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Review

The significant role of carnitine and fatty acids during pregnancy, lactation and perinatal period. Nutritional support in specific groups of pregnant women

Penelope D. Manta-Vogli [a], Kleopatra H. Schulpis [b], Yannis Dotsikas [c], Yannis L. Loukas [c, *]

[a] Department of Clinical Nutrition & Dietetics Agia Sofia Children's Hospital, Athens, Greece
[b] Institute of Child Health Agia Sofia Children's Hospital, Athens, Greece
[c] Laboratory of Pharm. Analysis, Department of Pharmacy, National and Kapodistrian University of Athens, Panepistimiopolis Zographou, GR-157 71, Athens, Greece

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SUMMARY

Background & aims: Pregnancy is characterized by a complexity of metabolic processes that may impact fetal health and development. Women's nutrition during pregnancy and lactation is considered important for both mother and infant. This review aims to investigate the significant role of fatty acids and carnitine during pregnancy and lactation in specific groups of pregnant and lactating women.
Methods: The literature was reviewed using relevant data bases (e.g. Pubmed, Scopus, Science Direct) and relevant articles were selected to provide information and data for the text and associated Tables.
Results: Dynamic features especially of plasma carnitine profile during pregnancy and lactation, indicate an extraordinarily active participation of carnitine in the intermediary metabolism both in pregnant woman and in neonate and may also have implications for health and disease later in life. Maternal diets rich in trans and saturated fatty acids can lead to impairments in the metabolism and development of the offspring, whereas the consumption of long chain-polyunsaturated fatty acids during pregnancy plays a beneficial physiologic and metabolic role in the health of offspring.
Conclusions: Pregnant women who are underweight, overweight or obese, with gestational diabetes mellitus or diabetes mellitus and those who choose vegan/vegetarian diets or are coming from socially disadvantaged areas, should be nutritionally supported to achieve a higher quality diet during pregnancy and/or lactation.

Introduction

Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is a natural-origin amino acid. In human omnivores, 75% of carnitine is coming from the diet, while the rest (25%) is provided by internal *de novo* synthesis from lysine and methionine, mostly in the liver, kidneys [1] brain [2] and placenta [3]. Carnitine is excreted *via* urine [4] milk and bile as free carnitine or carnitine esters [4].

Carnitine is critical for the transfer of long-chain fatty acids into the mitochondria for β-oxidation, a process which results in the esterification of carnitine to form acylcarnitine derivatives. Activity of mitochondrial enzymes (e.g. carnitine palmitoyltransferase, CPT1) regulates β-oxidation rates [5] (Fig. 1).

Changes of dietary habits influence carnitine and acylcarnitines concentrations. During feeding, fatty acid oxidation (FAO) is completed *via* transfer of acetyl-CoA to the tricarboxylic acid (TCA) cycle for ATP production [5]. During prolonged fasting, the TCA cycle is inhibited, leading to ketone production [6]. Under these conditions, carnitine may increase fatty acid (FA) flux through carnitine acyltransferase to produce ketones, but is also increased in the liver to react with activated acyl groups, forming acylcarnitines. Importantly, carnitine and its esters may be utilized by the brain for energy production under fasting conditions. During pregnancy the above process of FA metabolism occurs, as well, with

* Corresponding author. Department of Pharm. Chemistry, School of Pharmacy, University of Athens, Panepistimioupoli, Zografou, Athens, Greece. Fax: +30 211 1826131.
E-mail addresses: pinmada@yahoo.gr (P.D. Manta-Vogli), kh.schulpis@gmail.com (K.H. Schulpis), idotsik@pharm.uoa.gr (Y. Dotsikas), loukas@pharm.uoa.gr (Y.L. Loukas).

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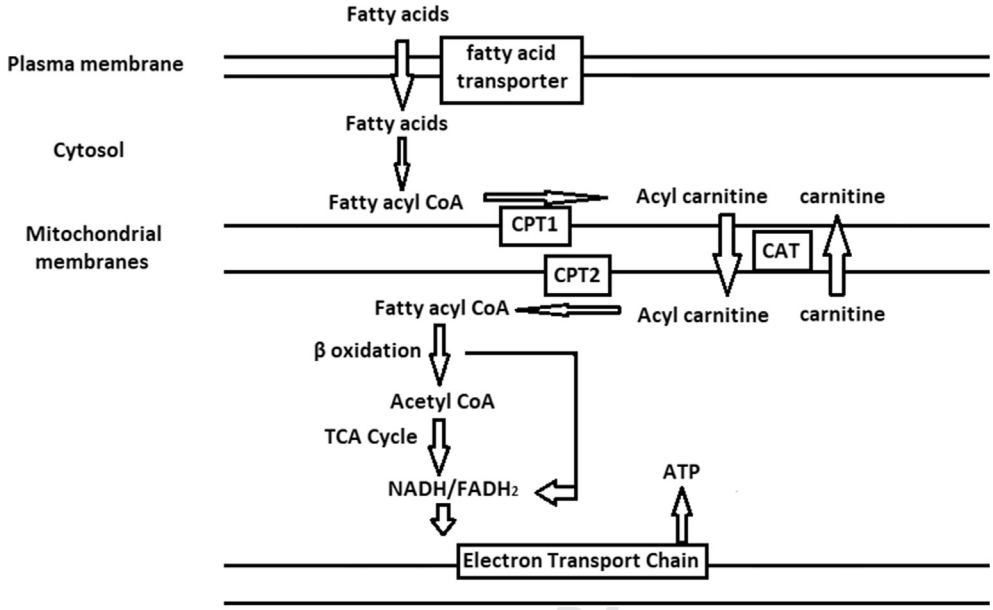

Fig. 1. Schematic presentation of fatty acid uptake and oxidation in the mitochondria (CPT: carnitine palmitoyltransferase, CAT: carnitine/acylcarnitine translocase).

specific changes in protein and lipid metabolism as gestation advances, in order to reflect the alterations from anabolic to catabolic state [7].

The main difference in pregnancy is that the switch from FAO to ketogenesis takes place more rapidly under fasting conditions than in non-pregnant state, probably due to increased fetal demands [7]. It has been reported that C5 abnormalities are related to type 2 diabetes mellitus (T2DM) [8,9], along with the reduction of C20:1 [9,10]. Additionally, modified amino acid and acylcarnitine concentrations in maternal serum during the first trimester of pregnancy, are significant indicators for gestational diabetes [11].

Acetyl carnitine also plays a role in the elongation–desaturation of the omega-3 (ω-3) polyunsaturated FAs to form 22:6n-3, DHA, in mitochondria [12]. Changes in membrane DHA content affect synaptic plasticity, response to inflammations, gene expression, ion channels, membrane proteins and neurotransmission [2,13].

Additionally, acetyl carnitines have been found to be protective against lipid peroxidation due to their antioxidant capacity and anti-apoptotic effects [14].

Consequently, nutritional support of specific groups of pregnant women, such as vegan-vegetarians in whom carnitine blood levels are considered low, should be established for the best outcome of pregnancy and fetus development.

The important role of carnitine and fatty acids during pregnancy

Carnitine is critical in fetal growth, and FAO in the fetoplacental-unit [3]. Decline in free carnitine, short-chain acylcarnitines and acetyl carnitine concentrations, across trimesters, in pregnancy [15–17] (Table 1), as well as increased renal excretion of acylcarnitines have been reported [18].

Significantly higher rise in acetyl carnitine and carnitine esters with longer chains is also reported in plasma of pregnant women at birth that reflects the enhanced FAO during late gestation [17], whereas moderate or no changes have been reported for the short-chain carnitine esters, which are derived mainly from amino acid catabolism [17]. This distribution may reflect the enhanced participation of carnitine in the FAO process, whereas the decrease of free carnitine indicates a decrease of total LC pool [3,19]. Consequently, maternal carnitine status enables mothers to supply adequate carnitine to their fetus [20].

The fetus is incapable of endogenous carnitine synthesis [3]. Carnitine transporter OCTN2 is expressed in human placenta [19], and is necessary for the transfer of carnitine into placenta and fetus, as well as for the oxidation of long-chain FAs in fetal-placental unit [19,20].

Determinants of placental nutrient transfer capacity are nutrient concentration gradients, placental morphology, utero- and feto-placental blood flows and efficiency of specific transport mechanisms [21–23]. In normal pregnancies fetal FAs, despite being strictly dependent on maternal levels, are significantly lower than in maternal plasma (fetal/maternal concentration ratio: 1/3) [24]. Particularly, the proportion of saturated fatty acids (SFAs) increases with gestation, with higher proportions in cord blood plasma, whereas ω-6 FAs decline, with only arachidonic acid (ARA) enhanced in umbilical blood. The proportion of ω-3 FAs is stable during pregnancy, whereas total cholesterol, triglycerides, VLDL and LDL increase, creating a hyperlipemic environment at the maternal–fetal interface, mostly near delivery [25].

During pregnancy, fetal demand for long chain polyunsaturated fatty acids (LCPUFAs) increases with maternal LCPUFAs intake to be critical for maintenance of adequate fetal levels [26,27].

Placental functionality may also affect fetal levels of LCPUFA, DHA or ARA, that have a beneficial effect on brain development. FA profile is characterized by higher proportions of the LCPUFA derivatives ARA and DHA, and lower percentages of their precursors, linoleic (LA) and a-linolenic (ALA) acids, in fetal compared to maternal plasma, a phenomenon called as 'biomagnification' [28]. This preferential transfer of LCPUFA across the placenta highlights its specific role in differential FA transfer to the fetus [28] and points out the important role of acylcarnitines in synthesizing lipids that have a neuroprotective brain effect [2]. These multifactorial mechanisms of carnitine production are significant under conditions of poor maternal carnitine supply, such as in the case of vegan diet [29]. However, an abnormal placental function, as occurs in Gestational diabetes mellitus (GDM) or intrauterine growth retardation (IUGR) could disturb the materno-fetal LCPUFA transport,

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Table 1
Plasma Carnitine concentrations (μmol/L) in pregnant women at different stages of gestation and in their newborns (N: total number of pregnant women or newborns, FC: free carnitine, TC: total carnitine, tAC: total acylcarnitines).

	Stages of gestation			Newborns	References
	20th week	**30th week**	**Term**		
FC	19.6 ± 1.3	16.7 ± 0.9	16.7 ± 0.9	20.0 ± 1.3	[17] [a] (N = 37, for newborns N = 20)
TC	27.3 ± 1.5	24.4 ± 1.3	27.2 ± 1.2	33.2 ± 2.6	
tAC	7.7 ± 0.4	7.7 ± 0.6	10.4 ± 0.5	13.2 ± 1.5	
	1st trimester	**2nd trimester**	**3rd trimester**		
FC	26.6	21.2	18.2	–	[16] [b] (N = 160)
FC	–	13.6 ± 3.1	11.5 ± 2.2	–	[15]* (N = 39)

[a] (mean ± SD) values.
[b] Median values.

with unknown consequences for the neurodevelopment of the offspring [24].

In pregnant women suffering from mitochondrial FAO disorders, emphasis should be given to the most common presented, such as medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), and very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) [30]. Common therapeutic processes include carnitine supplementation and provision of adequate energy supply.

Carnitine and fatty acids concentrations during labor and delivery

Participation of uterus and skeletal muscles is a natural function during labor and vaginal delivery. Several studies [31,32] have reported that normal and/or prolonged labor and delivery are implicated by low total antioxidant status (TAS). The decreased TAS levels at the end of the labor (post-delivery) may be due to the depletion of the antioxidants during the procedure [31,32]. Thus, lower carnitine blood concentrations have been reported post-delivery that may be due to the increased bioavailability of carnitine by the uterus and skeletal muscles [33]. In contrast, carnitine blood levels in women who underwent a scheduled cesarean section (CS) have been reported unaltered pre-*vs* post-delivery [33]. Consequently, neonates born by a scheduled CS are generously benefited with adequate carnitine levels to switch to a high FAO state immediately after birth and be able to face a possible hypoxia perinatally [33].

The effect of carnitine on the birth weight of newborns

Carnitine insufficiency during pregnancy is related to preterm birth (PTB) and low birth weight infants (LBW) [34,35], (Table 2). Determination of acylcarnitines measured in cord blood by tandem mass spectrometry (MS/MS) has revealed differences between term and preterm infants, although individual normal ranges for metabolic screening values are not yet utilized. BW, gestational age (GA) and age at the time of blood collection are critical for acylcarnitines blood concentrations [36]. In full-term neonates, total carnitine concentrations rise within the first postnatal days, mainly due to an increase of acylcarnitine levels [37] (Table 2). Neto et al. [8], investigated free carnitine and acylcarnitines in DBS (from umbilical cord and postnatally) in healthy exclusively breastfed neonates and found the major long-chain acylcarnitines increased, free carnitine and acetylcarnitine modestly increased and no correlations between BW or GA and the concentrations of the analytes in DBS.Additionally, Seliger et al. [38], Meyburg et al. [39] and Mandour et al. [40] have reported higher free carnitine levels in preterm than in full term infants, whereas a study on preterm infants in Japan [34] revealed GA-related carnitine deficiencies. Additionally, Liu et al. [41] reported higher concentrations of acylcarnitines in SGA infants, but lower in LBW and PTB infants, as compared to those of non-SGA, non-LBW and non-PTB neonates (Table 2).

Previous studies investigated the changes in free carnitine levels of preterm infants, by measuring the effects of its supplementation [38,42]. However, despite the high risk for carnitine deficiency in PTB neonates, there are no standards for carnitine supplementation in those who are on total parenteral nutrition (TPN) [43].

Mandour et al. [40] demonstrated that the age of newborns influenced the amino acids' and acylcarnitines' concentrations and no correlations between the postnatal free carnitine and acylcarnitine levels and GA were found [37].

Oppositely, high levels of C2, C3, total acylcarnitines and total short-chain acylcarnitines were reported in samples of large for gestational age (LGA) infants [44], similar to those measured in obese children and adults. Moreover, IUGR infants exhibit significantly abnormal carnitine profiles, especially those with BW below the 3rd percentile. Liu et al. [45] reported that with increasing BW, amino acids and acylcarnitines showed relative increases or reductions, and when BW reached the 10th percentile, the newborns with IUGR resembled the AGA newborns. Other studies recommended supplementation with amino acids and acylcarnitines for amelioration of fetal growth [46,47]. Recently, it was shown that IUGR may be associated with fetal–neonatal brain damage, leading to long-term neurobehavioral anomalies [48]. Obviously, strong evidence exists for therapeutic effect of carnitine and acylcarnitine administration for neuroprotection [2,49].

Dietary fat intake during gestation and/or lactation. Nutritional support in specific groups

Dietary lipids along with protein and carbohydrates affect fetal development and seem to be correlated with metabolic disorders in adolescent and adult life [50–52].

In the first trimester, the modified maternal metabolic status, due to the increased levels of hormones, is followed by pancreatic beta-cell hyperplasia, and subsequent high levels of insulin. Hyperinsulinaemia leads to decreased glucose level as a result of the peripheral utilization of the carbohydrate, followed by storage in tissues in form of glycogen. During second and third trimester, maternal fuel adjustments occur, leading to the sparing of glucose and an increased concentration of plasma FAs, resulting in GDM and hypertension respectively [53].

Consequently, as energy utilization is changed along with accumulation of fat during trimesters, it has been suggested that total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol increase in both second and third trimester [25], whereas HDL-cholesterol has been found decreased [53]. Therefore, nutritional support of pregnant women (Table 3) is necessary, focusing mainly

Table 2
Carnitine concentrations (μmol/L) in blood of newborns with different gestational age (GA) and birth weight (BW) (FC: free carnitine, TC: total carnitine, tAC: total acylcarnitines, SGA: small for gestational age AGA: appropriate for gestational age, LGA: large for gestational age, PTB: preterm birth, VLBW: very low birth weight, N: total number of newborns).

Newborns	N	FC	TC	tAC	References
SGA	250	33.58	57.57	22.16	[44] [a]
AGA	2018	27.96	49.01	20.49	
LGA	246	28.20	51.20	22.34	
LBW (2500 g)	8979	17.72	44.03		[41] [a]
Non-LBW (≥2500 g)		15.45	41.84		
PTB (GA < 37 w)		18.17	44.99		
Non-PTB (GA ≥ 37 w)		15.45	41.85		
SGA (BW < 10th percentile)		16.37	44.03		
Non-SGA (BW ≥ 10th percentile)		15.40	41.65		
PTB					
Premature day 5	131	30.0	68.7	37.4	[40] [a]
Full term day 5	143	26.28	57.2	28.1	
VLBW					
3–5day of life	108				[35] [b]
AGA		25.65 ± 16.0	51.81 ± 22.9	26.65 ± 9.6	
SGA		32.24 ± 14.4	63.43 ± 24.0	32.26 ± 12.2	
AGA	70				
Cord blood		31.6 ± 10.2	51.5 ± 14.4	19.9 ± 4.8	[37].[b]
5 day of life		30.6 ± 10.6	55.7 ± 16.0	25.1 ± 6.4	

[a] median values.
[b] (mean ± SD) values.

Table 3
Suggestions for macronutrient intake during pregnancy.

Energy	No additional during the 1st trimester 340 kcal/day II trimester 452 kcal/day III trimester [58] 85 kcal/day I trimester 285 kcal/day II trimester 475 kcal/day III trimester [86]
Protein	10–30% of energy [57] RDA 0.88–1.1 g/kg/day [56–58] RDA 1.2–1.52 g/kg/d [87]
Carbohydrates	45–65% of energy [57,58]
Fat	20–35% of energy [56–58] MUFA: 20% of energy intake (%E) [68] SFAs ≤ 10% E [56] SFAs < 7% E [59] TFAs < 1 %E [56] Total ω-3 PUFAs: 0.5–2.0 E% (AMDR) [56] LA: 2.5–9.0 E% (AMDR) [56], 4.0 E% [76] ALA: >0.5% E (L-AMDR) [56], 0.5%E [76] DHA:200.0 mg/day (ANR) [56], 100.0–200.0 mg/d [76] EPA + DHA:300.0 mg/d (ANR) [56], 250.0 mg/d [76]

MUFAs: monounsaturated fatty acids, SFAs: saturated fatty acids, TFAs: trans fatty acids, PUFAs: polyunsaturated fatty acids, mg/d: milligrams per day, E%: energy percentage, LA: linoleic acid, ALA: α-linolenic acid, n-3: omega-3 PUFA, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, ADMR: acceptable macronutrient distribution range, L-AMDR: lower acceptable macronutrient distribution range, ANR: average nutrient requirement.

on lipid profile, in order to prevent the damaging effect of hyperlipidemia during pregnancy.

The infant is also exposed to FAs *via* lactation. Both diet of lactating mothers and maternal body stocks of FAs may affect the fat composition of breast milk [54,55]. Nishimura et al. [55], demonstrated that the content of DHA and eicosapentaenoic acid (EPA) in mature breast milk is directly depended on the maternal levels during the third trimester of pregnancy.

Suggestions for dietary fat intake during pregnancy and lactation are presented in Table 3 [56–59].It is emphasized that a long-term consumption of diets high in SFAs is related to poorly controlled hyperglycemia, hyperinsulinemia and insulin resistance, that are characteristic findings of T2DM and gestational diabetes, resulting in a high risk pregnancy [60].

Maternal exposure to high fat diet (60% fat, rich in SFAs) induce SGA status and fetal resorption [61] and is likely related to modifications in brain development and increased risk of osteoporosis in the later life [60]. According to FAO/WHO, the consumption of trans fatty acids (TFAs) must be as low as possible (<1%E) [56]. It was reported that maternal plasma concentrations of TFAs, ARA, DHA, LA and ALA are significantly and positively correlated with infant's plasma concentrations of the same FAs [62–65]. Importantly, TFAs may replace LCPUFAs in human placental membranes, inhibiting the transport of LCUFAs to the placenta [66]. Negative association between industrial TFAs and ω-3 LCPUFAs in fetal plasma was measured at birth [67]. All the above mentioned reactions influence the levels of LA and ALA, which are responsible for brain and vision development [66].

FAO/WHO [56] does not recommend a specific level of monounsaturated fatty acids (MUFAs). It states, that an acceptable macronutrient distribution range (AMDR) for MUFA intake should be calculated by difference, subtracting from total fat intake levels those for SFAs, PUFAs and TFAs. Different nutritional habits exist worldwide therefore MUFA intake can vary. In Mediterranean countries (i.e. Spain) with high olive oil consumption, MUFA intake can account up to 20%E [68]. It is experimentally documented in piglets, that the enrichment of maternal diet with 10% extra olive oil during first or second half of gestation, had beneficial effects on the BW of their offsprings [69]. MUFA administration during pregnancy and lactation seems to prevent the development of obesity and steatosis in the offspring, as a result of stimulation in thermogenic capacity and changes in liver metabolism [70].

The fetus and newborn have the ability to synthesize SFAs and MUFAs, while they have low capacity to synthesize LCPUFAs. Consequently, they are dependent on the maternal LCPUFAs status [71]. PUFAs are subdivided into ω-3 and ω-6 FAs. LA and ALA are essential nutrients and precursors of LCPUFAs. LA can be endogenously converted to ARA, whereas ALA can be converted to EPA and

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DHA. High intake of ω-3 FAs increases EPA content in cell membrane phospholipids and lowers ARA levels in the immune cell membranes. Increased LA concentrations are indirectly related to EPA and DHA status [72,73]. These mechanisms show the importance of a balanced concentration between ω-6 and ω-3 FAs in diet, reflected by ω-6/ω-3 ratio. The LA predominantly exists in vegetable oil. ALA is found in soybean, walnut and some seeds of vegetable oils and algae. Among LCPUFAs, the ARA is scarcely found in the diet, whereas EPA and DHA are present in marine algae and fishes [52].

ω-3 fatty acids are important substrates for the synthesis of a variety of antiinflammatory and inflammation resolving mediators and also favorably alter the production of thromboxane and prostaglandin E2, which may account for the longer gestations and higher birthweights that are associated with diets based largely on fish [74]. Although the conversion of ALA to DHA increases during pregnancy [75], a dietary source of ω-3 LCPUFAs is required (Table 3) to meet mother/neonate needs [56,76]. Omega-3 LCPUFA supplementation during pregnancy is recommended for reducing the incidence of PTB, even though it probably increases the incidence of post-term pregnancies [77].

Pregnant women who do not reach the recommended DHA intake (Table 3) should be supplemented with at least 200 mg ω-3 DHA/day [56,78], as better childhood IQ scores, fine motor coordination, communication and social skills and reduced incidence of postpartum depression have been reported [79]. However in USA, pregnant women consumed significantly lower amounts of seafood than that recommended [80].

Although taking ω-3 fatty acids or fish oil supplements would seem to be a great way to reap the benefits of DHA and EPA without the risk of exposure to mercury and other toxins, all the beneficial effects from natural sources cannot be easily replaced by supplementation only [81].

Nutritional support in specific groups of pregnant women

Pregnant women should consume a balanced diet in accordance to dietary recommendations for the general population, enriched with thiamin, riboflavin, folate, iron, vitamins A, C, D and ω-3 LCPUFAs [78,82–84]. Carnitine intake is positively correlated with dietary intakes of protein, carbohydrates, FAs, iron and vitamin B complex. Therefore, its intake is primarily a function of overall nutrition [47,85].

The demand for both energy and nutrients is increased during pregnancy [58,86,87] (Table 3). However, caloric intake should be individualized according to woman's age, BMI, and lifestyle. Although balanced increased energy and protein supplementation may improve fetal growth, high protein or balanced-protein supplementation alone is not beneficial and may be harmful to the fetus [88]. Neonatal adiposity has been associated with increased maternal energy intake, containing mostly fat and carbohydrates with adequate protein, which is obviously unfavorable [89].

Additionally, pregravid BMI is commonly associated with infant BW, because it is related to maternal factors, such as genetics, environmental and lifestyle [90]. Underweight women tend to have LBW infants [91], while obese women tend to have LGA infants [92].

Maternal weight gain in pregnancy is strongly implicated in both maternal and newborn health [93]. Insufficient gestational weight gain (GWG) is associated with LBW and PTB, while excessive weight gain is involved in infant macrosomia and a 2-fold greater risk of obesity later in life [94–96].

US Institute of Medicine (IOM) published GWG guidelines for women in Western countries, based on pre-pregnancy BMI [97]. The scope of these guidelines was to minimize the risks of having LGA, SGAand PTB infants.

Both increased pre-pregnancy BMI and increased GWG, regardless of pre-pregnancy BMI, have been associated with the specific proinflammatory and metabolic phenotype, with dyslipidemia and insulin resistance during pregnancy [98,99]. Oppositely, nutritional insufficiency reflected by LBW or SGA is also implicated with glucose intolerance, diabetes, hypertension and coronary health disease later in life [100].

Some studies suggested that maternal weight gain in the second trimester is a key determinant of newborn BW [101]. Other studies implicated weight gain in both the second and third trimesters [102]. Retnakaran et al. [103] reported that maternal weight gain only during the first half of gestation is a characteristic determinant of newborn BW. Consequently, pregravity and early gestational weight gain may be the right period for dietetic intervention for the best pregnancy outcome.

Certain considerations with regard to specific groups of pregnant women, such as lean, obese, GDM, diabetic mothers, vegan-vegetarians, low-socioeconomic groups, should be also taken into account (Table 4).

LEAN: Diets providing energy and protein below recommendations result in an IUGR fetus [104,105]. The effect of maternal undernutrition during the periconceptional and the preimplantation periods must be stressed, as results in significant changes in the mRNA expression and/or protein abundance of factors regulating FAO, highlighting the need for optimal nutritional intakes preconceptionally [106]. In lean pregnant women, special attention should be paid on energy intake, macro- and micronutrient and vitamin intake (Table 4). Both free and total carnitines are important for monitoring of carnitine status, but preferentially free Carnitine is of special interest for *L*-carnitine supplementation [107]. The recommended dose is 1500–2000 mg per day [108] divided into 3 to 4 equal doses/day, with food rich in carnitine and iron [47]. Although the above laboratory tests referring to carnitine status could be considered expensive, they are of significant interest for both mother and fetus [47,109].

OBESE: Obesity has the highest prevalence among metabolic diseases in pregnancy, affecting one in five women. Obese women are at an increased risk of obstetric complications, including GDM, preeclampsia, and thromboembolic events. Fetal complications include intrauterine death, congenital anomalies, and macrosomia [110–114].

Several acylcarnitine species such as C2, C4–OH and C18:1, were determined higher in obese women compared to non-obese, predominantly in the third trimester of pregnancy [15], due to reduced insulin sensitivity, observed during late gestation [98,115,116]. Tipi-Akbas et al. [85] reported significantly lower total carnitine levels when BMI exceeds 29.9 kg/m^2 before and at term pregnancy, with serum total carnitine levels to be correlated significantly and negatively with pre-pregnancy body weight, pregnancy BMI and serum triglyceride levels. Additionally, a significant and positive correlation was found between carnitine and HDL values.

High maternal BMI is associated with lower ω−3 LCPUFA concentrations in their offspring [117]. ω-3 supplementation during mid-to late pregnancy may lower tissue lipid concentrations through increased FAO, decreased FA synthesis or esterification, or increased lipolysis of stored triglycerides. Enrichment of diet with fish oil has a beneficial effect on lowering placental lipid content associated with higherneonatal fat mass [118].

Since carnitine has been measured low during pregnancy, its administration could be beneficial in enhancing β-oxidation. Dietary plans of obese pregnant women should contain food rich in carnitine, such as red meat, fish, poultry, milk, avocado and asparagus [47,85].

Maternal pre-pregnancy BMI, weight gain, glucose and lipid levels could be under control along with an active lifestyle

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Table 4
Nutrition, laboratory and other suggestions for specific groups of pregnant women (GWG: Gestational Weight Gain, GDM: Gestational Diabetes Mellitus, DM: Diabetes Mellitus).

Lean	Assessment of BMI along with GWG per month. Special attention on energy intake, macro- and micronutrient and vitamin intake Frequent laboratory test including CBC, vitamin B12, folate, vitamin D, ferritin, total protein and albumin should be performed. Dietary supplementation of n-3 PUFAs Determination of free and total acylcarnitine levels in plasma may be measured [109]
Obese	Assessment of BMI along with GWG per month, as well as estimation of BMI between pregnancies Frequent measurement of blood pressure Measurement of lipids, carnitine, glucose and oral glucose tolerance test. Other laboratory tests, as above Dietary plan including red meat, fish, poultry, milk, avocado and asparagus. Supplementation of omega family polyunsaturated fatty acids. Lifestyle advice for maintaining the normal weight gain per month
GDM DM	BMI estimation not only before pregnancy but also between and after pregnancies. Attention on weight gain per month Frequent measurement of blood pressure Measurement of lipids and carnitine Frequent laboratory tests, as above. Fasting and postprandial self monitoring of blood glucose levels Dietary plan for glucose control, with or without hypoglycemic agents Omega polyunsaturated fatty acids supplementation and carnitine
Vegan Vegetarian	Assessment of BMI along with GWG per month. Evaluation of energy and protein intake. Frequent laboratory tests, as above Attention on vitamin B12, vitamin D, Ca, Zn and Ferritin concentrations in blood. Supplementation with fish oil, as well as vitamin B12, vitamin D, iron and carnitine
Low socioeconomic status	Assessment of BMI along with GWG per month. Evaluation of energy and protein intake. Laboratory testing as above Administration of omega family fatty acids, iron, Ca, Zn, vitamin C, vitamin B6, B12, folic acid and carnitine supplementation are of great value [154]
Normal (omnivorous)	Assessment of BMI along with GWG per month Evaluation of blood pressure Laboratory investigations as above Omega polyunsaturated fatty acids supplementation, folic acid and iron if needed Free and total carnitine measurement if symptoms and signs related to carnitine insufficiency occur [109]

[112–114,119]. In most cases of obese pregnant women, with or without family history of first-degree relatives with GDM or T2DM, oral glucose tolerance test with 50–100 g glucose is usually performed at early pregnancy [120].

GDM: The prevalence of GDM has increased, with variations within countries [121,122]. GDM is associated with increased BW, obesity, metabolic syndrome and subsequent development of T2DM and cardiovascular disease later in life [123–126]. Both Type 1 and T2DM during pregnancy, contribute to poor maternal and fetal outcome than GDM alone [127].

Both prepregnant BMI and GWG, are risk factors for GDM [90,113]. Women with GDM may have a distinctive FA profile [128], which suggests a possible relationship between FAs and glucose metabolism [129].

As glucose is the main substrate for cellular energy production, when it is not available for utilization, as occurs in insulin-resistant individuals, the cell uses FFAs and amino acids (AAs) as an alternative source, leading to disturbance in the balance between acylcarnitines and AAs [5,130–133]. It is also reported that elevated blood concentrations of BCAAs and aromatic AAs, as well as concentrations of certain acylcarnitines are considered to be predictive biomarkers of T2DM later in life [116].

Previous reports revealed an increase in acetyl-carnitines in GDM that seems to be a metabolic event of glucose homeostasis alterations, including impaired glucose tolerance (IGT) and diabetes, whereas long-chain acylcarnitines were decreased [134,135]. Furthermore, in another metabolomic research it was found that medium-chain acylcarnitines decrease with impairing glucose tolerance [136].

Additionally, plasma carnitine concentrations decrease as pregnancy progresses (Table 1). This decline could be due to reduced rate of carnitine biosynthesis, possibly because of an inadequate iron status [47]. L-carnitine supplementation in pregnancy avoids a striking increase in plasma FFAs, which are thought to be the main cause of insulin resistance and consequently GDM [137] and in cases of imminent premature delivery, stimulates fetal pulmonary surfactant production [138].

GDM women are susceptible to increased inflammatory factors and biomarkers of oxidative stress [139]. A study reported that plasma DHA levels increased during the third trimester in normoglycemic pregnant women but not in GDM women [117]. Women who developed GDM consumed less ω-3 and ω-6 PUFA than unaffected women [140]. The decreased DHA status in GDM women may be restored by dietary intervention [141,142]. Recent studies have shown the beneficial effects of ω-3 intake on glucose metabolism, lipid fractions, and inflammatory factors in GDM [143,144]. Similarly, a current study indicated that ω-3 supplementation for 6 weeks had beneficial effects on gene expression related to improving insulin function, and attenuating lipid and inflammation markers among women with GDM [145].

Currently, nutritional support is the most important treatment for GDM. The diet should be individualized and based on an assessment according to Dietary Reference Intakes (DRI), to provide adequate nutrients for fetal and maternal health, achieve euglycemia, and promote appropriate GWG [146–148]. Those not responding to diet are treated with insulin or oral hypoglycemic agents along with diet. Regular self monitoring of fasting and postprandial blood glucose concentrations, as well as blood pressure measurement are necessary [148]. L-carnitine supplementation in addition to dietetic rich in carnitine food intake should be beneficial [47]. Breastfeeding is encouraged in women with diabetes, due to its nutritional and immunological benefits for the infant [149].

Vegan-vegetarian: The type of vegetarian or vegan diet followed determines the proper dietary advice that is applicable to this specific group during pregnancy. Vegetarian diets, as compared

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to omnivorous-diets, are known to contain more folate, fiber, antioxidants, phytochemicals and carotenoids, whereas are considered deficient in iron, vitamin B_{12}, Zn and carnitine [150]. In this context, a vegetarian diet can result in vitamin B_{12} and iron deficiency, as well as LBW, whereas a vegan diet may additionally lead to inadequate DHA intake, resulting in impaired brain development. However, a well-balanced ovo-lacto vegetarian diet usually enables good nutrient status in pregnancy, if combined with supplementation of vitamin D, folic acid, iodine, iron, vitamin B_{12} and Zn, and in cases of a fish-free diet, with DHA [151]. A considerably lower proportion of dietary energy from total fat and SFAs is utilized by lactoovo-vegetarians and vegans than omnivorous. Thus, vegetarians and omnivorous are recommended to minimize the intake of atherogenic SFAs [152]. Additionally, a vegan diet might contain significantly more saturates if vegetable oils rich in saturates, such as coconut oil or palm oil are utilized in substantial quantities. According to the American Dietetic Associations 'well-planned vegetarian diets are appropriate during all stages of the life cycle, including pregnancy [153].

Vegan–vegetarian diets have remarkable differences in richer and poorer countries, being associated with a higher educational level and income in rich countries and with poverty in poor countries [154]. In the latter cases, prenatal dietary supplementation with energy, protein, micro-elements and vitamins, improved fetal outcomes [155]. Quantitation of carnitine in plasma during pregnancy could be needed, as well. Consequently, future parents should be informed about the laboratory investigation cost, in correlation with the best pregnancy outcome [109].

Low socio-economic status: Imbalanced macro- and micronutrients, insufficient energy intake and predominantly vegan-vegetarian diets are commonly met in this group [154,156]. Iron deficiency is observed in more than 50% of pregnant women in developing countries as well as, low concentrations of Vitamins A, C, B6, B12, D, and folate, Ca and Zn [157–159]. Replacement of iron and folic acid with multiple-micronutrient (MMN) supplements is of great importance [84]. Additionally, a higher incidence of low plasma carnitine values was found [29]. Dietary recommendations for proper intake of energy, macro- and micronutrients and fish oil supplementation, along with carnitine are needed (Table 4).

Conclusions

Carnitine and FAs, especially unsaturated and polyunsaturated, are very important preconceptionally, throughout pregnancy and lactation. Specific groups, lean, obese, GDM, diabetes mellitus, vegan-vegetarian and these with low-SES, should be closely followed up and nutritionally supported. Laboratory tests, including quantitation of carnitine, FAs, vitamin B_{12}, vitamin D, ferritin and supplementation with omega family FAs should be necessary.

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Conflicts of interest

The authors have no competing interests to declare.

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