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Pregnancy-related changes of carnitine and acylcarnitine concentrations of plasma and erythrocytes

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1 Introduction

L-Carnitine serves two major biochemical functions. It is essential for the transport of long chain fatty acids into the mitochondrial matrix and it is important as a reversible sink for acyl residues and the generation of free coenzyme A [5]. L-Carnitine is mainly localized in myocardial and skeletal muscles, which depend upon the oxidation of fatty acids as their major source of energy. These tissues derive their carnitive via the blood since carnitine is either synthesized in the liver and kidney, or supplied from external sources [5].

Plasma carnitine levels on delivery are decreased to about half of the concentrations seen in non-pregnant women [3, 8, 11, 27, 33]. Similar low levels are only found in patients with carnitine deficiency [16]. Whole blood carnitine is divided between plasma and blood cells, representing two different pools which are influenced by different factors [1, 6, 7, 13, 25]. The erythrocyte levels of free carnitine are comparable to those of plasma, whilst acylcarnitine is more concentrated intracellularly. Red blood cell free carnitine and acylcarnitine do not exchange freely with the plasma pool [6, 13]. It has been suggested that the L-carnitine concentration of the red blood cells is already fixed during hemopoiesis [13]. Reticulocytes contain mitochondria, where L-carnitine is needed for fatty acid transport, whereas mature erythrocytes do not [29]. In mature red blood cells L-carnitine and its derivatives are important for membrane stability and several membrane functions [2, 17].

The concentrations of plasma L-carnitine and acylcarnitine in the term neonate correlate with the concentrations of the umbilical cord plasma [31]. Erythrocytes account for more than 70% of whole blood carnitine in the newborn [25]. By the third week of life the contribution of carnitine in erythrocytes declines to 36% of whole blood carnitine which is comparable to adult values [25].

The purpose of this study was to determine the changes of total-, free-, and acylcarnitine concentrations in blood and the distribution between plasma and red blood cells during pregnancy, on delivery, and in umbilical cord blood. These data provide a basis to evaluate the success of any carnitine supplementation during pregnancy.

2 Materials and methods

2.1 Preparation of samples

EDTA blood was collected from 88 pregnant women every four weeks from the 12th week until delivery, and from twenty non pregnant healthy women who served as controls. RBC preparation was performed according to COOPER et al. [13]. In brief, red blood cells were separated from whole blood by centrifugation at 1200 × g for 5 min at room temperature and the plasma and leucocyte layers were removed. The cells were

resuspended in 2 vol of 0.9% NaCl and centrifuged as before. The washing procedure was repeated twice more, and the cells were finally resuspended in an equal volume of saline.

2.2 Carnitine assay

Perchloric acid extracts of plasma and erythrocytes were used for assaying free and short-chain acylcarnitine. The carnitine esters were saponified and assayed as free carnitine by the radioenzymatic method of CEDERBLAD and LINSTEDT [10], with two modifications: HEPES instead of TRIS buffer [12], and N-ethylmaleimide instead of tetrathionate [9].

2.3 Statistics

Statistical comparisons were made using analysis of variance followed by Dunnet's t-test for multiple comparison [15].

3 Results

3.1 Whole blood carnitine

Already by the 12th week of gestation the mean whole blood total carnitine level was significantly ($p < 0.01$) lower than that of the controls. From the 12th gestational week up to parturition there was a further decrease, which was significant ($p < 0.01$) between the 12th and the 28th, 36th and 40th week of gestation and at delivery. This reduction of total carnitine was caused by a significant ($p < 0.01$) decrease of free carnitine but no marked changes of short chain acylcarnitine values were found throughout pregnancy. Consequently the percentage of acylcarnitine on total carnitine was significantly increased between controls and pregnant women at the 12th week of gestation ($p < 0.05$) and between the 12th gestational week and delivery ($p < 0.01$) (table I).

3.2 Plasma carnitine levels

The total plasma carnitine level at the 12th gestational week was significantly ($p < 0.01$) lower than that of non pregnant women. Between week 12 and week 20 of gestation there was a further significant ($p < 0.01$) diminution. Again, this was mainly caused by a significant ($p < 0.01$) decrease of free carnitine.

Plasma short chain acylcarnitine levels at the 12th gestational week were significantly ($p < 0.01$)

Table I. Whole blood carnitine content

	n	Total carnitine [µmol/l] Mean ± SD	Free carnitine [µmol/l] Mean ± SD	Short chain carnitine [µmol/l] Mean ± SD	Acyl/total carnitine (%) Mean ± SD
Controls	20	41 ± 8.4	32 ± 4.4	9 ± 3.1	23 ± 8.1
Weeks					
12	13	24 ± 6.6[1]	16 ± 5.0[1]	8 ± 2.9	34 ± 9.3[2]
16	27	21 ± 7.2	12 ± 5.1[3]	9 ± 3.7	41 ± 12.2
20	36	22 ± 6.0	13 ± 4.1[3]	9 ± 5.1	41 ± 15.3
24	55	20 ± 5.5	12 ± 3.6[3]	8 ± 3.3	39 ± 10.4
28	71	18 ± 6.2[3]	11 ± 4.2[3]	8 ± 3.5	42 ± 13.0
32	53	17 ± 5.5[3]	10 ± 4.1[3]	7 ± 3.4	43 ± 15.6
36	59	18 ± 6.0[3]	10 ± 3.9[4]	8 ± 3.4	43 ± 12.7[4]
40	49	19 ± 7.2[3]	10 ± 3.7[3]	9 ± 5.0	46 ± 12.8[3]
Delivery	88	20 ± 7.8[3]	10 ± 5.1[3]	10 ± 4.5	53 ± 14.0[3]
Cord blood	82	34 ± 13.7[5]	18 ± 7.6[5]	16 ± 7.9[5]	46 ± 11.1[5]

n = number of cases
[1] = $p < 0.01$ vs controls
[2] = $p < 0.05$ vs controls
[3] = $p < 0.01$ vs week 12
[4] = $p < 0.05$ vs week 12
[5] = $p < 0.01$ vs delivery

lower than those of non pregnant women; the values determined at delivery, however, approached those of the controls. At parturition the percentage of short chain acylcarnitine on total carnitine was significantly ($0 < 0.01$) higher than those during pregnancy, although it was already higher in pregnant women at the 12th week of gestation compared to controls. A further significant ($p < 0.01$) increase between the 12th gestational week and the period lasting to delivery was found (table II).

3.3 Red blood cell carnitine levels

Already in the 12th week of gestation the total carnitine content of red blood cells (nmol/g Hb) was significantly ($p < 0.01$) lower compared to the control values. From the 12th gestational week the total carnitine content showed a slight increase during pregnancy and a significant ($p < 0.01$) increase at delivery.

The red blood cell free carnitine levels remained nearly unchanged during pregnancy but were significantly ($p < 0.05$) lower than the control values. At the 12th week of gestation the content of short chain acylcarnitine was significantly ($p < 0.05$) lower than those of controls, but increased continuously from the 12th week of gestation. This increase was significant between the gestational weeks 12 and 24 through 40 ($p < 0.05$) and at delivery ($p < 0.01$). Thus the contribution of short chain acylcarnitine to total carnitine in erythrocytes increased from 49% at the 12th week to 61% at the 40th week of pregnancy and to 63% at delivery (table III).

3.4 Partitioning of carnitine between plasma and red blood cells

Plasma carnitine represented approximately 60% of the total blood carnitine pool in non pregnant women. The concentration of free carnitine was higher in plasma than in red blood cells but the major pool of short chain acylcarnitine was present in red blood cells.

During pregnancy the contribution of red blood cell carnitine to whole blood carnitine increased significantly from 39% (controls) to 45% (12th gestational week) and 61% at delivery ($p < 0.05$) (figure 1).

Table II. Plasma carnitine content

	n	Total carnitine [µmol/l] Mean ± SD	Free carnitine [µmol/l] Mean ± SD	Short chain carnitine [µmol/l] Mean ± SD	Acyl/total carnitine (%) Mean ± SD
Controls	20	40 ± 14.3	34 ± 12.5	6 ± 2.8	14 ± 7.3
Weeks					
12	13	21 ± 3.4[1]	17 ± 3.9[1]	4 ± 2.6[1]	18 ± 11.3
16	27	18 ± 5.8	14 ± 4.8[3]	4 ± 2.5	22 ± 10.9
20	36	16 ± 3.6[2]	13 ± 3.3[2]	3 ± 1.6[2]	18 ± 8.9
24	55	15 ± 3.4[2]	12 ± 2.9[2]	3 ± 1.8[2]	21 ± 10.1
28	71	14 ± 3.5[2]	11 ± 2.9[2]	3 ± 1.9[2]	23 ± 11.4
32	53	14 ± 4.5[2]	11 ± 3.1[2]	3 ± 2.9[2]	23 ± 12.2
36	59	14 ± 4.9[2]	11 ± 3.9[2]	3 ± 2.3[2]	22 ± 12.2
40	49	16 ± 5.7[2]	12 ± 4.5[2]	4 ± 3.2	24 ± 12.9
Delivery	88	15 ± 6.0[2]	10 ± 4.6[2]	5 ± 3.1	35 ± 13.9[2]
Cord blood	82	17 ± 6.9[4]	12 ± 4.9[4]	5 ± 3.3	28 ± 12.5[4]

n = number of cases
[1] = $p < 0.01$ vs controls
[2] = $p < 0.01$ vs week 12
[3] = $p < 0.05$ vs week 12
[4] = $p < 0.01$ vs delivery

3.5 Comparison between maternal blood at delivery and cord blood

Free and total carnitine levels in the umbilical cord blood were significantly ($p < 0.01$) higher than the corresponding maternal levels (tables I–III). The significant higher levels of free carnitine in whole blood, plasma, and erythrocytes were mainly responsible for these differences. Thus the percentage of acylcarnitine on total carnitine was significantly lower in umbilical cord blood than in maternal blood.

In cord blood; plasma carnitine represented only 31% of the total carnitine pool (figure 1). Consequently the contribution of red blood cell carnitine to whole blood carnitine was higher in cord blood than in maternal blood (figure 1).

4 Discussion

A significant decrease of total and of free carnitine was found during pregnancy in whole blood and plasma. Most of this decrease – to almost half of the concentration of the controls – had occured by the 12th week. The acylcarnitine content of red blood cells dropped in the first 12 weeks but increased continuously thereafter. Both, low L-carnitine levels and a high ratio acylcarnitine/total carnitine indicate a secondary carnitine deficiency [5, 16]. It has been shown in rats that maternal carnitine levels are significantly lower not only in blood but also in kidney, heart, and skeletal muscle compared to those levels determined in non pregnant female controls [14].

In omnivores, L-carnitine synthesis normally provides only about one-eight to one-half of the total carnitine available to the organism [30]. It is now recognized that endogenous biosynthesis alone is not sufficient to keep L-carnitine concentrations at an adequate level [16, 30]. The biosynthetic pathway of carnitine has been well characterized [5, 14, 30]. The first step in the pathway is the methylation of lysine residues in specific proteins to form trimethyllysine [28]. The regulation of trimethyllysine biosynthesis is controlled via protein turnover, based on the proposition that free lysine is not methylated in man [14]. Consequently there is no feedback between increased renal loss of carnitine and the rate of carnitine

Table III. Carnitine content of erythrocytes

	n	Total carnitine [nmol/g Hb] Mean ± SD	Free carnitine [nmol/g Hb] Mean ± SD	Short chain carnitine [nmol/g Hb] Mean ± SD	Acyl/total carnitine (%) Mean ± SD
Controls	20	164 ± 67.9	74 ± 35.5	90 ± 30	55 ± 9.9
Weeks					
12	13	96 ± 33.1[1]	49 ± 29.3[1]	47 ± 19.6[1]	49 ± 17.6
16	27	133 +- 48.2	66 ± 31.2	66 ± 30.7	50 ± 15.2
20	36	117 ± 53.2	52 ± 41.7	66 ± 29.7	56 ± 18.0
24	55	127 ± 70.8	54 ± 34.7[2]	74 ± 43.9[3]	58 ± 15.3
28	71	129 ± 77.4	54 ± 38.2[2]	75 ± 54.1[3]	58 ± 18.7
32	53	127 ± 73.6	53 ± 39.7[2]	74 ± 52.4[3]	57 ± 18.5
36	59	120 ± 60.9	48 ± 31.9	72 ± 40.3[3]	60 ± 18.8
40	49	121 ± 85.7	47 ± 40.8	74 ± 55.7	62 ± 15.7
Delivery	88	155 ± 93.4[2]	58 ± 37.5[2]	97 ± 70.2[2]	63 ± 17.0
Cord blood	82	199 ± 88.8[5]	89 ± 47.1[4]	110 ± 53.8	55 ± 12.1

n = number of cases
Hb = hemoglobine
[1] = $p < 0.05$ vs controls
[2] = $p < 0.01$ vs week 12
[3] = $p < 0.05$ vs week 12
[4] = $p < 0.01$ vs delivery
[5] = $p < 0.05$ vs delivery

synthesis [14]. Under normal conditions the plasma carnitine concentration is regulated, at least in part, by the kinetics of L-carnitine reabsorption by the kidney. More than 90% of the filtered L-carnitine is reabsorbed [5, 16]. Although L-carnitine levels are low during pregnancy, the renal clearance of acylcarnitine is significantly higher in comparison to non pregnant women [8]. Consequently the decrease in plasma carnitine may not be caused by an increased demand in the first weeks of gestination. Carnitine may also facilitate removal of excess and potentially toxic acyl groups from the cell, which are excreted as acylcarnitine into urine. It is possible that there is an increased need of carnitine during pregnancy to perform this metabolic function.

Sufficient carnitine availability is important in the perinatal and even more in the postnatal period. During the perinatal period the activity of L-carnitine acetyltransferase and L-carnitine palmitoyl

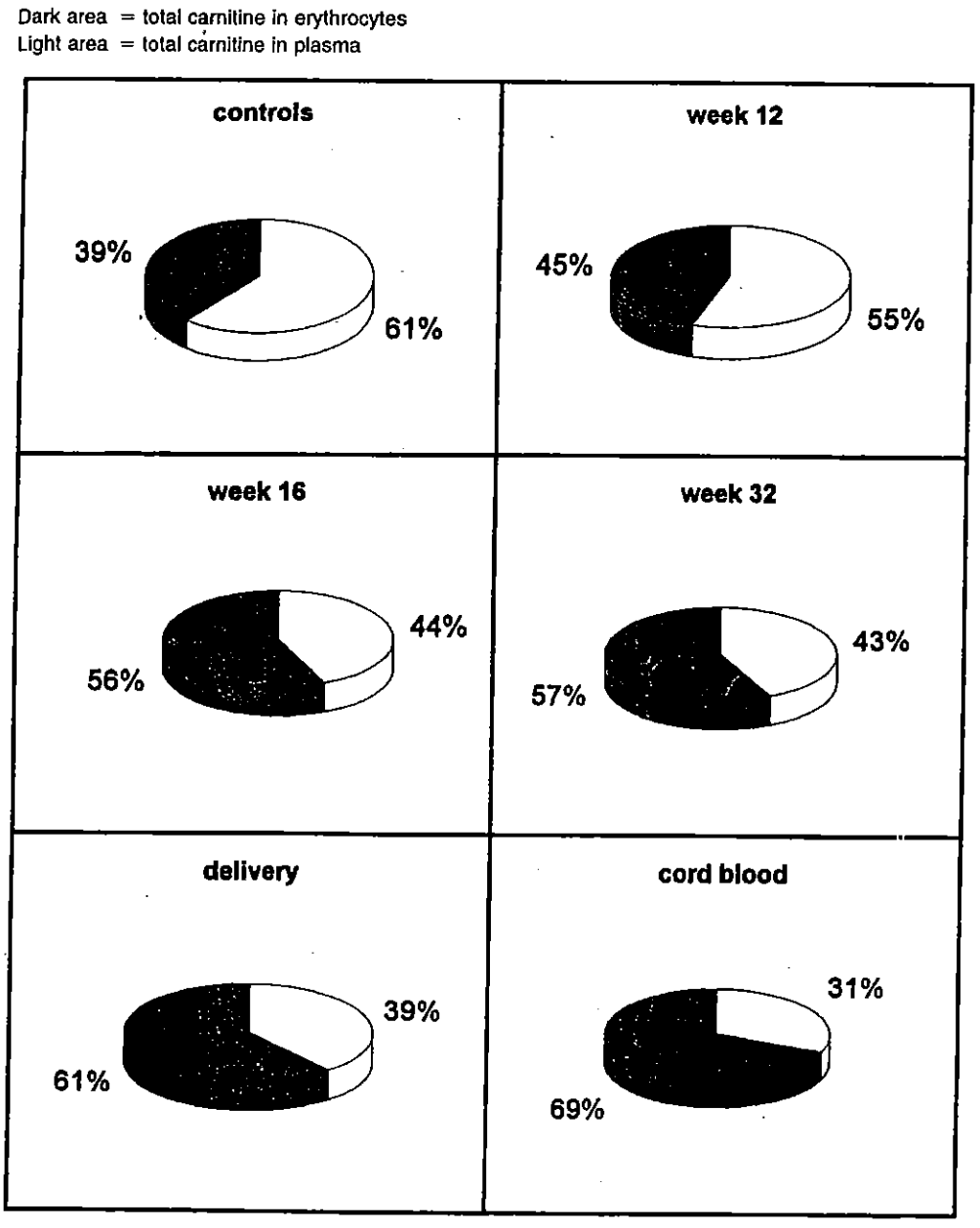

Figure 1. Partition of total carnitine between plasma and erythrocytes.

transferase increases in various tissues. β-Oxidation of fatty acids also increases in parallel [18]. Ketone bodies resulting from the β-oxidation of fatty acids are a vital source of energy for the developing central nervous system in many species, including men, and can already be metabolized by the fetus between week 13 and 21 of pregnancy [18]. The necessary enzymatic activities are elevated in the second half of pregnancy [18] although the substrate is limited until birth [18].

Skeletal muscle L-carnitine concentration is positively correlated with gestational age at birth [34, 35]. At week 25 gestational age, the skeletal muscle L-carnitine concentration is less than half of that at week 42 of gestation. Thus during normal maturation L-carnitine is accumulated in fetal tissues in the third trimester [34]. The accumulation of short chain acylcarnitine is more pronounced than that of free carnitine [22]. Acylcarnitine has the same energy levels as the corresponding acyl-coenzyme A [5]. As a consequence L-carnitine may facilitate the storage of readily transportable energy.

In the immediate postnatal period, sufficient L-carnitine availability is crucial for the neonate [19, 20]. It is important for the metabolic adaptation occurring postnatally since the newborn has to switch its energy production from predominately glucose to predominately fatty acid utilization [26].

There is a correlation between the L-carnitine levels in the maternal and the fetal compartment [32], because L-carnitine, as well as nonessential amino acids, is not concentrated in the fetal circulation [4]. It is known that perinatal L-carnitine substitution to the mother enhances L-carnitine availability to the fetus [24]. We have previously shown that antepartum administration of L-carnitine [22, 23] or L-carnitine-betamethasone combinations [24] enhanced the fetal rat lung content of dipalmitoyl phosphatidylcholine, the main lipid constituent of the pulmonary surfactant complex [36]. In cases of imminent premature delivery, maternal treatment with a L-carnitine-betamethasone-combination was more effective in prevention of RDS than the standard betamethasone therapy [21].

It has been suggested that free and total carnitine of erythrocytes are localized in the circulating reticulocytes, which have mitochondria and carnitine-dependent fatty acid metabolism. Normal healthy adult subjects had an average of 39% of the whole blood total carnitine in their erythrocytes, while the cord blood specimens had erythrocyte contributions of 69%. Adults have normal whole blood reticulocyte counts of 1.0 ± 0.5% compared to term infant reticulocyte counts of 4.1 to 6.3% on the first day of life [29].

In summary, during pregnancy in whole blood and plasma a gradual decrease of total and free carnitine was found. In normal pregnancies a secondary carnitine deficiency will hardly be noticed. But if there are complications during pregnancy, or in cases of premature delivery, a secondary carnitine deficiency is an additional risk factor.

Since L-carnitine administration has no known side effects, it could be supplied during gestation. This may prove advantageous to the present usage [21], where L-carnitine is only given in cases of imminent premature delivery in high doses over a period of three days.

Abstract

Total-, free-, and acylcarnitine concentrations were determined in whole blood, plasma, and red blood cells of 88 women during pregnancy. Already in the 12th week of gestation the mean whole blood carnitine level was significantly ($p < 0.01$) lower than those of the controls. From the 12th gestational week up to parturition there was a further significant ($p < 0.01$) decrease. This reduction of total carnitine in whole bloods was mainly caused by a significant ($p < 0.01$) decrease of free carnitine levels, since no marked changes of short chain acylcarnitine values were found throughout pregnancy. The contribution of red blood cell L-carnitine to whole blood carnitine increased significantly ($p < 0.05$) to 61% at delivery versus 39% (controls). In umbilical cord blood free and total carnitine levels were significantly ($p < 0.05$) higher than the corresponding maternal levels. The contribution of red blood cell L-carnitine to whole blood carnitine was higher in cord blood than in maternal blood.

The results of the present study demonstrate that during pregnancy whole blood and plasma carnitine levels decrease to those levels found in patients with carnitine

deficiency. Also the percentage of acylcarnitine on total carnitine, found in the present study, is characteristic for a secondary carnitine deficiency. Thus L-carnitine substitution in pregnant women, especially in risk pregnancies, may be advantageous.

Keywords: Cord blood, L-carnitine, maternal blood, plasma, pregnancy, red blood cells, secondary carnitine deficiency.

Zusammenfassung

Veränderung der Carnitin- und Acylcarnitinkonzentration im Plasma und Erythrozyten während der Schwangerschaft

Bei 88 Schwangeren wurden die Konzentrationen von Gesamtcarnitin, unverestertem Carnitin und kurzkettigem Acylcarnitin im Gesamtblut, im Plasma und in den Erythrozyten bestimmt. Bereits in der 12. Schwangerschaftswoche wurde eine signifikante ($p < 0.01$) Verminderung des Carnitinspiegels im Gesamtblut, verglichen mit den Werten einer Kontrollgruppe, nachgewiesen. Im weiteren Verlauf der Schwangerschaft bis zur Geburt wurde eine weitere signifikante ($p < 0,01$) Reduzierung der Plasmacarnitinspiegel festgestellt. Parallel zur Verminderung der Gesamtcarnitinspiegel kam es zu einer signifikanten ($p < 0,01$) Verminderung des freien Carnitins, während sich die Spiegel der kurzkettigen Acylcarnitinester während der Schwangerschaft nur wenig änderten. Der Anteil des Erythrozytencarnitins am Carnitingehalt des Gesamtblutes stieg in der Schwangerschaft signifikant ($p < 0,05$) auf 61%, im Vergleich zu 39% bei den Kontrollen, an.

Die Spiegel an freiem und Gesamtcarnitin waren im Nabelschnurblut, im Vergleich zu den korrespondierenden und den maternalen Werten, signifikant ($p < 0,05$) höher. Auch der Anteil des Erthrozytencarnitins am Gesamtblutcarnitin war im Nabelschnurblut höher als im mütterlichen Blut.

Die Regulation der endogenen Carnitinsynthese steht im Zusammenhang mit dem Proteinumsatz, da im menschlichen Organismus freies Lysin nicht methyliert wird. Es gibt daher auch keine Rückkopplung zwischen gesteigerter Carnitinausscheidung über die Nieren und einer Stimulierung der endogenen Carnitinbiosynthese. Bei normaler Stoffwechsellage wird mehr als 90% des Carnitins aus dem Primärharn von den Nieren rückresorbiert. Obwohl die Carnitinspiegel im Blut bei Schwangeren nur halb so hoch sind, wie bei nicht schwangeren Frauen, ist die renale Ausscheidung von Acylcarnitinestern signifikant höher. Daher ist die Verminderung der Carnitinspiegel während der ersten Wochen der Schwangerschaft nicht auf einen erhöhten Bedarf zurückzuführen.

Carnitin dürfte auch die Entfernung von überschüssigen und potentiell toxischen Acylgruppen aus den Zellen beschleunigen, die dann als Acylcarnitinester über die Nieren ausgeschieden werden. Es ist daher möglich, daß für diese metabolische Funktion während der Schwangerschaft ein erhöhter Bedarf an Carnitin besteht.

In der vorliegenden Studie wurden während der Schwangerschaft Gesamtblut- und Plasmacarnitinwerte gefunden, wie sie sonst nur bei Patienten mit Carnitinmangel auftreten. Auch der hohe Anteil des veresterten Carnitins am Gesamtcarnitin, wie er ebenfalls in der vorliegenden Studie bei Schwangeren nachgewiesen wurde, ist charakteristisch für einen sekundären Carnitinmangel. Daher dürfte sich eine Carnitinsubstitution bei Schwangeren, besonders bei Risikoschwangerschaften, günstig auswirken.

Schlüsselwörter: Erythrozyten, L-Carnitin, maternales Blut, Nabelschnurblut, Schwangerschaft, sekundärer Carnitinmangel.

Résumé

Modifications des concentrations de carnitine et d'acylcarnitine du plasma et des érythrocytes en relation avec la grossesse

Nous avons mesuré les concentrations de carnitine totale, de carnitine libre et d'acylcarnitine sur le sang, le plasma et les érythrocytes de 88 femmes pendant la grossesse. D'une façon générale, à la 12e semaine de la grossesse, le taux moyen de carnitine sanguine a été nettement plus bas ($p < 0,01$) que sur les sujets témoins. A partir de la 12e semaine de grossesse et jusqu'à l'accouchement, nous avons relevé une baisse significative ($p < 0,01$). Cette diminution de la carnitine totale dans le sang total est provoquée généralement par une baisse nette ($p < 0,01$) du taux de carnitine libre alors que nous n'avons pas noté de modifications prononcées des valeurs des chaînes courtes de l'acylcarnitine pendant toute la grossesse. L'apport de la L-carnitine des érythrocytes à la carnitine du sang total a progressé nettement ($p < 0,05$) pour atteindre 61% à l'accouchement contre 39% chez les témoins. Sur le sang du cordon ombilical, les taux de carnitine libre et de carnitine total étaient nettement plus élevés ($p < 0,05$)

que les taux maternels correspondants. L'apport de la L-carnitine des érythrocytes à l'ensemble de la carnitine du sang total était plus élevé dans le sang du cordon que dans le sang maternel.
Chez les omnivores, la synthèse de L-carnitine intervient pour le huitième à la moitié de la carnitine disponible dans l'organisme. Nous savons maintenant que la biosynthèse endogène à elle seule ne suffit pas pour porter le taux de L-carnitine à un niveau suffisant. La biosynthèse de la carnitine est désormais bien connue. La première étape est constituée par la méthylation des résidus de lysine des protéines spécifiques donnant la triméthyllysine. La biosynthèse de la triméthyllysine est contrôlée par reconstitution de la protéine, l'hypothèse étantque la lysine libre n'est pas méthylée chez l'homme. En conséquence, il n'y a pas d'interaction entre l'accroissement des pertes rénales de carnitine et le taux de la synthèse de carnitine. En conditions normales, la concentration de carnitine dans le plasma est réglée partiellement par la cinétique de la réabsorption de L-carnitine par les reins. Plus de 90% de la L-carnitine filtrée est réabsorbée. Bien que le taux de L-carnitine soit bas pendant la grossesse, la clairance rénale de l'acylcarnitine est nettement plus élevée que chez les sujets non enceintes. En conséquence, la diminution de la carnitine du plasma ne provoque pas de demande durant les premières semaines de la grossesse.
La carnitine facilite donc le rejet des cellules des groupes acyles excédentaires et potentiellement toxiques, qui sont rejetées avec l'urine sous forme d'acylcarnitine. Il est possible que les besoins de carnitine augmentent pendant la grossesse pour pouvoir réaliser cette fonction métabolique.
Les résultats de la présente étude établissent que pendant la grossesse, les taux de carnitine su sang total et du plasma diminuent pour atteindre ceux des sujets souffrant de déficience de carnitine. Les taux d'acylcarnitine dans la carnitine totale établis par la présente étude sont eux aussi typiques d'un déficit de carnitine secondaire. En conséquence, la substitution de L-carnitine peut être avantageuse, tout spécialement dans les grossesses à risque.

Mots-clés: Déficit secondaire en carnitine, érythrocytes, grossesse, L-cartinine, plasma, sang du cordon, sang maternel.

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