Intake of major nutrients by women in the Maternal Phenylketonuria (MPKU) Study and effects on plasma phenylalanine concentrations[1–3]

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ABSTRACT

Background: Women with untreated phenylketonuria (PKU) often have poor reproductive outcomes.

Objective: We assessed the effects of intakes of major nutrients on plasma phenylalanine concentrations and we measured phenylalanine hydroxylase activity and phenylalanine intakes in pregnant women with PKU.

Design: Dietary intakes and plasma phenylalanine concentrations were compared in 4 subject groups defined on the basis of plasma phenylalanine concentrations: group 1 (n = 23), <360 μmol/L by 10 wk gestation and 120–360 μmol/L throughout the remainder of pregnancy; group 2 (n = 46), <600 μmol/L but not <360 μmol/L by 10 wk gestation and 120–600 μmol/L throughout the remainder of pregnancy; group 3 (n = 24), <600 μmol/L by 10 wk gestation but >600 μmol/L at least once thereafter; group 4 (n = 147), never <600 μmol/L.

Results: Except in the first trimester, mean intakes of phenylalanine, energy, and fat tended to be greater in group 1 than in the other groups. The mean protein intake of group 1 tended to be greater than that of the other groups. Intakes of protein (P < 0.0001), fat (P < 0.0001), and energy (P < 0.007) were negatively correlated with maternal plasma phenylalanine concentrations. It appeared that genotype did not affect phenylalanine tolerance.

Conclusions: Maternal genotype appeared to have little influence on phenylalanine requirements during the first trimester. Early decline and maintenance of maternal plasma phenylalanine concentrations at <360 μmol/L and mean protein intake greater than the recommended dietary allowance (RDA) with mean energy intake near the RDA resulted in the best reproductive outcomes. Inadequate intakes of protein, fat, and energy may result in elevated plasma phenylalanine concentrations and may contribute to poor reproductive outcomes. *Am J Clin Nutr* 2001;73:792–6.

KEY WORDS Maternal Phenylketonuria Study, phenylketonuria, PKU, genotype, plasma phenylalanine, protein, fat, energy, reproductive outcome, phenylalanine hydroxylase, pregnancy, pregnant women, birth outcome

INTRODUCTION

Women with untreated phenylketonuria (PKU) often have poor reproductive outcomes (1). In women with PKU, poor reproductive outcomes were also observed when dietary treatment was started late in gestation or when plasma phenylalanine concentrations remained elevated (2, 3). Limited information is available on nutrient intake and weight gain by women with treated PKU (4, 5).

In normal pregnancies, adequate nutrient intakes and weight gains have positive effects on infant birth weight (6–8). The purpose of this article is to describe intakes of major nutrients throughout gestation in relation to plasma phenylalanine concentrations in women enrolled in the Maternal Phenylketonuria Study. First-trimester phenylalanine intakes of the women with the best control of plasma phenylalanine concentrations are reported by phenylalanine hydroxylase activity. Infant anthropometric measurements at birth are reported according to maternal plasma phenylalanine concentrations.

SUBJECTS AND METHODS

All subjects were enrolled in the international Maternal Phenylketonuria Study in the United States, Canada, or Germany. We obtained 3-d diet diaries, maternal body weight, and plasma phenylalanine concentrations routinely (monthly, if possible) throughout pregnancy. A software program, AMINO ACID ANALYZER (Ross Products Division, Abbott Laboratories, Columbus, OH) was used to calculate nutrient intakes. Nutrient intake data and plasma phenylalanine concentrations were collapsed

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TABLE 1
Height and weight of women with phenyketonuria grouped according to plasma phenylalanine concentration[1]

Group[2]	Height	Prepregnancy weight	Pregnancy weight gain
	cm	*%*[3]	*%*[3]
1 (n = 23)	164.8 ± 5.9	114 ± 16	159 ± 107
2 (n = 46)	162.6 ± 5.2	111 ± 20	143 ± 79
3 (n = 24)	160.5 ± 6.2	108 ± 10	142 ± 101
4 (n = 147)	161.3 ± 6.4	116 ± 27	129 ± 109

[1] $\bar{x}$ ± SD. There were no significant differences among groups by ANOVA.
[2] Defined on the basis of plasma phenylalanine concentrations: group 1, <360 μmol/L by 10 wk gestation and 120–360 μmol/L (2–6 mg/dL) throughout the remainder of pregnancy; group 2, <600 μmol/L (10 mg/dL) but not <360 μmol/L by 10 wk gestation and 120–600 μmol/L throughout the remainder of pregnancy; group 3, <600 μmol/L by 10 wk gestation but >600 μmol/L at least once thereafter; group 4, never <600 μmol/L.
[3] Percentage of recommended.

into trimester means for each woman and were then further summarized by subject group. The study was approved by the human rights review committee of each institution. The women provided written, informed consent to participate in the study.

Women were grouped according to their plasma phenylalanine concentrations (9). Women in group 1 (n = 23) achieved a plasma phenylalanine concentration <360 μmol/L (<6 mg/dL) by 10 wk gestation and their plasma phenylalanine concentrations remained between 120 μmol/L (2 mg/dL) and 360 μmol/L throughout the remainder of pregnancy. Women in group 2 (n = 46) achieved plasma phenylalanine concentrations <600 μmol/L (<10 mg/dL) but not <360 μmol/L by 10 wk gestation and their plasma phenylalanine concentrations remained between 120 and 600 μmol/L throughout the remainder of pregnancy. Women in group 3 (n = 24) achieved plasma phenylalanine concentrations <600 μmol/L by 10 wk gestation, but their plasma phenylalanine concentrations were >600 μmol/L at least once thereafter. Women in group 4 (n = 147) never achieved a plasma phenylalanine concentration <600 μmol/L. Of the 4 groups, women in group 1 achieved the best control of their plasma phenylalanine concentrations.

Mean intakes of selected nutrients by groups of women, with their infants grouped according to anthropometric z scores at birth adjusted for sex and gestational age, were compared by using analysis of variance, with multiple comparisons by the Tukey method. Mean first-trimester phenylalanine intakes were calculated for subgroups of women in group 1; the subgroups were classified by imputed phenylalanine hydroxylase activity on the basis of gene mutation analysis (10). Spearman's correlation coefficients (r values) were calculated to determine the relations between maternal intakes of phenylalanine, protein, fat, and energy and plasma phenylalanine concentrations. $P < 0.05$ was considered statistically significant. SAS (version 6, 3rd ed; SAS Institute Inc, Cary, NC) was used for all statistics.

RESULTS

On average, women in group 1 gained the most weight during pregnancy and women in group 4 gained the least (**Table 1**). However, mean weight gain was not significantly different between the groups of women.

Mean (±SD) phenylalanine intakes of the 4 groups of women during each trimester are shown in **Table 2**. Mean intakes ranged from 456 mg/d by women in group 3 during the first trimester to 1248 mg/d by women in group 1 during the third trimester.

TABLE 2
Intakes of major nutrients by pregnant women with phenylketonuria grouped according to plasma phenylalanine concentrations[1]

Dietary intake	Group[2] 1 (n = 23)	2 (n = 46)	3 (n = 24)	4 (n = 147)
Phenylalanine (mg/d)				
First trimester	609 ± 220	572 ± 296	456 ± 233	684 ± 413
Second trimester	824 ± 411	723 ± 394	528 ± 269	750 ± 538
Third trimester	1248 ± 513	1062 ± 711	938 ± 542	947 ± 586
Protein (g/d)				
First trimester	69.1 ± 13.8	66.4 ± 21.4	65.8 ± 16.1	63.2 ± 21.0
Second trimester	82.7 ± 19.6	78.7 ± 19.5	73.5 ± 19.0	71.5 ± 17.7
Third trimester	97.2 ± 17.8	90.9 ± 35.6	82.1 ± 16.7	80.5 ± 19.7
Fat (g/d)				
First trimester	54 ± 23	55 ± 8	53 ± 19	48 ± 25
Second trimester	75 ± 20	75 ± 24	56 ± 26	59 ± 31
Third trimester	74 ± 18	69 ± 28	65 ± 30	63 ± 30
Fat (% of energy)				
First trimester	25 ± 9	23 ± 8	23 ± 6	23 ± 9
Second trimester	29 ± 7	29 ± 7	23 ± 8	24 ± 9
Third trimester	27 ± 6	26 ± 7	23 ± 7	24 ± 9
Energy (MJ/d)				
First trimester	8.34 ± 2.02	8.81 ± 2.38	8.61 ± 1.86	7.76 ± 2.41
Second trimester	9.94 ± 1.76	9.99 ± 2.36	9.11 ± 2.80	9.14 ± 2.63
Third trimester	10.39 ± 1.70	10.15 ± 2.57	9.74 ± 3.14	9.86 ± 2.78

[1] $\bar{x}$ ± SD.
[2] Defined on the basis of plasma phenylalanine concentrations: group 1, <360 μmol/L by 10 wk gestation and 120–360 μmol/L (2–6 mg/dL) throughout the remainder of pregnancy; group 2, <600 μmol/L (10 mg/dL) but not <360 μmol/L by 10 wk gestation and 120–600 μmol/L throughout the remainder of pregnancy; group 3, <600 μmol/L by 10 wk gestation but >600 μmol/L at least once thereafter; group 4, never <600 μmol/L.

TABLE 3
First trimester dietary intakes of phenylalanine, protein, fat, and energy by 19 of the 23 women with the best control (plasma phenylalanine <360 μmol/L) according to phenylalanine hydroxylase activity

Phenylalanine hydroxylase	Number of alleles analyzed	Dietary intake			
		Phenylalanine	Protein	Fat	Energy
		mg	*g*	*g*	*MJ*
One allele analyzed					
<1% activity (n = 5)	5	857 ± 158 (650–1047)[1]	69.6 ± 20.7 (34.6–86.0)	68.1 ± 19.5 (37.5–85.7)	7.38 ± 1.72 (5.58–9.54)
Two alleles analyzed					
<1%, <1% activity (n = 7)	7, 7	518 ± 182 (267–767)	66.9 ± 14.6 (46.4–87.2)	54.5 ± 28.2 (19.1–108.4)	8.26 ± 2.34 (5.75–11.14)
1–10% , <1% activity (n = 5)	5, 5	503 ± 205 (267–642)	73.4 ± 4.5 (68.7–77.7)	48.4 ± 21.3 (29.4–71.5)	8.57 ± 3.00 (5.65–11.65)
>10%, <1% activity (n = 2)	2, 2	417, 514[2]	71.8, 73.8	41.0, 43.9	7.03, 8.91

[1] $\bar{x}$ ± SD; range in parentheses.
[2] Individual values.

Women in group 3 tended to have the lowest mean phenylalanine intakes by trimester, although none of the mean intakes were significantly different because of the large SDs.

No significant differences occurred among the 4 groups in mean protein intake (from phenylalanine-free medical foods plus intact protein) in any single trimester (Table 2). However, in each trimester, women in group 1 tended to have a greater mean protein intake than did women in group 2, whose mean protein intake tended to be greater than that of women in group 3, who tended to have a greater mean protein intake than did women in group 4. During the first trimester, mean protein intakes of women in all 4 groups failed to meet the recommended dietary allowance (RDA; 11) of 74 g/d. Thereafter, all mean protein intakes of all groups exceeded the RDA except for intakes of women in groups 3 and 4 during the second trimester. Mean fat intake, expressed as g/d and as a percentage of energy intake, did not differ significantly among the groups of women. Mean energy intake also did not differ significantly by group. All group means for energy intake were <10.47 MJ/d, the RDA for pregnant women (11).

Genotypes were available for 19 of the 23 women in group 1. Mean phenylalanine, protein, fat, and energy intakes according to phenylalanine hydroxylase activity of the alleles are shown in **Table 3**. First trimester mean phenylalanine intakes ranged from 417 mg/d (for a woman whose phenylalanine hydroxylase alleles had >10% and <1% activity) to 518 mg/d (mean for 7 women who each had 2 phenylalanine hydroxylase alleles with <1% activity). The 5 women for whom only one phenylalanine hydroxylase allele was analyzed and was found to have <1% activity (the mutation in the other allele was unknown) had a mean phenylalanine intake of 857 mg/d. Because of the small sample sizes and large SDs, meaningful statistical comparisons among the groups could not be made.

Intakes of various nutrients were negatively correlated with plasma phenylalanine concentrations (**Table 4**). Of the nutrients correlated with plasma phenylalanine concentrations, only maternal protein and fat intakes were significantly and negatively correlated with plasma phenylalanine during the entire pregnancy. Maternal energy intake was significantly and negatively correlated with plasma phenylalanine concentration during the last 2 trimesters.

Infant anthropometric measures at birth (**Table 5**) indicated that only mean head circumference in group 1 was significantly greater than head circumferences in groups 3 and 4. Mean head circumference in group 1 tended to be greater than that of group 2, but the difference was not significant.

DISCUSSION

The women with PKU who achieved plasma phenylalanine concentrations <360 μmol/L by 10 wk gestation (group 1) tended to have the highest mean protein intakes (from phenylalanine-free medical foods plus intact protein), tended to gain the most weight, and gave birth to infants with the greatest mean head circumference. However, dietary phenylalanine intake did not differ during the first trimester between the 7 women who had 2 mutations that resulted in <1% phenylalanine hydroxylase activity and the 5 women who had 1 allele with 1–10% activity and 1 allele with <1% activity, although all the women had classic PKU. It is clear that factors other than phenylalanine intake influence the utilization of phenylalanine throughout pregnancy. Acosta et al (12) and Michals et al (13) reported that maternal dietary protein intake was negatively correlated with plasma phenylalanine concentration. Similarly, Acosta and Yannicelli (14) found that infants with PKU who had higher protein intakes had higher dietary phenylalanine tolerance than did infants with lower protein intakes.

A significant increase in phenylalanine tolerance during pregnancy with no increase in plasma phenylalanine concentrations,

TABLE 4
Spearman correlation coefficients between nutrient intakes and plasma phenylalanine concentrations in pregnant women with phenylketonuria

Dietary intake	Weeks		Trimester		
	0–4 (n = 213)	4–8 (n = 236)	First (n = 247)	Second (n = 249)	Third (n = 241)
Protein					
r	−0.1441	−0.2277	−0.1630	−0.2283	−0.1713
P	0.0356	0.0004	0.0103	0.0003	0.0077
Fat					
r	−0.1467	−0.1863	−0.1432	−0.1895	−0.1350
P	0.0324	0.0041	0.0244	0.0027	0.0362
Energy					
r	−0.0053	−0.0637	−0.0763	−0.2049	−0.1615
P	0.9381	0.3299	0.2321	0.0011	0.0121

TABLE 5
Infant anthropometric measures at birth according to maternal plasma phenylalanine concentration[1]

	Group[2]			
	1	2	3	4
Length (cm)	50.5 ± 1.7	49.9 ± 2.5	49.3 ± 2.5	48.1 ± 3.1
Weight (kg)	3.38 ± 0.45	3.20 ± 0.44	3.17 ± 0.40	2.94 ± 0.59
Head circumference (cm)[3]	34.6 ± 1.5[a]	33.7 ± 1.8	33.0 ± 1.0[b]	32.2 ± 1.9[b]

[1] $\bar{x}$ ± SD. Values with different superscript letters are significantly different, $P < 0.05$.

[2] Defined on the basis of plasma phenylalanine concentrations: group 1, <360 μmol/L by 10 wk gestation and 120–360 μmol/L (2–6 mg/dL) throughout the remainder of pregnancy; group 2, <600 μmol/L (10 mg/dL) but not <360 μmol/L by 10 wk gestation and 120–600 μmol/L throughout the remainder of pregnancy; group 3, <600 μmol/L by 10 wk gestation but >600 μmol/L at least once thereafter; group 4, never <600 μmol/L.

[3] The 50th percentile for head circumference is ≈34.5 cm.

beginning about midpregnancy, was reported (15, 16). This same trend was found in the present study: women in group 1 had substantial increases in phenylalanine intake during the second and third trimesters, but their plasma phenylalanine concentrations remained <360 μmol/L. The women in group 1 tended to have greater intakes of dietary protein, fat, and energy in the second and third trimesters than did the other groups of women. The greater mean nutrient intakes by women in group 1 than by women in the other groups may be responsible for the improved phenylalanine tolerance and the higher mean infant head circumference, which reached the 50th percentile. Women in group 1 also tended to have the greatest mean weight gain, which was 159% of the recommended amount. The increase in weight improves the utilization of dietary phenylalanine and may be related to increased maternal phenylalanine tolerance. Generally, it is not advisable to gain more than the recommended amount of weight during pregnancy because of associated complications that may occur during delivery (17). This was not a problem in our study subjects. However, excessive weight gained during pregnancy may remain after delivery. This in turn can lead to obesity, which may cause complications in future pregnancies or other health risks for these women.

The women in group 1 tended to have the highest intakes of protein and fat. Their higher protein intakes without increases in plasma phenylalanine concentrations suggest improved intake of the phenylalanine-free medical foods. Because the medical foods are supplemented with minerals and vitamins, improved protein intake was associated with improved mineral and vitamin intakes as well. The women in group 1 also tended to consume the highest percentage of energy as fat. Some of the medical foods provide fat and others do not. If there is no fat in a medical food, it becomes especially difficult to obtain adequate fat in the diet. None of the women with PKU in any trimester exceeded a mean fat intake of 29% of energy. Compared with the usual American diet, which supplies 35–40% of energy as fat (18), these women with PKU had low fat intakes. Essential fatty acid intakes and status were not evaluated in this study, which began in 1986. However, it seems prudent to recommend that pregnant women with PKU consume adequate amounts of fat from canola oil or soy oil (19).

Genotype of the infants and fetal growth are other factors that may have influenced maternal phenylalanine requirements; however, we did not assess these factors in this study. Stegink et al (20) reported that when adult heterozygotes for PKU and control subjects consumed similar amounts of phenylalanine, the heterozygotes had significantly higher plasma phenylalanine concentrations at baseline and for 8 h after the meal than did the control subjects. These data suggest that heterozygotes for PKU have a lower tolerance for dietary phenylalanine than do control subjects. The present study did not evaluate which mutated allele was inherited by each infant. It was reported that genotype has a significant influence on the amount of phenylalanine tolerated daily by persons with PKU (21). However, in the present study, this was not found to be the case during the first trimester of pregnancy in those women for whom mutation analyses were completed. In future research with a larger sample of pregnant women with PKU, both maternal and infant genotypes should be evaluated to determine the possible effects on maternal phenylalanine tolerance.

In this study, we showed that maternal protein and fat intakes throughout pregnancy and energy intake during the second and third trimesters were negatively correlated with plasma phenylalanine concentration. These data clearly indicate that the total diet, not just the phenylalanine intake, is important to pregnancy outcome in women with PKU. These results suggest that in women who have difficulty lowering their plasma phenylalanine concentrations, protein intake from medical foods and fat and energy intakes should be increased.

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