Carnipure™ *Focus*

Pregnancy

Lonza

Introduction

Maternal nutrition is a burgeoning area, illustrated by an increasing number of research papers. Women are becoming more aware of the importance of maternal nutrition for both the immediate and future health of their children. Thus it may come as a surprise that even in the industrialised world, lifestyle factors such as dieting, vegetarianism, smoking and use of the oral conceptive pill mean that a woman's supply of several important nutrients may be significantly below recommended levels – and that can have an impact on both mother and her baby. The importance of taking supplementary folic acid is quite well established[1–3], but in fact, folate is only part of the whole nutrition story. Almost all vitamins and minerals as well as other important factors such as L-Carnitine play vital roles in the optimal health and development of the new life.

What is Carnipure™?

Carnipure™ is a special grade of L-Carnitine, manufactured by the Swiss life sciences company Lonza. Thanks to a unique production process based on fermentation, Lonza is the only L-Carnitine manufacturer capable of producing L-Carnitine in the same way as nature. Products carrying the Carnipure™ quality seal on the packaging show the consumer that they contain pure Lonza L-Carnitine.

Carnipure™ offers purest L-Carnitine and is a trademark of Lonza Ltd, Switzerland.

Metabolic Roles of L-Carnitine

L-Carnitine serves two major functions. It is essential for the transport of long chain fatty acids into the mitochondrial matrix for subsequent energy generation, and it is responsible for the modulation of the rise in intramitochondrial acyl-CoA : CoA-ratio, which relieves the inhibition of many intramitochondrial enzymes involving glucose and amino acid catabolism. L-Carnitine exists in both free and acyl (ester bond) form in all tissues including plasma.

Small quantities of L-Carnitine are produced within the human body on a daily basis (approximately 20 mg in adults). For the major part, however, the daily L-Carnitine requirement is met by food intake, with red meats being the richest sources of dietary L-Carnitine. Fruits and vegetables contain very little of this nutrient. Thus people following a meat-reduced or vegetarian diet will take up very limited amounts of dietary L-Carnitine.

Over the past years increased attention has been paid to the significance of L-Carnitine in the pregnant woman's diet. Many reports suggest that the fetus is not capable of substantial L-Carnitine synthesis[4, 5]. Adequate blood and tissue concentrations of L-Carnitine may be important, though, in enhancing utilization of fat for energy generation, and in promoting growth in neonates[6, 7].

Pregnancy-related changes in L-Carnitine metabolism

L-Carnitine plays a critical part in the well-being of mother and child[8]. A significant decrease in L-Carnitine plasma levels is found already by the 8–12th week of gestation, which further decreases with gestational age[9–13]. It is well-established that plasma L-Carnitine levels at delivery are decreased to about half of the concentrations seen in non-pregnant women[14]. The reduction of plasma L-Carnitine is mainly caused by a significant decrease in free L-Carnitine levels, since no marked changes of short chain acyl-L-Carnitine values are found throughout pregnancy[15].

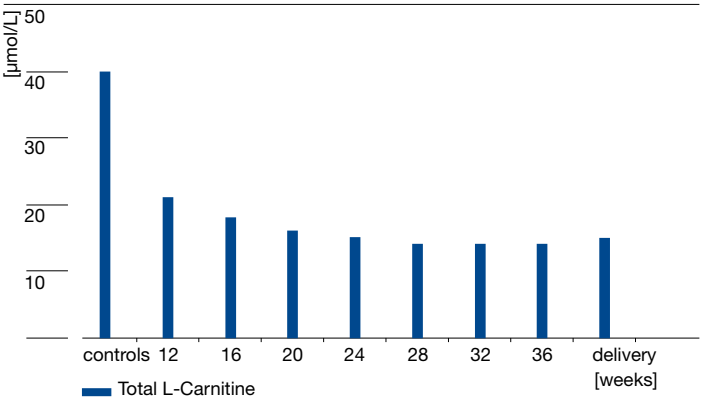

Figure 1: The plasma levels of total L-Carnitine significantly decrease during pregnancy[12]

The decrease in plasma L-Carnitine levels during early pregnancy is probably not only due to an increased requirement from the fetus: at 8 weeks of gestation, the fetus' weight is only 0.22 g, but plasma L-Carnitine concentrations are already markedly decreased[13]. Also the increase in total body water during pregnancy cannot explain this large difference[16].

In 50 pregnant Korean women aged 24-28, decreasing L-Carnitine plasma levels have been observed even though dietary intake of L-Carnitine with the normal diet increased from 44.6 µmol/day in early pregnancy to 96.1 µmol/day in late pregnancy[17, 18].

In 12 women examined in late pregnancy (weeks 28–37), renal excretion of L-Carnitine esters was found to be about four times higher than in the control group, whereas excretion of free L-Carnitine was about the same in both groups despite low plasma-L-Carnitine concentrations in pregnant women[13]. It is possible that there is an increased need of L-Carnitine during pregnancy to perform the metabolic function of facilitating the removal of excess and potentially toxic acyl groups from the cell, which are excreted as acyl-L-Carnitine into urine[12, 19]. Interestingly, L-Carnitine content in amniotic fluid has been found to decrease with gestational age, too[20].

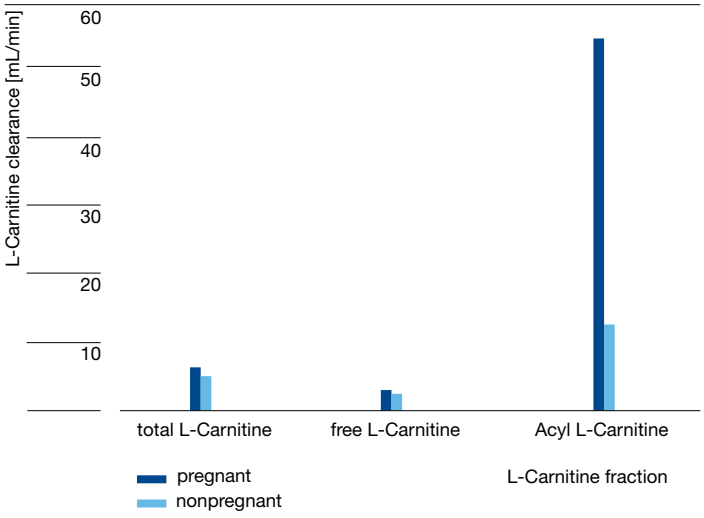

Figure 2: Renal excretion of total, free and acyl-L-Carnitines in pregnant and non-pregnant women[13]

Hormonal changes during pregnancy could also influence plasma concentration and urinary excretion equilibrium. A putative link between L-Carnitine and reproductive system hormones has been demonstrated[9].

L-Carnitine insufficiency

Both low L-Carnitine levels and a high ratio of acyl-L-Carnitine / total L-Carnitine indicate an L-Carnitine insufficiency in pregnant women[9]. Similar low levels of free L-Carnitine are only found in patients with L-Carnitine deficiency.

It has been shown in rats that maternal L-Carnitine levels are significantly lower not only in blood, but also in kidney, heart and skeletal muscle compared to the levels determined in non-pregnant female controls[12]. In mothers after caesarean section, skeletal muscle L-Carnitine content was found to be reduced to 51% of the levels found in non-pregnant women[21].

Definition: Secondary L-Carnitine Deficiency

L-Carnitine deficiency is defined as a metabolic state in which the L-Carnitine concentration in plasma and tissues falls below 10-20% of normal values. Generally, a secondary L-Carnitine deficiency is characterised by a plasma level of free L-Carnitine of <20 µmol/L and/or a ratio of acyl-L-Carnitine / free L-Carnitine >0.4. Sufficient free L-Carnitine is a prerequisite for normal functioning of cells and organelles.

A clinical trial in pregnant women showed that the inclusion of 1 g L-Carnitine/day starting the 20th week of gestation up to parturition resulted in a small increase in total L-Carnitine, and a significant increase in free L-Carnitine and a corresponding decrease in short-chain acyl-L-Carnitine in maternal plasma, cord blood and placenta. The author suggests that the inclusion of L-Carnitine during pregnancy is indicated and recommends a daily dose of at least 1 g/day to prevent secondary L-Carnitine deficiency[19, 22].

L-Carnitine and the placenta

The placenta is a unique organ in a sense that, although genetically of fetal origin, it has to interact with maternal circulation to provide the fetus with all nutrients needed for growth and serve as an excretory organ to eliminate waste products of fetal metabolism[23]. Studies in various animal species have demonstrated a transfer of L-Carnitine from the mother to the fetus during pregnancy. Also in humans, the positive correlation between maternal and fetal levels of free and acyl-L-Carnitine indicates placental transfer of these substances[24]. It is known that perinatal oral L-Carnitine supplementation to the mother enhances L-Carnitine availability to the fetus[12].

The umbilical cord blood contains significantly higher levels of free and total L-Carnitine than the corresponding maternal levels[15, 25]. The L-Carnitine content was found to be 7- to 10- fold higher in murine placentas than in tissues such as the heart, which preferentially use L-Carnitine for energy production[23].

Maternofetal transport of L-Carnitine is thought to be important in preparing the fetus for its lipid-rich postnatal milk diet[26]. The placental brush border membrane forms the interface between the fetus and the maternal circulation, and brush border membrane transport is the first step of uptake from mother to fetus. The human placental L-Carnitine uptake is mediated by the high-affinity L-Carnitine transporter OCTN2[26–28].

For a long time, the human fetus and placenta were considered to be primarily dependent on glucose oxidation for energy metabolism. Recently, new data support the fact that the placenta is capable of fatty acid oxidation as well. Several key enzymes of the fatty acid oxidation process, especially CPT2, have been found to be expressed and active in the placenta throughout gestation[29].

These findings, however, bring up the issue of L-Carnitine status in this tissue again. Today it seems the placental L-Carnitine transport

system may have dual functions: to transfer L-Carnitine from the mother to the developing fetus and to provide L-Carnitine to the placenta for its own metabolic needs[23].

This may also explain the remarkable association between severe maternal pregnancy complications and the carriage of a fetus with an inborn error of mitochondrial long-chain fatty acid oxidation[23, 29]. Some authors have also suggested that L-Carnitine deficiency leads to intrauterine growth retardation[23], and others have postulated that L-Carnitine supplementation could improve placental insufficiency[30].

Pregnancy-related changes in lipid metabolism

It is well-known that during pregnancy free fatty acids, free cholesterol and cholesterol esters are elevated in maternal plasma and increase significantly during the course of gestation[18,31].

In healthy adults, Carnipure™ supplementation has been shown to stimulate *in vivo* long chain fatty acid metabolism[32,33]. The researchers concluded that these studies are important to all people who exercise or have a high energy demand such as during pregnancy.

The fetus accumulates nutrients for energy metabolism, tissue turnover, and growth from the maternal plasma via placental transfer[14]. Both the developing fetus and the placenta require fatty acids for the synthesis of complex lipids necessary for the biogenesis of plasma membranes, intracellular membranes, organelles, triglyceride stores and secreted products such as lipoproteins, bile and pulmonary surfactant. It is estimated that close to 50% of the fatty acids required by the fetus are derived from the mother. High levels of free fatty acids are an important cause of insulin resistance, though[31].

Healthy glucose and lipid levels

Maintaining healthy blood glucose and lipid levels during pregnancy is a common concern[31,34–36]. L-Carnitine supplementation can increase the amount of whole body glucose utilization, and an increase of both glucose uptake and glucose oxidation has been reported[37]. In a recent study, 14 pregnant women were supplemented with 2 g Carnipure™ tartrate (U.S. Patent 5,073,376 and other international patents; equivalent to 1.5 g L-Carnitine) from the 20th week of gestation until parturition. Their plasma free fatty acids were significantly lower than those of non-supplemented pregnant controls, indicating that Carnipure™ tartrate supplementation could help in supporting healthy blood glucose and lipid levels during pregnancy[31].

There is evidence that L-Carnitine may support normal gestation, and pregnant women with imminent preterm births, for many years scientists have recommended to supplement with L-Carnitine[38]. Since L-Carnitine has no known side effects[39], it can be advantageous to be supplied during every gestation[12].

And so to conclude

One simple fact becomes increasingly clear: the healthier the mother-to-be is, the healthier her baby is likely to be. Overall, there is increasing evidence that Carnipure™ may play an important role during pregnancy, particularly in women following a meat-reduced or vegetarian diet in whom daily L-Carnitine intake may be too low to meet the increased needs during pregnancy. Due to its excellent safety profile, Carnipure™ supplementation may be appropriate for pregnant women to restore their L-Carnitine plasma levels and at the same time decrease plasma free fatty acids. Of course, pregnant women should **always** consult a physician before taking any dietary supplement.

References

1. Smithells RW et al. (1976). Arch Dis Child 51:944–950
2. MRC Vitamin Study Research Group (1991). Lancet 338:131–137
3. Botto LD et al. (2005). BMJ 330(7491):571–577
4. Rebouche CJ & Engel AG (1980). Biochim Biophys Acta 630:22–29
5. Scientific Committee on Food (2003). www.europa.eu.int
6. Schmidt-Sommerfeld E et al. (1978). Pediatr Res 12:660–664
7. Arenas J et al. (1998). Early Hum Dev 53:S43–S50
8. Talián GC et al. (2007). Pediatr Res 62(1):88–92
9. Marzo A et al. (1994). Gynecol Endocrinol 8:115–120
10. Bargen-Lockner C et al. (1981). Am J Obstet Gynecol 140:412–414
11. Winter SC et al. (1995). Clin Chim Acta 243:87–93
12. Schoderbeck M et al. (1995). J Perinat Med 23:477–485
13. Cederblad G et al. (1986). Am J Clin Nutr 44:379–383
14. Lohninger A (1996). In: Seim H & Löster H (Eds), Carnitine – Pathobiochemical basis and clinical applications. Ponte Press Bochum
15. Genger H et al. (1988). Z Geburtsh u Perinat 192:134–136
16. Cederblad G et al. (1985). Acta Paediatr Scand 74:500–504
17. Cho S-W et al. (2003). FASEB abstract #447.1
18. Cho S-W & Cha Y-S (2005). Brit J Nutr 93:685–691
19. Lohninger A et al. (1996). Wien Klin Wochenschr 108(2):33–39
20. Hahn P et al. (1977). Pediat Res 11:878–880
21. Scholte HR & De Jong PC (1987). In: Gitzelmann R, Baerlocher K, Steinmann B (eds), Carnitin in der Medizin. Schattauer, Stuttgart 21–59
22. Lohninger A (2000). Ann Nutr Metab 44:75–96
23. Shekhawat PS et al. (2004). Pediatr Res 56:323–328
24. Schmidt-Sommerfeld E et al. (1981). Early Human Development 5:233–242
25. Lohninger A et al. (2001). FASEB abstract 36
26. Lahjouji K et al. (2004). Am J Physiol Cell Physiol 287:C263–C269
27. Wu X et al. (1999). J Pharmacol Exp Ther 290(3):1482–1492
28. Grube M et al. (2005). Drug Metab Dispos 33(1):31–37
29. Oey NA et al. (2003). J Inher Metab Dis 26(4):385–392
30. Genger H et al. (1988). Z Geburtsh u Perinat 192:155–157
31. Lohninger A et al. (2005). Chem Month 136:1523–1533
32. Müller DM et al. (2002). Metabolism 51(11):1389–1391
33. Wutzke KD & Lorenz H (2004). Metabolism 53(8):1002–1006
34. Clore JN et al. (2004). Am J Physiol Endocrinol Metab 287(2):E358–65
35. American Diabetes Association (2005). www.diabetes.org
36. Pappa KI et al. (2007). Am J Obstet Gynecol 196(1):65.e1-5
37. Mingrone G et al. (1999). J Am Coll Nutr 18(1):77–82
38. Jinniate S et al. (1993). Gynäkol Geburtshilfliche Rundsch 33(S1):261
39. Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (ACF) (2003). EFSA J 19:1–13

Note: This document is an overview of published scientific information on L-Carnitine and published scientific information on clinical and nutritional trials with L-Carnitine and its derivatives. No claims are made herein for any particular consumer product, nor can these statements be used on such consumer products.

The recommended use for L-Carnitine is as a nutrient or dietary supplement. The statements in this document have not been evaluated by any Food and Drug Administration. Lonza's Carnipure™ is not intended to diagnose, treat, cure or prevent any disease.

No statement is intended or should be construed as a recommendation to infringe any existing patent. The information contained herein is believed to be correct and corresponds to the latest state of scientific and technical knowledge.

This Carnipure™ Focus has been reviewed by Professor Alfred Lohninger from the University of Vienna, Austria.

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