

## Review Article

# Influence of L-carnitine on metabolism and performance of sows

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(Received 21 January 2009 – Revised 15 May 2009 – Accepted 18 May 2009 – First published online 22 June 2009)

In recent years, L-carnitine has been used increasingly as a supplement in livestock animals. The present review gives an overview of the effects of dietary L-carnitine supplementation on the reproductive performance of sows. Results concerning the effect of L-carnitine supplementation during pregnancy on litter sizes are controversial. There are some studies reporting an increased number of piglets born alive per litter, while others could not find such an effect. In contrast, most studies performed show consistently that L-carnitine supplementation to a sow diet low in native carnitine during gestation increases piglet and litter weights at birth and enhances growth of litters during the suckling period. Biochemical mechanisms underlying the favourable effect of carnitine on intra-uterine growth have not been fully elucidated. There is, however, some evidence that carnitine influences the insulin-like growth factor-axis in sows and leads to greater placentae, which in turn improves intra-uterine nutrition, and stimulates oxidation of glucose in the fetuses. These effects may, at least in part, be responsible for higher birth weights of piglets. The stimulating effect of carnitine on growth of the litters might be due to an improved suckling behaviour of piglets born to L-carnitine-supplemented sows, causing the sows' milk production to rise. In conclusion, recent studies have clearly shown that dietary L-carnitine supplementation increases the reproductive performance of sows. These findings suggest that endogenous *de novo* synthesis of carnitine is insufficient to meet the metabolic requirement of sows during gestation.

### L-Carnitine: Sows: Litters: Metabolism: Performance

L-Carnitine (L- $\beta$ -hydroxy-4-*N*-trimethylaminobutyric acid) is an important compound in mammals. It serves as an essential cofactor for mitochondrial fatty acid oxidation by transferring long-chain fatty acids as acylcarnitine esters across the inner mitochondrial membrane. Carnitine, moreover, shuttles acyl moieties out of peroxisomes in the liver. It also regulates the intramitochondrial acyl-CoA/CoA ratio and acts as a CoA buffer in mammalian cells<sup>(1)</sup>. Carnitine is derived from dietary sources and endogenous biosynthesis<sup>(2,3)</sup>. It is taken up from blood into tissues by novel organic cation transporters (OCTN), particularly OCTN2 which is the most important carnitine transporter<sup>(1,4)</sup>. The fact that inborn or acquired defects of OCTN2 lead to primary or secondary systemic carnitine deficiency demonstrates the essential role of these transporters for reabsorption of carnitine in the kidney and delivery of carnitine from blood into body cells<sup>(1)</sup>.

In recent years, L-carnitine has been used increasingly as a supplement in livestock and sport animals. Feeding trials were designed to investigate whether dietary L-carnitine supplementation is capable of improving performance characteristics of animals. Such studies have been conducted in sport horses<sup>(5–7)</sup>, dairy cows or steers<sup>(8–11)</sup>, laying hens and broilers<sup>(12–19)</sup>, growing–finishing pigs<sup>(20–22)</sup>, suckling and

weanling pigs<sup>(23–30)</sup>, boars<sup>(31)</sup> and pigeons<sup>(32,33)</sup>. In several experiments, L-carnitine supplementation exerted beneficial effects on performance of these species. L-Carnitine supplementation improved the gain:feed ratio due to an increase in body protein accretion at the expense of body fat deposition, e.g. in growing pigs<sup>(20–22,25,26,28–30)</sup>. The most impressive effects of L-carnitine supplementation on animal performance, however, have been observed in sows. Musser *et al.*<sup>(34)</sup> were the first to describe a positive effect of L-carnitine supplementation during gestation on the reproductive performance of sows. They observed higher litter weights at birth and increased weight gains of litters during the suckling period in sows supplemented with L-carnitine compared with untreated control sows. Initially, these positive effects of carnitine could not be explained at a biochemical base as the effects were obviously not primarily due to the primary function of carnitine, namely an alteration of  $\beta$ -oxidation of fatty acids. In the last 10 years, several experiments have been performed, which aimed to identify the mechanisms underlying the favourable effects of L-carnitine in sows. The present review gives an overview about the results of these experiments and summarises the present knowledge about the effects of L-carnitine in sows.

**Abbreviations:** IGF, insulin-like growth factor; OCTN, organic cation transporters.

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## The carnitine status of sows during pregnancy and lactation

In women, a strong decrease in plasma carnitine concentrations during pregnancy has been well established<sup>(35–37)</sup>. Concentrations of total carnitine at delivery are decreased to about half of the concentration of non-pregnant women<sup>(38,39)</sup>. The decline of total carnitine concentrations is mainly due to a reduced concentration of free carnitine, while that of acylcarnitine is slightly increased compared to non-pregnant women. High ratios between acylcarnitine and free carnitine (>0.4) are designated as ‘carnitine insufficiency’<sup>(40)</sup>. In pregnant women, the concentration of carnitine in plasma could be markedly increased and the ratio between acylcarnitine and free carnitine decreased by supplementation of carnitine<sup>(41,42)</sup>. After delivery, plasma carnitine concentrations are quickly increasing to the levels before conception<sup>(42)</sup>.

The behaviour of the plasma carnitine concentration in sows during pregnancy is different from that in women. In the study of Musser *et al.*<sup>(34)</sup>, the concentration of free and total L-carnitine was measured in sows at days 10, 60, 90 and 110 of pregnancy. Plasma-free and total carnitine concentrations at day 60 were lower than at days 10, 90 or 110. However, the concentrations at day 110 were even slightly higher than at day 10. This indicates that a strong decline in plasma carnitine during the late pregnancy as seen in pregnant women does not occur in sows. Supplementation of sows’ diets with L-carnitine caused a moderate increase in plasma carnitine concentrations during pregnancy and lactation. In the study of Musser *et al.*<sup>(34)</sup>, daily supplementation of 100 mg L-carnitine increased the concentrations of free and total carnitine in plasma during gestation by approximately 10%. In another study, supplementation of 125 mg L-carnitine per day increased the concentration of total carnitine from 7.5 to 11.1  $\mu\text{mol/l}$  at day 95 of pregnancy<sup>(43)</sup>. In human subjects and rodents, carnitine can be delivered in the placenta from maternal to fetal blood by OCTN2<sup>(44,45)</sup>. The role of placental OCTN2 for the accumulation of carnitine in the fetus is evident from a study using OCTN2 null mice. Fetuses of these mice have markedly reduced (<20%) carnitine concentrations compared with of wild-type mice<sup>(46)</sup>. The transfer of carnitine through placenta has not yet been investigated in pigs. It is, however, likely that carnitine is delivered to the fetus in a similar way as in human subjects or rodents. Accordingly, it is expected that an elevated maternal plasma carnitine concentration might lead to increased carnitine concentrations in fetal tissues. Indeed, it has been shown that supplementation of sows with 50 mg L-carnitine/kg diet increases free and total carnitine concentrations in liver, skeletal muscle and heart of the fetus at days 55 and 70 of gestation, and moreover increases the activity of carnitine palmitoyltransferase-I in the liver<sup>(47,48)</sup>. Piglets from sows supplemented with L-carnitine moreover had higher carnitine concentrations in plasma and carcass at birth than piglets of unsupplemented control sows at birth<sup>(49)</sup>. These findings demonstrate that L-carnitine supplementation of sows improves the carnitine status of the fetuses already during gestation.

L-Carnitine supplementation of sows during the lactation causes also an increase of carnitine concentrations in plasma and milk. In the study of Musser *et al.*<sup>(34)</sup>, supplementation of the diets of lactating sows with 50 mg L-carnitine/kg

**Table 1.** Concentrations of carnitine in milk and in piglets from control sows or sows supplemented with L-carnitine during gestation and lactation†

	Control	+L-Carnitine (50 mg/kg diet)
Milk ( $\mu\text{mol/l}$ )		
Day 1 (colostrum)	183	221
Day 10	137	212*
Day 20	126	179
Piglets, plasma ( $\mu\text{mol/l}$ )		
Day 1 (birth)	15.1	20.0*
Day 10	15.6	22.9*
Day 20	12.8	17.5*
Piglets, carcass ( $\mu\text{mol/g DM}$ )		
Day 1 (birth)	0.94	1.05*
Day 10	1.32	1.73*
Day 20	1.39	1.84*

Values were significantly different from those of the control sows: \*  $P < 0.05$ .

† Data from Birkenfeld *et al.*<sup>(49)</sup>.

increased the concentrations of free carnitine in plasma and milk by 22 and 5%, respectively, and that of total carnitine by 15 and 24%. In another study, daily supplementation of 250 mg L-carnitine per sow increased the concentration of free carnitine in the milk by 50% and that of total carnitine by 35%<sup>(50)</sup>. The carnitine concentration of the milk might be important for the development of the suckling piglets because they have a low capacity for an endogenous carnitine synthesis, particularly at the first days after birth<sup>(51–53)</sup>. The low carnitine status of neonatal pigs is evident by the fact that carnitine supplementation increases their activity of carnitine palmitoyltransferase-I in the liver and their ability to oxidise fatty acids<sup>(25,54,55)</sup>. Piglets suckled from sows supplemented with L-carnitine during gestation and lactation had higher carnitine concentrations in plasma and carcass than piglets suckled from control sows, an effect that is due to the higher milk carnitine concentration (Table 1).

## Impact of L-carnitine supplementation on number and weight of piglets

The number of piglets born alive is one of the most important criteria of the reproductive performance of sows. Results concerning the impact of L-carnitine supplementation in sows during pregnancy on the number of piglets born are controversial (Table 2). In the study by Musser *et al.*<sup>(34)</sup>, sows receiving a diet supplemented with 48 mg L-carnitine per kg did not differ in the number of piglets born alive to unsupplemented controls. In another study, performed under practical conditions in a sow unit with Leicoma sows, L-carnitine supplementation at a level similar with that used in the study of Musser *et al.*<sup>(34)</sup> increased the number of piglets born alive by 0.5 per litter<sup>(56)</sup>. In a further study performed in crossbred sows, L-carnitine supplementation caused an even greater increase in the number of piglets born, both in the first and the second parity<sup>(50)</sup>. It should be noted, however, that this experiment was conducted with a small number of sows. In a more recent trial with a great number of sows in production stocks, the effect of two different carnitine doses, either 25 or 50 mg per kg diet, on the reproductive performance has been investigated<sup>(57)</sup>. In that study, number of piglets born alive per litter was increased by 0.47 and 0.58 for supplementary levels of 25 and 50 mg per kg, respectively.

**Table 2.** Effects of L-carnitine supplementation of pregnant sows on the number of piglets born alive in various studies

Reference	Supplementation level	Total number of sows ( <i>n</i> )	Number of piglets born alive ( <i>n</i> /litter)		Change ( <i>n</i> /litter)
			Control sows	L-Carnitine-supplemented sows	
Musser <i>et al.</i> <sup>(34)</sup>	100 mg L-carnitine/d	150	10.3	10.4	+0.1
Musser <i>et al.</i> <sup>(62)</sup>	50 mg L-carnitine/kg diet	232	11.5	11.1	-0.4
Ramanau <i>et al.</i> <sup>(56)</sup>	125 mg L-carnitine/d	175	10.6	11.1	+0.5
Ramanau <i>et al.</i> <sup>(50)</sup>					
First birth	125 mg L-carnitine/d	32	9.6	12.4*	+2.8
Second birth	125 mg L-carnitine/d	26	10.3	13.1*	+2.8
Ramanau <i>et al.</i> <sup>(57)</sup>					
25 mg L-carnitine/kg diet	25 mg L-carnitine/kg diet	1026	10.6	11.1*	+0.5
50 mg L-carnitine/kg diet	50 mg L-carnitine/kg diet	1012	10.6	11.2*	+0.6

Values were significantly different from those of control sows: \* $P < 0.05$ .

Several studies concurred that L-carnitine supplementation of sows during pregnancy reduces the number of stillborn or non-viable piglets. In the study of Musser *et al.* <sup>(34)</sup>, dietary L-carnitine supplementation reduced the number of stillborn piglets from 0.76 to 0.49 per litter. In two other studies, the number of stillborn piglets remained unaffected by dietary L-carnitine, but the number of non-viable piglets with a birth weight below 800 g was significantly lower in L-carnitine-supplemented sows than in control sows <sup>(50,58)</sup>.

Birth weights of piglets are largely influenced by the intra-uterine nutrient supply of fetuses. Several studies <sup>(34,50,56–59)</sup> have shown that L-carnitine supplementation of sows during pregnancy increases birth weights of litters (Table 3). This effect is slightly greater at a dose of 50 mg/kg than at a dose of 25 mg/kg of supplemented L-carnitine <sup>(57)</sup>. The favourable effect of L-carnitine supplementation on piglet and litter birth weights was observed in sows across the whole range of parities <sup>(57)</sup>.

### Hormonal and metabolic changes by L-carnitine supplementation in pregnant sows

Biochemical mechanisms underlying the favourable effects of carnitine on piglet and litter birth weights have not been completely clarified. There are, however, some studies that

indicated that effects of carnitine during gestation could at least in part be mediated by alterations of the insulin-like growth factor (IGF) system. Three independent studies showed that L-carnitine-supplemented pregnant sows have higher concentrations of IGF-1 in blood than control sows <sup>(34,43,60)</sup>. One study, moreover, showed additionally increased plasma concentrations of growth hormone, a trigger for the release of IGF-1, and IGF-2 in pregnant sows supplemented with L-carnitine <sup>(43)</sup>. IGF-1 is a key hormone for intra-uterine fetal development and promotes fetal secondary muscle fibre development <sup>(61)</sup>. Piglets of L-carnitine-supplemented sows had a greater number of primary muscle fibres in the semitendinosus muscle than piglets of control sows <sup>(62)</sup>. It has been suggested that alterations in muscle fibre characteristics could be due to increased maternal plasma IGF-1 concentrations. Sows supplemented with L-carnitine had increased mRNA concentrations of IGF-1 and IGF-binding proteins-3 and -5 in endometrium at days 40, 55 and 70 of gestation <sup>(63)</sup>, suggesting that carnitine influences the IGF axis at the fetal–maternal interface. In a more recent study, fetuses from gilts supplemented with L-carnitine were heavier, had lower IGF-1 mRNA concentrations in the liver and lower IGF-II concentrations in plasma at day 70 of gestation compared with fetus of control gilts <sup>(47)</sup>. Biochemical mechanisms underlying the increase in

**Table 3.** Effects of L-carnitine supplementation of pregnant sows on birth weights of piglets and litters in various studies

Reference	Supplementation level*	Total number of sows ( <i>n</i> )	Control sows	L-Carnitine-supplemented sows	Change
Weights of piglets (kg/piglet)					
Musser <i>et al.</i> <sup>(34)</sup>	100 mg L-carnitine/d	294	1.48	1.58*	+0.10
Musser <i>et al.</i> <sup>(62)</sup>	50 mg L-carnitine/kg diet	232	1.54	1.61*	+0.07
Ramanau <i>et al.</i> <sup>(56)</sup>	125 mg L-carnitine/d	175	1.38	1.48*	+0.10
Ramanau <i>et al.</i> <sup>(50)</sup>					
First birth	125 mg L-carnitine/d	32	1.54	1.39	-0.15
Second birth	125 mg L-carnitine/d	26	1.70	1.53	-0.17
Ramanau <i>et al.</i> <sup>(57)</sup>					
25 mg L-carnitine/kg diet	25 mg L-carnitine/kg diet	1026	1.40	1.48*	+0.08
50 mg L-carnitine/kg diet	50 mg L-carnitine/kg diet	1012	1.40	1.51*	+0.11
Weights of litters (kg/litter)					
Musser <i>et al.</i> <sup>(34)</sup>	100 mg L-carnitine/d	294	14.6	15.6*	+1.0
Musser <i>et al.</i> <sup>(62)</sup>	50 mg L-carnitine/kg diet	232	17.9	18.2	+0.3
Ramanau <i>et al.</i> <sup>(56)</sup>	125 mg L-carnitine/d	175	14.5	16.3*	+1.8
Ramanau <i>et al.</i> <sup>(50)</sup>					
First birth	125 mg L-carnitine/d	32	14.2	16.8*	+2.6
Second birth	125 mg L-carnitine/d	26	17.3	19.6*	+2.3
Ramanau <i>et al.</i> <sup>(57)</sup>					
25 mg L-carnitine/kg diet	25 mg L-carnitine/kg diet	1026	15.1	16.4*	+1.3
50 mg L-carnitine/kg diet	50 mg L-carnitine/kg diet	1012	15.1	16.8*	+1.7

Values were significantly different from those of the control sows: \* $P < 0.05$ .

plasma IGF-1 concentrations by dietary carnitine in pregnant sows have not yet been elucidated. However, effects of dietary carnitine on plasma IGF-1 concentrations have been also observed in other species and under certain pathophysiologic conditions. In broiler chicks, supplementation of 200 or 500 mg of L-carnitine per kg diet increased plasma IGF-1 concentrations and body weight gains<sup>(64)</sup>. There was also a significant correlation between changes in body weight gains and plasma IGF-1 concentrations suggesting that increased body weight gains in broiler chicks were at least in part due to an increased IGF-1 concentration. In streptozotocin-induced diabetic rats, which have reduced plasma carnitine and IGF-1 concentrations compared with normal rats, supplementation of 50, 100 or 200 mg L-carnitine per kg diet also caused a dose-dependent increase in plasma IGF-1 concentration<sup>(65)</sup>. It was suggested that supplementation of L-carnitine is a means to restore plasma IGF-1 concentrations in diabetic subjects to nearly normal levels. In HIV-1-infected subjects, supplementation of 3 g of acetyl-L-carnitine per day over a period of 5 months also led to an increase in plasma IGF-1 concentration. As IGF-1 is a major survival factor able to protect cells from apoptosis by different stimuli and conditions, the increase in plasma IGF-1 concentration could represent an important mechanism underlying the anti-apoptotic effects of acetyl-L-carnitine in HIV-1-infected subjects<sup>(66)</sup>. These studies indicate that carnitine could generally increase the release of IGF-1 by a mechanism to be elucidated in future studies.

A recent study has found that sows supplemented with L-carnitine during gestation have greater chorions, the fetal parts of the placentae, than control sows<sup>(43)</sup>. Chorions of sows supplemented with L-carnitine, moreover, had a higher concentration of glucose transport protein, the rate-limiting system of glucose transport through the placenta<sup>(44)</sup>. This suggests that carnitine increased glucose transfer from maternal to fetal blood. Glucose derived from maternal blood is the principle source of energy for fetal growth. Thus, it is likely that an increased supply of fetuses with glucose contributes to their increased birth weights. A similar phenomenon is known from pregnant women with diabetes mellitus, whose fetuses show accelerated intra-uterine growth due to hyperglycaemia<sup>(67)</sup>. It has been established that maternal IGF-1 and IGF-2 play a key role in the development of the placenta and that IGF-1 upregulates glucose transport protein expression in the placenta<sup>(68–71)</sup>. Therefore, it is likely that an improved development of the placenta in sows supplemented with L-carnitine was, at least in part, due to increased plasma IGF-1 and IGF-2 concentrations observed in recent studies<sup>(34,43,60)</sup>.

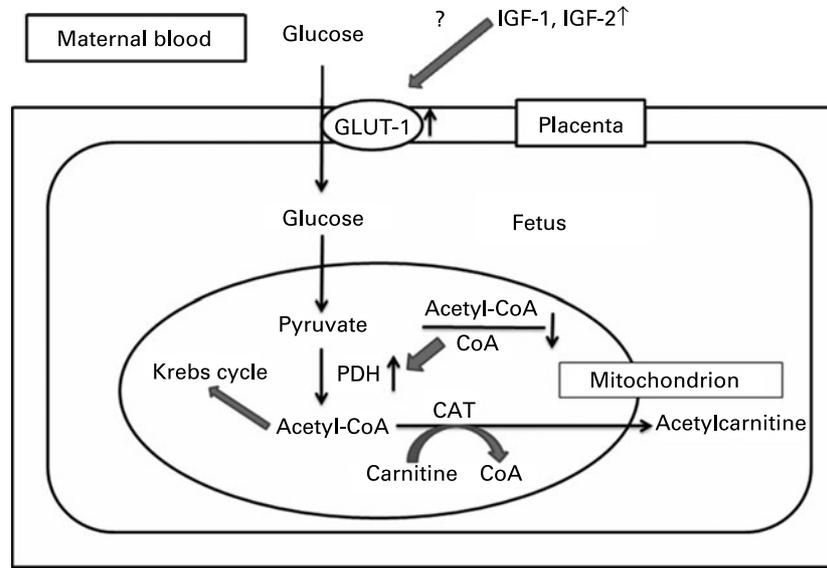
It has been shown that carnitine influences not only  $\beta$ -oxidation of fatty acids but influences also the metabolism of glucose. Carnitine supplementation in type-2 diabetic patients increased oxidation and storage of glucose, and thus improved oral glucose tolerance<sup>(72)</sup>. Similar effects were recently observed in pregnant sows and healthy ponies<sup>(73,74)</sup>. Xi *et al.*<sup>(48)</sup> have recently shown that L-carnitine supplementation of pregnant sows stimulates glucose oxidation in their fetuses. The effect of carnitine on glucose oxidation is due to an increase in the activity of pyruvate dehydrogenase. Within the mitochondria, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase. Pyruvate dehydrogenase is a multienzyme complex, whose activity is also influenced by

the concentration of acetyl-CoA. Carnitine stimulates the export of acetyl groups out of the mitochondria, thus decreases the ratio of acetyl-CoA/CoA and thereby activates pyruvate dehydrogenase, resulting in an increased glucose oxidation. In fetuses, the stimulation of glucose oxidation may improve energy metabolism that is critical to embryonic and fetal development<sup>(48)</sup>. An enhanced oxidation of glucose in fetuses, besides an increased transfer of glucose from maternal to fetal blood, may therefore contribute to increases in birth weight (see Fig. 1). Carnitine supplementation of sows increased also the activity of carnitine palmitoyltransferase-I in fetal liver, indicative of an increased  $\beta$ -oxidation rate. This effect could also contribute to an increased energy production, although  $\beta$ -oxidation of fatty acids plays a minor role for energy production in the fetus compared to oxidation of glucose.

An increased supply of glucose through placenta and an increased efficiency of energy production could also explain the smaller number of stillborn or non-viable piglets born to sows supplemented with L-carnitine<sup>(34,56,58)</sup>.

Woodworth *et al.*<sup>(60)</sup> showed that carnitine has further effects on the metabolism of pregnant sows besides an improved glucose tolerance and increased plasma IGF-1 concentrations. These authors observed reduced concentrations of NEFA and urea in plasma of sows supplemented with L-carnitine. Their findings suggested that dietary L-carnitine enhanced the uptake of fatty acids into tissues and their utilisation for energy production and diminished muscle protein catabolism. The reason for a reduced muscle protein catabolism could be that sows did not need to rely on branch chain amino acids for energy because their fatty acid utilisation was improved<sup>(60)</sup>. It has been, moreover, found that L-carnitine increases body weight and backfat thickness in sows during gestation<sup>(34)</sup>. This finding prompted Young *et al.*<sup>(75)</sup> to the hypothesis that carnitine improves energy utilisation in sows. These authors were able to demonstrate that Carnichrome, a combination of L-carnitine and chromium, improves the digestibility of energy and organic matter from the diet but has no influence on heat production. An increased digestibility of energy and nutrients could provide an explanation for the finding that litter weights were increased by dietary L-carnitine supplementation, while feed intake remained unchanged and backfat thickness was unchanged or even increased compared to control sows<sup>(34,50)</sup>. It cannot be excluded that carnitine has also an influence on energy utilisation by affecting the physical activity of the sows, which, however, has not yet been investigated. Woodworth *et al.*<sup>(73)</sup> observed, moreover, increased plasma concentrations of leptin in gestating sows supplemented with L-carnitine, suggesting that carnitine influenced biochemical pathways involved in energy metabolism by an increased secretion of leptin.

During the intra-uterine phase, the supply of the fetus with amino acids, glucose, minerals and fatty acids from the mother via the placenta is necessary for its development. The rate of fatty acid oxidation in the fetus is low<sup>(76)</sup>. However, immediately after birth the oxidation of fatty acids becomes extremely important because of the disruption of the supply with glucose and the rapid exhaustion of the glycogen storage<sup>(77)</sup>. Sufficient concentrations of L-carnitine in tissues are required for an efficient utilisation of fatty acids for the production of energy.



**Fig. 1.** Proposed mechanism by which L-carnitine supplementation of sows increases birth weights of their offspring. Carnitine supplementation of sows improves the development of the placenta and increases glucose transport protein (GLUT-1) concentration in the chorion, likely due to increased maternal plasma insulin-like growth factor (IGF)-1 and IGF-2 concentrations. This leads to an increased transfer of glucose from maternal to fetal blood. Carnitine moreover stimulates oxidation of glucose in fetal cells, which enhances the efficiency of energy production. This effect is based on the ability of carnitine to shuttle acetyl groups out of the mitochondrion as acetylcarnitine (formed by the action of carnitine acetyl transferase (CAT)), resulting in a reduction in the acetyl-CoA:CoA ratio, which in turn activates pyruvate dehydrogenase (PDH).

It is possible that piglets of sows supplemented with L-carnitine were able to switch faster on the oxidation of fatty acids due to their better carnitine status than piglets of control sows. This could have contributed to the lower number of losses of piglets observed in sows supplemented with L-carnitine.

The finding that sows benefit from dietary L-carnitine supplementation implies that endogenous *de novo* synthesis of carnitine is insufficient to meet the metabolic requirement during gestation. Thus, the question arises whether other components of the diet could have been limiting for carnitine biosynthesis. Carnitine biosynthesis involves a complex series of reactions. Lysine in protein peptide linkage provides the carbon backbone of carnitine. It undergoes methylation of the  $\epsilon$ -amino group to yield trimethyllysine, which is released upon protein degradation. Methyl groups required for this process are derived from methionine. The released trimethyllysine is further oxidised to  $\gamma$ -butyrobetaine, which is then hydroxylated by  $\gamma$ -butyrobetaine dioxygenase to form carnitine<sup>(78)</sup>. Fe and ascorbic acid as well as the coenzymes NAD and PLP are essential cofactors for the carnitine biosynthesis pathway. In most species, including the pig, liver and kidney are the major sites of carnitine synthesis<sup>(78,79)</sup>. Previous studies in rats and human subjects have shown that not the activity of  $\gamma$ -butyrobetaine dioxygenase but the availability of carnitine precursors, particularly  $\gamma$ -butyrobetaine, for the enzymatic reaction is rate limiting for carnitine biosynthesis<sup>(80,81)</sup>. Although this has not directly been proven, it is likely that the availability of  $\gamma$ -butyrobetaine in liver and kidney is the limiting factor for carnitine biosynthesis in pigs like in other species<sup>(82)</sup>. Due to their role as initial precursors, it has previously been suggested that carnitine biosynthesis is stimulated by additionally dietary lysine or methionine<sup>(80)</sup>. However, excess amounts of lysine plus methionine led only to a slightly increased carnitine production in human

adults<sup>(80)</sup>. In pigs and rats, excess dietary lysine did not increase but lowered plasma and tissue carnitine concentrations, probably due to a reduced availability of  $\gamma$ -butyrobetaine for carnitine synthesis<sup>(82,83)</sup>. Therefore, an insufficient lysine supply can be ruled out as a factor, which could have been limiting for carnitine synthesis during gestation. A potential role of the supply of methionine on the carnitine synthesis in sows has not yet been investigated. It is, however, unlikely that carnitine synthesis was restricted by methionine as this indispensable amino acid was supplied adequately in all the studies that exerted beneficial effects of carnitine on reproductive performance of sows. More likely, carnitine synthesis is generally reduced during gestation. Gestation represents an anabolic state in which the rate of protein degradation in the body is reduced compared to the non-pregnant organism. In women, concentrations of trimethyllysine and  $\gamma$ -butyrobetaine in plasma are reduced during pregnancy, probably due to a reduced release of trimethyllysine from body protein<sup>(42)</sup>. It is possible that the release of trimethyllysine from body protein is also reduced in sows during gestation, which in turn might lead to a reduced carnitine synthesis. This suggestion, however, has to be proven in future studies.

#### Development of piglets during the suckling period

Several studies have shown that supplementation of L-carnitine during pregnancy and lactation increases weight gains of litters during the suckling period (Table 4). This effect is the greatest in sows of the first and the second parity in which L-carnitine supplementation (50 mg/kg diet) increased litter gains during a 21-d-suckling period by 28 and 29%, respectively, compared with unsupplemented control sows. In sows with three and more parities, the effect of carnitine on litter weight gains was in average 10%<sup>(57)</sup>. Weight gain of litters during the suckling period is

**Table 4.** Effects of L-carnitine supplementation of sows during pregnancy and lactation on litter weight gains during the suckling period in various studies

Reference	Supplementation level	Suckling period (d)	Litter weight gains (kg)		Change (kg)
			Control sows	L-Carnitine-supplemented sows	
Musser <i>et al.</i> <sup>(34)</sup>	P: 100 mg L-carnitine/d L: 50 mg L-carnitine/kg diet	15	26.8	29.0*	+2.2
Ramanau <i>et al.</i> <sup>(56)</sup>	P: 125 mg L-carnitine/d L: 250 mg L-carnitine/d	28	51.2	57.9*	+6.7
Ramanau <i>et al.</i> <sup>(50)</sup>					
First birth	P: 125 mg L-carnitine/d L: 250 mg L-carnitine/d	25	61.1	67.7*	+6.6
Second birth	P: 125 mg L-carnitine/d L: 250 mg L-carnitine/d	30	91.4	99.2*	+7.8
Ramanau <i>et al.</i> <sup>(57)</sup>					
	P: 25 mg L-carnitine/kg diet L: 25 mg L-carnitine/kg diet	21	32.4	37.0*	+4.6
	P: 50 mg L-carnitine/kg diet L: 50 mg L-carnitine/kg diet	21	32.4	38.9*	+6.5

P, pregnancy; L, lactation.  
Values were significantly from those of the control sows: \* $P < 0.05$ .

mainly dependent on the sow's milk production<sup>(84)</sup>. It has been demonstrated that sows supplemented with L-carnitine are able to produce more milk than control sows<sup>(50,59)</sup>. The nutrient composition of the milk did not differ between control sows and sows supplemented with L-carnitine<sup>(50,59,85)</sup>. The amount of nutrients and energy secreted with the milk, however, was higher in L-carnitine-supplemented sows than in control sows<sup>(50,59)</sup>. This clearly indicates that increased litter weights of piglets during the suckling period are due to more energy and nutrients being transferred from the sow to the piglets with the milk. An interesting finding was that sows supplemented with L-carnitine during gestation and lactation are able to maintain a very high milk yield even in the case of a strong energy deficiency. Under the condition of energy deficiency, sows supplemented with L-carnitine were able to mobilise more energy from adipose tissue than control sows, which can be used for the production of surplus milk<sup>(59)</sup>. This finding is interesting as a considerable energy deficit and loss of body mass during lactation can occur also in practical feeding situations, particularly in primiparous sows<sup>(86,87)</sup>. In such situations, dietary L-carnitine can help sows to maintain a high milk yield and fast growth of suckling litters.

Milk production of sows is influenced by several factors such as the age of the sows and their energy and nutrient supply. The suckling behaviour of the piglets is another

important factor that has a bearing on milk production of sows. It is well established that the suckling interval and the vigour with which piglets stimulate the teats both affect milk yield. If piglets suckle more frequently they will obtain more milk, thus causing milk production to rise<sup>(88-90)</sup>. It has been supposed therefore that piglets of sows supplemented with L-carnitine can suckle for longer periods than piglets of control sows and therefore stimulate milk production by the sow. In order to investigate this hypothesis, the suckling behaviour of piglets born to sows supplemented with L-carnitine and piglets of sows born to control sows has been studied. The number of sucklings per day was not different between both groups of piglets<sup>(91)</sup>. However, duration of one suckling and total suckling time per day were clearly higher in piglets born to sows given L-carnitine during gestation than in piglets born to control sows (Table 5). The suckling behaviour of the pigs was reflected in the body weight gain of the litters during lactation, which was higher in litters born to sows given L-carnitine than in litters born to control sows. It is assumed that the longer suckling time per day is the reason for higher milk production by sows and faster growth of piglets during the suckling period. Interestingly, L-carnitine supplementation during lactation had no effect on the suckling behaviour and body weight gains of the piglets<sup>(91)</sup>. This finding is confirmed by studies of Musser *et al.* <sup>(34,92)</sup>. These authors showed that L-carnitine supplementation of sows

**Table 5.** Suckling behaviour of piglets born to control sows and piglets born to sows supplemented with L-carnitine, suckled either by control sows or by sows supplemented with L-carnitine, at day 3 of age†

Litter born to	Litter suckled by	n	Number of sucklings/d (n)	Average duration of one suckling (min)	Total suckling time per day (h)
Control sow	Control sow	5	43.6	3.7 <sup>b</sup>	2.7 <sup>a</sup>
Control sow	L-carnitine-treated sow	5	45.1	3.7 <sup>b</sup>	2.8 <sup>ab</sup>
L-carnitine-treated sow	Control sow	5	43.3	4.2 <sup>a</sup>	3.0 <sup>ab</sup>
L-carnitine-treated sow	L-carnitine-treated sow	5	44.3	4.3 <sup>a</sup>	3.2 <sup>b</sup>
Control sow		10	44.4	3.7 <sup>b</sup>	2.7 <sup>b</sup>
L-carnitine-treated sow		10	43.8	4.2 <sup>a</sup>	3.1 <sup>a</sup>
	Control sow	10	43.4	3.9	2.8
	L-carnitine-treated sow	10	44.7	4.0	3.0

<sup>a,b</sup> Means values within a column with unlike superscript letters were significantly different ( $P < 0.05$ ).

† Data from Birkenfeld *et al.* <sup>(91)</sup>.

during pregnancy increased litter-weaning weights<sup>(34)</sup>. However, in sows that were not supplemented with L-carnitine during pregnancy, L-carnitine supplementation during lactation did not influence litter-weaning weights<sup>(92)</sup>. These studies also showed that increased litter gains during the suckling period are due to the effects of L-carnitine during pregnancy, while L-carnitine during lactation has no effects in this respect if sows were not supplemented with L-carnitine during pregnancy.

The reason for the improved suckling behaviour of piglets from L-carnitine-supplemented sows has not yet been completely elucidated. However, it has been shown that L-carnitine increases fatty acid oxidation in tissues of newborn pigs<sup>(54,93,94)</sup>. These findings indicate that piglets of sows supplemented with L-carnitine are able to switch on fatty acid oxidation faster than piglets of control sows due to their superior carnitine status. This may improve their energy production and in turn increase their suckling persistence during the first few days after birth. Another possibility is that piglets born to sows supplemented have a higher vitality at birth, which might have been associated with increased suckling persistence, due to an improved fetal development.

### Growth performance of piglets after weaning

It has been well established that maternal diet can influence intra-uterine nutrition, which in turn influences fetal and birth weights. Nutrition during fetal life and birth weights may affect animal metabolism and performance in later life, which is also termed 'fetal programming'<sup>(95)</sup>. In human subjects and experimental animal models, it has been found that increased or decreased level of intra-uterine nutrition can result in adiposity in later life<sup>(96)</sup>. In pigs, it has been observed that low birth weights result in a lower number of muscle fibres in semitendinosus muscle, and lower carcass weights, meat percentages and loin muscle area at slaughter (182 d of age) compared with high birth weights<sup>(97)</sup>. Assuming that carnitine supplementation of sows with L-carnitine improves intra-uterine nutrition, induction of epigenetic effects in their fetuses is possible. Musser *et al.*<sup>(62)</sup> indeed observed that piglets of L-carnitine-supplemented sows have more muscle fibres than those of control sows. However, growth performance (feed intake, daily body weight gains and gain:feed ratio) of piglets born to sows supplemented with L-carnitine during the rearing phase did not differ from that of piglets born to control sows<sup>(30)</sup>. Postnatal growth capability from weaning until slaughter at a body weight of 118 kg was also not different between pigs born to sows supplemented with L-carnitine and those of control sows<sup>(98)</sup>. This means that L-carnitine supplementation of sows does not influence the post-weaning growth performance of their offspring. Obviously, possible epigenetic effects during fetal life induced by maternal carnitine supplementation were not pronounced enough to induce effects on growth performance in the later life.

### Effects of carnitine supplementation on the reproductive performance in rats

To elucidate the effect of carnitine on reproductive performance, few studies have been also performed with rats. In a study performed in our laboratory, supplementation of a diet

with a low native carnitine content with 1 g/kg during gestation and lactation had no effect on litter sizes and litter weights at birth and at weaning over three consecutive pregnancies in rats<sup>(99)</sup>. In the study of Davis<sup>(100)</sup>, pregnant rats were carnitine depleted by administration of sodium pivalate, a drug commonly used to study the effects of secondary carnitine deficiency in rats. Litter sizes and pup weights at birth were, however, not affected by carnitine depletion. In another study, treatment of pregnant rats with pivalate lowered litter sizes and litter weights, without having an effect on individual pup weights<sup>(101)</sup>. In that study, supplementation of carnitine, even in high levels, did, however, not restore normal litter sizes. Thus, the conclusion of that study was that the adverse effects of pivalate are independent of its effect on the carnitine status. Taken together, these studies indicate that carnitine does not have important functions on intra-uterine development of litters in rats, which is in clear contradiction to findings in sows. It rather seems that even a low carnitine status is sufficient to ensure a normal reproductive outcome in rats, while sows benefit from additional carnitine with respect to litter sizes and weights. The reason for this obvious difference in the role of carnitine during gestation between these two species is unknown.

### Conclusion

Studies reported in the literature clearly show that supplementation of diets with L-carnitine during pregnancy has beneficial effects in sows. This implies that endogenous *de novo* synthesis of carnitine is insufficient to meet the metabolic requirement in the gestating sow. Results of several studies indicate that L-carnitine supplementation of sows increases birth weights of piglets. Although biochemical mechanisms underlying this phenomenon have not yet been completely elucidated, increased maternal IGF-1 concentrations, an improved transfer of glucose from maternal to fetal blood through the placenta and improved oxidation of glucose, leading to a more efficient energy production, in the fetuses may be key events responsible for an improved fetal development. Piglets born to sows supplemented with L-carnitine are moreover able to suckle for longer, therefore receive more milk from the sow and are growing faster during the suckling period.

### Acknowledgements

The author declares no conflicts of interest. The present research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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