Umbilical Cord and Maternal Plasma Thiol Concentrations in Normal Pregnancy, Maarten T.M. Rijmakers,1 Eva Maria Roes,2 Eric A.P. Steegers,2 Bas van der Wildt,3 and Wilbert H.M. Peters7 (Departments of 1 Gastroenterology and 3 Obstetrics and Gynecology, University Hospital St. Radboud, PO Box 9101, 6500 NB Nijmegen, The Netherlands; 2 Department of Obstetrics and Gynecology, Nij Smellinghe Hospital, PO Box 20200, 9200 DA Drachten, The Netherlands; 4 author for correspondence: fax 31-24-3540103, e-mail w.peters@gastro.azn.nl)

Cysteine is the only sulphhydril-containing amino acid in proteins and is the thiol residue in glutathione (1). In addition to its importance in the storage and transport of cysteine, glutathione plays a pivotal role in detoxification by the action of glutathione S-transferases and in scav-
umbilical cord blood values. The Spearman rank coefficient of correlation was calculated when appropriate using Astute for Microsoft Excel 5.0. \( P < 0.05 \) was considered significant.

The median (central 0.95 interval) characteristics for the study group (\( n = 195 \)) were as follows: maternal age, 29 years (20–41 years); gestational age, 40 weeks, 3 days (37 weeks, 3 days to 42 weeks, 3 days); maternal blood pressure, 80 mmHg, phase IV Korothoff (K4; 60–90 mmHg); birth weight, 3510 g (2800–4570 g); and placental weight, 695 g (500–980 g). These characteristics were representative of the population as admitted for term deliveries in the Drachten Hospital. The maternal characteristics of the subgroup (\( n = 35 \)) were not different from the total study group.

In arterial umbilical cord plasma, median (central 0.95 interval) values for the following were significantly lower than in venous umbilical cord plasma: \( \text{PO}_2 \), 17 kPa (9–34 kPa) for arterial vs 28 kPa (16–43 kPa) for venous (\( P < 0.0001 \)); \( \text{HCO}_3^- \), 19.2 mmol/L (14.7–24.5 mmol/L) for arterial vs 20.2 mmol/L (16.7–23.0 mmol/L) for venous (\( P < 0.0001 \)); \( \text{pH} \), 7.27 (7.20–7.37) for arterial vs 7.34 (7.26–7.43) for venous (\( P < 0.0001 \)); and base deficit (\( -4.4 \) (9.1 to 0.5) for arterial vs \( -4.0 \) (−8.1 to 0.5) for venous (\( P = 0.0001 \)). \( \text{Pco}_2 \) was significantly higher in umbilical cord blood: 52 kPa (35–64 kPa) for arterial vs 40 kPa (29–50 kPa) for venous (\( P < 0.0001 \)).

Concentrations of tCys and tHcy were significantly lower in arterial compared with venous umbilical cord plasma (\( P = 0.0002 \) and \( P = 0.009 \), respectively; see Table 1), whereas concentrations of tCysGly were significantly higher in arterial compared with venous umbilical cord plasma (\( P = 0.005 \)).

Maternal and venous and arterial umbilical cord plasma in the subgroup of 35 cases are presented in Fig. 1. Maternal tCys concentrations were lower than venous umbilical cord plasma (\( P = 0.04 \)), whereas there was a tendency for higher tCys concentrations in venous vs arterial umbilical cord plasma (\( P = 0.06 \)). Arterial umbilical cord tCys concentrations tended to be higher than maternal concentrations (\( P = 0.1 \)). Associations were found between tCys concentrations in maternal and venous umbilical cord plasma (\( r = 0.84; P < 0.0001 \)), venous and arterial umbilical cord plasma (\( r = 0.82; P < 0.0001 \)), and arterial umbilical cord and maternal plasma (\( r = 0.81; P < 0.0001 \)).

Fig. 1. Maternal and corresponding venous and arterial umbilical cord thiol concentrations (\( n = 35 \)).
Median (central 0.95 interval) values are given in \( \mu \text{mol/L} \). NS, not significant.

Concentrations of tCys and tHcy were lower in arterial vs venous umbilical cord plasma, and arterial umbilical cord and maternal plasma concentrations of tHcy were correlated (\( r = 0.83, P < 0.0001 \); \( r = 0.82, P < 0.0001 \); and \( r = 0.79, P < 0.0001 \), respectively). No associations were found between maternal, arterial, and venous umbilical cord tHcy concentrations and neonatal weight (\( r = 0.07, P = 0.9; r = 0.12, P = 0.1 \); and \( r = 0.0076, P = 0.9 \), respectively).

No differences were found between maternal and umbilical venous or arterial tCysGly concentrations, whereas an association was found between arterial and venous cord tCysGly concentrations (\( r = 0.59; P < 0.0001 \)).

The samples analyzed in this study were from uncomplicated pregnancies, and consequently the neonatal thiol values can be used as reference values.

Concentrations of tCys and tHcy are lower in arterial vs venous umbilical cord plasma, indicating uptake of both thiole into the fetal circulation, where they may be used in the biosynthesis of glutathione and proteins. tHcy may pass the maternal-fetal barrier driven by a concentration gradient. In contrast, tCys is transported from mother to fetus against a gradient, probably by active transport. tCys must be taken up by the fetus in this way because tHcy cannot be converted to tCys by the fetus because of an absence in the fetus of cystathionine-\( \beta \)-synthase, which is the enzyme that catalyzes this conversion in adults (10).

Maternal thiol concentrations are comparable to those we reported previously in a study group on increased nonpregnant vs normal pregnant plasma thiol values, most probably because of an increased plasma volume in normal pregnancy (2). Although the median maternal tHcy concentrations seemed higher compared with our previous findings (2), no statistical difference was found (\( P = 0.45 \)). Our tHcy values are higher than those found

| Table 1. Thiol concentrations in umbilical cord (\( n = 195 \)). |
|-----------------|-----------------|-----------------|-----------------|
|                 | Venous*         | Arterial*       | \( P \)         |
| Cysteine        | 207 (146–299)   | 203 (134–303)   | 0.0002          |
| Homocysteine    | 9.6 (4.8–17.4)  | 8.8 (4.9–20.4)  | 0.009           |
| Cysteinylglycine| 33 (20–50)      | 35 (20–51)      | 0.005           |

* Medians (central 0.95 intervals) are given in \( \mu \text{mol/L} \).
previously in a Northern American population (8, 11), which may be explained by a higher intake of folate and B vitamins in the American population, as discussed by den Heyer et al. (12).

In conclusion, tCys, which is an essential amino acid in the human fetus, may be actively transported in the placenta from the maternal to the fetal circulation where it is used in biosynthesis. Similarly, the fetus may extract tHcy from the maternal circulation.

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References


Effect of Storage on Phenylalanine and Tyrosine Measurements in Whole-Blood Samples, Martin Beck, Arend Bökenkamp,* Nicolas Liappis, and Michael J. Lentze (The Children's Hospital, Medical Center of Bonn University, D-53113 Bonn, Germany; * address correspondence to this author at: Universitätskinderklinik Bonn, Adenauerallee 119, D-53113 Bonn, Germany; fax 49-228-287-3444, e-mail a.boekenkamp@uni-bonn.de)

With an incidence of 1 in 6600 newborns, phenylketonuria (PKU) is among the most common inborn errors of metabolism. PKU is caused by a deficiency of hepatic phenylalanine hydroxylase (1). The increase in the blood Phe concentration leads to permanent structural damage of the central nervous system as a result of disturbed myelination and neurotransmitter deficiency (2). If plasma Phe concentrations are normalized by a low-protein diet with supplementation of essential amino acids before 3 weeks of age, irreversible mental retardation is prevented (2). Still, strict metabolic control is mandatory throughout childhood (2) and perhaps into adult life (3). This is achieved by regular measurement of blood Phe and Tyr concentrations. Tyr is monitored because Phe hydroxylase deficiency renders it an essential amino acid in PKU. Recommendations for the duration and intensity of dietary control are not uniform (2); likewise, there is some variation in the local practices of PKU monitoring. The current guidelines of the German “Arbeitsgemeinschaft für Pädiatrische Stoffwechselkrankungen” (The German Working Group for Metabolic Diseases) set a target range for Phe concentrations of 40–250 μmol/L, at least until age 10 (≥900 μmol/L is acceptable during adolescence) (4). These recommendations were based on data from samples that were analyzed immediately after sampling (Udo Wendel, University Children's Hospital, Düsseldorf, Germany, personal communication). Pregnant women with even mild hyperphenylalaninemia also require strict dietary control of Phe concentrations to prevent PKU-induced fetopathy (1).

To ensure optimal metabolic control, patients are monitored in specialized clinics where dietary Phe intake recommendations are adjusted according to weekly Phe and Tyr measurements. To reduce the inconvenience of regular outpatient visits, most German metabolic centers (like centers in other countries) have established methods that allow patients to have capillary blood samples collected at home and mailed to the laboratory as whole blood (5). Postal transfer of whole-blood samples takes 24–48 h. Storage of whole blood for 6 h at 20 °C has been shown not to significantly affect the recovery of Phe and Tyr (6). To our knowledge, a delay of 48 h until sample preparation, which is introduced by the mailing process, has not been formally evaluated. We therefore studied the effect of delayed sample preparation on Phe and Tyr serum concentrations from whole blood.

Forty-nine blood samples from 35 PKU patients (11.9 ± 10.1 years of age) were obtained by venipuncture during routine monitoring at the metabolic unit of Bonn University Children’s Hospital. Blood was collected into tubes that contained bead-activating coagulation (Serum Monovette; Sarstedt). After informed consent, Phe and Tyr were measured immediately in one aliquot (Phec, Ty,early), whereas the second aliquot was stored as whole blood at room temperature for 48 h until sample analysis (Phe, late, Tyr,late), thus simulating the mailing process.

Serum sample preparation included centrifugation for 10 min at 500g and deproteinization with 50 g/L sulfosalicylic acid (1:1 by volume). Ammonium acid analysis was performed by ion-exchange chromatography using a