UA), xanthine (XA), xanthosine monophosphate (XMP); 1-nucleotidase, 2- adenosine deaminase (ADA), 3-nucleoside phosphorylase, 4-deaminase, 5- xanthine oxidase (XAO); (Created with BioRender.com)

no significant effect of drink consumption on the level of β-hydroxybutyrate in the compared groups was demonstrated [21].

In turn, Li et al., in order to estimate the effect of fasting time on the acid-base balance, used blood pH [22]. On the other hand, Burstaj et al. examined the general level of ketone bodies in patients undergoing elective and emergency surgical procedures. In this study, β-HB levels were not specifically analyzed [13].

In cord blood plasma of the oral carbohydrate loading group, negative correlations between blood pH and xanthine, and also blood pH and lactate concentrations were found, as well as a significant negative correlation between blood pH and lactate concentration in the standard fasting group of our study. In a study performed by Irestedt et al., a strong inverse correlation between arterial hypoxanthine concentration and pH (r = -0.81, p less than 0.01) was found [17], suggesting that increased purinergic pathway stimulation and adenosine release influences the stress response of vaginal delivery and may offer protection against asphyxia in the perinatal period. Moreover, in patients supplemented with carbohydrates before the procedure blood pH was significantly higher ($p = 0.0013$) as was plasma lactate concentration ($p < 0.00001$). Intuitively, an improved metabolic profile with limited oxidative stress through glucose supplementation would lead to a decrease in the level of lactate and not an increase as seen in our study. Similarly, however, Scheepers et al. showed that intake of carbohydrates immediately before the second stage of labor also caused lactate increase leading to a conclusion that the difference between venous and arterial lactate levels may suggest its transport to the fetal circulation without consequent fetal acidemia [21].

It should also be mentioned that in the context of our primary analysis involving the same group of mothers undergoing spinal anesthesia before planned cesarean delivery, the carbohydrates supplementation reduces the incidence of vomiting or dry retching at 24 h after

cesarean delivery compared with standard fasting group, which is an important clinical outcome [18].

The number of studies is limited regarding the biochemical parameters evaluated in maternal and umbilical cord plasma in response to fasting versus CHO before cesarean delivery. This study therefore serves as an important pilot and a call for further research to measure the dynamics of purine metabolites. The methodology for purine metabolic studies is very time-sensitive, requiring meticulous attention during sample collection and handling. Despite these challenges, a continuation of this research may lead to improved perioperative guidelines for minimizing metabolic stress during cesarean delivery. Understanding the purinergic pathway's role in maternal and neonatal health with in-depth biochemical analysis is the starting point that may guide future interventions and procedures to optimize outcomes and could lead to a change in clinical guidelines.

Study limitations

Two major limitations of the study include a relatively small sample size (although calculated in advance for study power) and single-center observation that may preclude generalizability and make this research a pilot study. This means that the study reports preliminary data that would need further confirmation in larger, multicenter trials. Nevertheless, the biochemical signal in the preference for CHO by pregnant women waiting for elective cesarean delivery is clear. Another limitation was the exclusion of diabetic mothers. This was the result of calls for cautious use of CHO in diabetic patients due to fear of hyperglycemia and ketone production. Performing research regarding purinergic pathway is especially important in the context of the increasing prevalence of gestational diabetes.

Conclusions

Our observation that oral carbohydrate loading before cesarean delivery was associated with lower plasma purine levels in maternal and umbilical cord blood may suggest a clinically important relationship between CHO and maternal and neonatal ATP metabolism and the purinergic pathway. The concentration of β-HB was not significantly different between the two groups, meaning that the mobilization of energy stores alternative to glucose did not occur. Further research is needed to understand the nuances of the ATP degradation pathway after fasting before cesarean delivery to define the benefits of CHO in this vulnerable population. The necessity to understand the role of the purinergic pathway in maternal and neonatal health should guide future research and consequently future interventions and procedures to optimize outcomes leading to a change in clinical guidelines.

Abbreviations

A	Adenine
Ado	adenosine
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
CHO	oral carbohydrate
β-HB	beta-hydroxybutyrate
G	guanine
GMP	guanosine monophosphate
GTP	Guanosine-5′-triphosphate
Guo	guanosine
HPLC	high-performance liquid chromatography
HYP	hypoxanthine
IMP	inosine monophosphate
INO	inosine
LA	lactate
UA	uric acid
XA	xanthine
XAO	5- xanthine oxidase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07637-6.

Supplementary Material 1

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Author contributions

K.K. - study protocol, literature review, results analysis, drafting the manuscript, manuscript revision, study supervision; D.JM.- material collection, material analysis, results analysis, drafting the manuscript, figures preparing, manuscript revision; A.W. - study protocol, data collection, material collection, results analysis, drafting the manuscript; manuscript revision; A.S. - data collection, data analysis, statistical analysis, manuscript revision; A.D. - material analysis, results analysis, drafting the manuscript; manuscript revision; M.Z. - data collection, material collection, manuscript revision; B.D. - material analysis, results analysis, manuscript revision; S.K. - data collection, manuscript revision; V.D. - results analysis, statistical analysis, manuscript revision; K.S. - results analysis, statistical analysis, manuscript revision; All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

The individual participant data are not available. Data were deposited in a publicly available dataset on the Mendeley Data website: "POC-NaVoP", Mendeley Data, V2, doi: https://doi.org/10.17632/fx8394xnh4.2. https://data.mendeley.com/datasets/fx8394xnh4/2. Other documents are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed according to the Declaration of Helsinki, IRB approval (KB-0012/113/19, 13.05.2019).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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