Plasma carnitine and renal-carnitine clearance during pregnancy[1-3]

Gitten Cederblad, MD, Lars Fåhraeus, MD, and Klas Lindgren, BS

ABSTRACT This study assessed the time course of decrease in plasma carnitine during pregnancy and compared the renal clearance of carnitine during late pregnancy with nonpregnant women. As early as the 8th wk of pregnancy, the mean (±SD) value of total plasma-carnitine concentration in 19 women was significantly decreased from 39.0 ± 6.3 to 32.8 ± 4.6 μmol/l and the values continued to fall to 17.3 μmol/l by the 36th wk. The pattern was due to a fall in free-carnitine level; acylcarnitine remained unchanged. In 12 other women examined during late pregnancy, the renal clearance of acylcarnitine was significantly higher than in nonpregnant women, 53.9 ± 29.4 versus 13.3 ± 3.0 ml/min, in contrast to free carnitine, 3.5 ± 2.8 versus 2.8 ± 1.9 ml/min. Urinary excretion of carnitine (expressed per mol creatinine) did not differ between the two groups. Pregnant women showed sustained excretion of carnitine in the presence of low plasma-carnitine concentrations. *Am J Clin Nutr* 1986;44:379-383.

KEY WORDS Pregnancy, plasma carnitine, time course, urinary carnitine, renal-carnitine clearance

Introduction

Carnitine is an essential cofactor in the transfer of long-chain fatty acids across the inner mitochondrial membrane (1). Furthermore, carnitine may also play a part in other metabolic processes, such as the facilitation of branched-chain 2-oxo acid oxidation and, as a reversible sink for acyl residues, the generation of CoASH (2). The body's supply of carnitine is derived in part from digestion of food and in part from endogenous synthesis of lysine and methionine. The final reaction, hydroxylation to gamma-butyrobetaine, occurs in the liver and kidney of humans.

The relative contributions of endogenously synthesized and dietary carnitine in maintaining tissue stores in physiological and pathological states have not been established to date. In the immediate postnatal period in full-term babies, fat is the main source of energy. Optimum oxidation of fatty acids requires carnitine (3). Some evidence suggests that the ability of neonates to synthesize carnitine is limited because of immature hepatic gamma-butyrobetaine-hydroxylase activity (4).

Very little is known about the transport of carnitine across the placenta and the ability of the human fetus to synthesize carnitine. Carnitine concentration in the blood, serum, or plasma of pregnant women is reported to decrease as gestation proceeds (5, 6). Moreover, a significant positive correlation has been found between maternal and fetal plasma at delivery (6, 7). The aim of the present study was to investigate in more detail the time course of the changes in plasma concentrations of carnitine and its derivatives during pregnancy. In addition, the renal clearance of carnitine and its derivatives in pregnant women during late gestation and in nonpregnant women has been compared.

[1] From the Department of Clinical Chemistry (GC, KL), Karolinska Institute, Danderyd's Hospital, Danderyd and the Department of Obstetric and Gynecology (LF), University of Linköping, Sweden.

[2] Supported by grants from the Swedish Medical Council No B85-03X-07136-01, the Swedish Nutrition Foundation, the Swedish Society of Medical Sciences, the Swedish Baby Food Industry Fund for Nutritional Research, the Medical Research Fund of the County Council of Östergötland, and "Förenade Liv" Mutual Group Insurance Company.

[3] Address reprint requests to: Dr G Cederblad, Department of Clinical Chemistry, Karolinska Institute, Danderyd's Hospital, S-182 88, Danderyd, Sweden.

Received September 18, 1985.
Accepted for publication February 18, 1986.

Subjects and methods

Subjects

Two groups of pregnant women were studied. The first group (P1) comprised 19 subjects who planned to conceive and who later succeeded. None had used any hormonal drug or had been pregnant during the 6 mo prior to the study. Exact duration of gestation was determined by ultrasonography. They had a mean age of 26 yr, range 20–35. One woman had a femoral-vein thrombosis during the 32 wk and was thereafter excluded. From this group, it was possible to obtain only blood samples. Of the 19 women, 12 breast-fed their infants. The second group (P2), from whom both blood and urine samples were obtained, comprised 12 women who were studied from 28 wk gestation through delivery. They had a mean age of 32 yr (range 24–37). None of the pregnant women used any medication except iron and vitamin supplements. All women, except the one mentioned above, remained healthy during the period of observation and had an uneventful delivery.

The control group (N), comprised 12 healthy nonpregnant women. Their, mean age was 19 yr (range 17–21). Informed consent was obtained from all subjects. The procedures of the study were in accord with the Helsinki Declaration (Tokyo, Japan, 1975).

Design

The P1 group provided blood samples within 4 mo of conception; 15 of them provided two specimens. Further blood samples were taken in the 8th, 14th, 20th, 28th, and 36th wk of gestation. Additional samples were obtained from the 12 breast-feeding women 8 wk after delivery. Blood and urine samples were collected from the P2 group on 2–6 occasions between the 28th and 40th wk.

Blood samples were drawn from an antecubital vein—after an overnight fast for P1 and N, but not for P2. Urine was collected in bottles containing 2 ml thymol-isopropanol (8) or 10 ml HCl, 6 mol/l as preservatives. Plasma and urine samples were stored at −20°C before analysis.

Chemical procedures

Carnitine was assayed by an enzymatic radioisotope method (9), modified as described previously (10). Acylcarnitine was calculated as the difference between total carnitine, obtained after alkaline hydrolysis, and free carnitine. Analysis of a control serum gave values (mean ± SD, n = 23) of 47.0 ± 1.5 (CV = 3.2%), 39.7 ± 1.4 (CV = 3.5%), and 7.3 ± 2.1 (CV = 28.8%) μmol/l for total, free, and acylcarnitine, respectively.

Statistical analysis

"Student's" *t* tests for two samples, paired and unpaired, were used (11).

Results

The plasma-free carnitine level in the P1 group decreased continuously during gestation and, in the end, it was approximately half of the concentration found before conception (**Fig 1**). The prepregnancy value had been reached on the first postpartum sampling occasion, after 8 wk in the breast-feeding women. In contrast, no significant change in the acylcarnitine values occurred during pregnancy. However, during lactation, acylcarnitine concentration was higher than the value before the conception. The mean (±SD) total carnitine level of 37.0 ± 4.6 μmol/l in nonpregnant women (N) did not differ significantly from the corresponding mean value (±SD) obtained before conception in the P1 group, 39.0 ± 6.3 μmol/l.

In the pregnant women (P2) followed from the 28th wk to delivery, mean plasma-carnitine concentrations during this period did not differ significantly from those of the P1 group who were followed thoughout pregnancy. Mean values (±SD) for total-, free-, and acylcarnitine concentrations for P1 (week 28) versus P2 (week 28–37) were 18.8 ± 3.8 vs 21.4 ± 7.4 μmol/l, 16.3 ± 2.7 vs 19.1 ± 5.8 μmol/l, and 2.7 ± 2.4 vs 2.4 ± 2.7 μmol/l, respectively.

Renal clearance of acylcarnitine was about four times higher whereas free-carnitine clearance was the same in the pregnant (P2) compared to the nonpregnant women (**Table 1**). The mean (±SD) total-carnitine excretion of 21.3 ± 8.0 mmol/mol creatinine in the pregnant women did not differ from the corresponding value of 23.7 ± 8.7 in nonpregnant women.

Discussion

Several authors (5–7, 12) have reported that plasma-free and total-carnitine levels at delivery are decreased to about half the concentrations seen in nonpregnant women. The present study provides new data on the time course of the carnitine decrease during pregnancy. From conception, there was a gradual decrease in free- but not in acylcarnitine concentration. The decrease in free carnitine was larger in the first half of the pregnancy, about 0.9 μmol · l · wk compared to about 0.2 μmol · l · wk after the 20th wk.

Remarkable also is that the major decrease in plasma carnitine, to almost half the initial

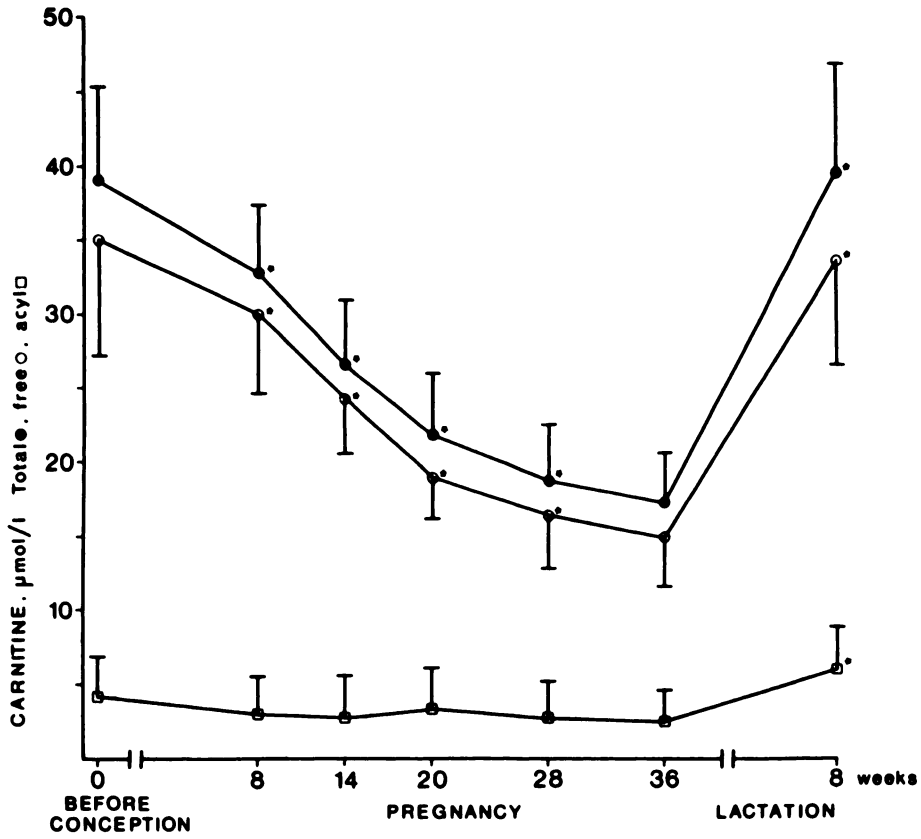

FIG 1. Plasma-carnitine concentration (µmol/l) before conception, during pregnancy, and during lactation. * means significant difference ($p < 0.05$) compared to the last previous mean value.

value, occurred during the first half of the pregnancy. The reduction was significant as early as in the 8th wk when the weight of the fetus is only 0.22 g. In the 20th wk, the weight of the fetus is about 316 g (13). Thus it seems that additional factors, other than the needs of the fetus, govern the observed decrease in plasma-carnitine concentration.

Borum (14) has shown that plasma-carnitine levels in rats were influenced by androgens

TABLE 1
Urinary excretion and renal clearance of carnitine in nonpregnant women (N) and in women (P2) during pregnancy (weeks 28–37)

Group	n	Total carnitine	Carnitine clearance		
			Total	Free	Acyl-
		mmol/mol creatinine	*ml/min**	*ml/min**	*ml/min**
N	12	23.7 (8.7)†	4.9 (2.0)	2.8 (1.9)	13.3 (3.0)
P2	12	21.3 (8.0)	7.5 (3.4)	3.5 (2.8)	53.9 (29.4)
Significance (one-tailed)		ns	< 0.025	ns	< 0.001

* Clearance = UV/P, where U and P indicate urine- and plasma-carnitine concentrations and V is urine flow (ml/min). 24 h-Samples of urine were collected.
† Mean (SD).

and estrogens. Although it is difficult to relate these findings to humans, it cannot be ruled out that a possible factor influencing plasma carnitine could be hormonal changes during pregnancy. The decrease in plasma carnitine cannot be due only to volume dilution because, by the 20th wk of pregnancy, levels had already fallen to 50% of prepregnancy values. Carnitine may also facilitate removal of excess and potentially toxic acyl groups from the cell, which are excreted as acylcarnitine into urine (15). It is possible that there is an increased need of carnitine during pregnancy to perform this metabolic function. If so, it would decrease the free-carnitine level and increase the clearance of acylcarnitine, in agreement with our findings.

Urinary excretion of carnitine (expressed per mol creatinine) did not differ between women during late pregnancy and nonpregnant women, despite the low plasma-carnitine levels in the pregnant women. Consequently, renal clearance of carnitine, especially of acylcarnitine, was higher in the pregnant women. The higher renal clearance of acylcarnitine than of free carnitine is in accordance with earlier results. In normal subjects, Cederblad et al (16) reported 25 and 4 ml/min and Carrol et al (17) reported 24.6 and 1.2 ml/min for acyl- and free carnitine, respectively. The corresponding figures in pregnant women were 54 and 3.5 ml/min. Thus, the clearance of acylcarnitine was further increased in pregnant women.

Explanations for the sustained carnitine excretion in the presence of low plasma-carnitine concentration in late pregnancy could be an altered regulation of plasma-carnitine with redistribution within the body or an increased renal synthesis of carnitine. Both explanations would not affect the woman's total body store of carnitine. However, muscle-carnitine levels have not been determined in pregnant women and it is not known whether a decrease in muscle-carnitine concentration (representing over 90% of total body carnitine) also occurs. In a study of multiple injuries, the lowest value was found in a woman in the 30th wk of pregnancy, although the value was not in the region found in carnitine-deficient patients (18). In a woman with carnitine deficiency, rapid deterioration following delivery has been reported (19).

The mechanism by which carnitine is supplied to the human fetus is not understood. Despite decreasing carnitine concentrations in maternal and fetal plasma (20) as well as in amniotic fluid (6), the full-term fetus seems to accumulate carnitine in its muscle tissue so that, at delivery, the level is similar to the level in adults (21). However, there is a risk that especially premature infants may have suboptimal carnitine levels at birth (21, 22).

Further studies of maternal carnitine status are needed. Such information could elucidate answers to questions that are still not fully explained: Are the carnitine stores of the fetus sufficient before birth? What is the source of fetal carnitine? Is a transplacental transfer of carnitine a significant source for the fetus?

The authors gratefully acknowledge the expert technical assistance of Kristina Weiderling and Inga Wirström.

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