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Original article

Maternal phenylketonuria: newborn outcomes in women treated and not treated before pregnancy

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Abstract. The aim of this study was to determine the relationship between the low-phenylalanine diet and perinatal parameters in children of women with phenylketonuria. An attempt was also made to determine whether starting the diet only after the beginning of pregnancy increases the risk of maternal phenylketonuria syndrome in children. Forty-five women from Poland, who were diagnosed with phenylketonuria PKU were recruited. Each subject completed a two-part medical questionnaire. The questions in the first part concerned pregnancy. Part two of the questionnaire referred to the neonates and asked for perinatal parameters. 13% of the surveyed women did not use a low-phenylalanine diet in the period prior to conception, and thus reported that they did not achieve metabolic control of phenylketonuria. The remaining 87% of respondents following this diet during the period prior to conception. Women using the low-phenylalanine diet in the period prior to conception gave birth to children with significantly higher birth weights and larger head circumferences. In all the women, regardless of whether they used the low phenylalanine diet prior to pregnancy or not, the average blood phenylalanine concentration decreased over subsequent trimesters. Birth defects were significantly more common in the case of women who didn't employ the low-phenylalanine diet in the period prior to conception. We underline that the treatment of pregnant women with phenylketonuria is of great importance to prevent neonatal sequelae. We strongly recommend starting treatment prior to conception, as the deleterious effect of not using the low-phenylalanine diet in period prior to conception is very clear.

Key words: phenyloketonuria, PKU, maternal, nutrition, diet

Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder of amino acid metabolism. It most commonly involves a defective phenylalanine hydroxylase (PAH) enzyme, which is required for the metabolism of phenylalanine (Phe) to tyrosine in the liver. PKU can also be caused by a deficiency of the cofactor of PAH, namely tetrahydrobiopterin (BH4), which is needed for the normal function of the enzyme. The resulting inability to convert dietary Phe to tyrosine (Tyr) leads to varying degrees of hyperphenylalaninemia a condition that involves serum phenylalanine concentrations of over 1200 μmol/L (for classical phenylketonuria), between 600 and 1200 μmol/L (mild phenylketonuria), or under 600 μmol/L (hyperphenylalaninemia) (1). This diet-dependent condition is found in Poland in 1 in 8000 live births. Its prevalence in Europe (in screened populations) is estimated at 1:10,000, and in the USA at 1:15,000, where every 55th individual is a carrier of the defective phenylalanine hydroxylase gene (2,3). Untreated PKU leads to severe intellectual disability.

Metabolic control of PKU, which involves maintaining serum phenylalanine concentration at

120–360 μmol/L, can be achieved by a strict diet with minimal phenylalanine intake. This decreases the serum phenylalanine concentration, and should be combined with tyrosine supplementation (4). A low phenylalanine diet is of great importance for pregnant women and for those planning pregnancy. Untreated maternal phenylketonuria or hyperphenylalaninemia during pregnancy can lead to maternal PKU syndrome in the neonate, which can manifest as low birth weight, microcephaly, craniofacial dysmorphism, congenital heart disease, developmental delays, and mental retardation. The problem occurs when a woman is unaware of her pregnancy for 4–5 weeks, and thus does not modify her dietary Phe intake. One of the first studies on dietary therapy for PKU was that of Lenke et al. (5) who described 523 pregnancies in 155 women with untreated PKU and 34 women following a low-phenylalanine diet. The frequency of mental retardation, microcephaly, and congenital heart disease was far greater than in the general population, and was correlated with maternal Phe concentrations.

The Maternal Phenylketonuria International Collaborative Study provided evidence that normal fetal outcome is possible if maternal blood Phe levels of 2–6 mg/dl can be achieved by 8–10 weeks of gestation and maintained throughout the pregnancy. Current guidelines recommend maintaining Phe levels between 2 and 6 mg/dl, starting from the period prior to conception (1,6).

The aim of this study was to determine the relationship between the low-phenylalanine diet and perinatal parameters in children of women with PKU. An attempt was also made to determine whether starting the diet only after the beginning of pregnancy increases the risk of maternal PKU syndrome in children.

Material and Methods

Forty-five women from Poland, who were diagnosed with PKU and had completed at least one pregnancy by December 31, 2018 were recruited to the study. Only one women had mild-moderate PKU, and the rest of the participants had classic PKU.

Each subject completed a two-part authors medical questionnaire. Data were obtained retrospectively from the women's medical records. The questions in the first part concerned pregnancy: diet in the period prior to conception, phenylalanine concentration before and during pregnancy or tyrosine supplementation, well-being and discomfort during pregnancy. Part two of the questionnaire referred to the neonates and asked for perinatal parameters, such as Apgar score, birth defects, head circumference, and birth weight. Statistical analysis considered the last phenylalanine measurement before pregnancy and the mean values of the results for the individual trimesters.

Statistical analysis comparing the outcomes of treated and untreated pregnancies was performed in the patients with classical PKU. The Shapiro–Wilk test was used to test for normality. The significance of the differences in pregnancy outcomes was determined using Fisher's exact test and the differences in Phe levels were examined with the Mann–Whitney U-test. The correlation between Phe levels and birth weight was assessed using Spearman's rank correlation. P values below 0.05 were taken as statistically significant. Statistical analysis was carried out using Statistica 13.0 software (StatSoft, Tulsa, OK, USA).

Written informed consent was obtained from all participants.

Results

13% of the women did not use a low-phenylalanine diet in the period prior to conception, and thus reported that they did not achieve metabolic control of phenylketonuria. The remaining 87% of respondents following this diet during the period prior to conception. All respondents followed the low phenylalanine diet throughout the entire pregnancy. Despite this, most women experienced the negative effects of the disorder, such as irritability (40%), impaired concentration (24.4%), problems in interpersonal relations (8.9%), depression (4.4%), tearfulness (4.4%), and agitation (4.4%).

The use of a low-phenylalanine diet in the period prior to conception proved to be the most important factor in phenylalanine levels measured during preg-

nancy, and thus also for the perinatal parameters of the newborn. Women using the low-phenylalanine diet in the period prior to conception gave birth to children with significantly higher birth weights and larger head circumferences. In all the women, regardless of whether they used the low phenylalanine diet prior to pregnancy or not, the average blood phenylalanine concentration decreased over subsequent trimesters. However, individual tolerance to the Phe also increased (Tables 1 & 2). In addition, it was also found that the better the tolerance of phenylalanine during pregnancy, the greater the birth weight (Fig. 1). The use of a low-phenylalanine diet can thus be seen to be the best way of preventing birth defects in this group. Birth defects were significantly more common in the case of women who didn't employ the low-phenylalanine diet in the period prior to conception, at 15% (5 children) vs. 50% (3 children). The most common defects were cerebral palsy, microcephaly, hypertonia, strabismus, heart defect, and Asperger's syndrome (Table 1).

Neither Phe concentration in the individual trimesters nor the perinatal parameters of newborns were affected by the use of tyrosine supplements (Table 3).

Discussion

The purpose of this study was to assess the offspring of pregnancies among women with phenylketonuria and to identify the maternal and environmental characteristics associated with the offspring outcome. To our knowledge, this is the first study to describe the

Table 1. Differences in perinatal parameters and in levels of Phe concentration during pregnancy, by use of low-phenylalanine diet during the period prior to conception

	Low-phenylalanine diet applied during the period prior to conception?		
	Yes (n = 39)	**No (n = 6)**	**p-value[2]**
Birth weight (g)	3242 ± 380	2723 ± 310	0.004
Head circumference (cm)	35.0 ± 3.4	30.8 ± 1.9	0.004
Phe concentration (mg/dl) in trimester 1	5.2 ± 2.3	13.4 ± 7.5	0.02
Phe concentration (mg/dl) in trimester 2	3.5 ± 1.2	10.9 ± 4.2	0.0001
Phe concentration (mg/dl) in trimester 3	2.1 ± 0.8	10.2 ± 8.2	0.003
Mean tolerance of Phe during pregnancy (mg/dl)	1226.7 ± 660.2	430.8 ± 232.3	< 0.0001
Birth defect occurrence (n[1],%)	4, 15%	3, 50%	< 0.0001

[1] *n, number of children*

[2] *p-value, Mann–Whitney U-test*

Table 2. Differences in Phe concentration, by whether normalization was achieved in the period prior to conception

	Phenylalanine concentration normalized before pregnancy?		
	Achieved (n[1] = 40)	**Not achieved (n = 5)**	**p-value[2]**
Phe concentration (mg/dl) in trimester 1 of pregnancy	5.35 ± 2.51	14.22 ± 7.68	0.002
Phe concentration (mg/dl) in trimester 2 of pregnancy	3.76 ± 1.68	10.16 ± 5.95	0.002
Phe concentration (mg/dl) in trimester 3 of pregnancy	2.13 ± 0.82	11.3 ± 8.79	0.002
Mean tolerance of Phe during pregnancy (mg/dl)	1214.6 ± 654.5	368 ± 242.6	< 0.0001

[1] *n, number of children*

[2] *p-value, Mann–Whitney U-test*

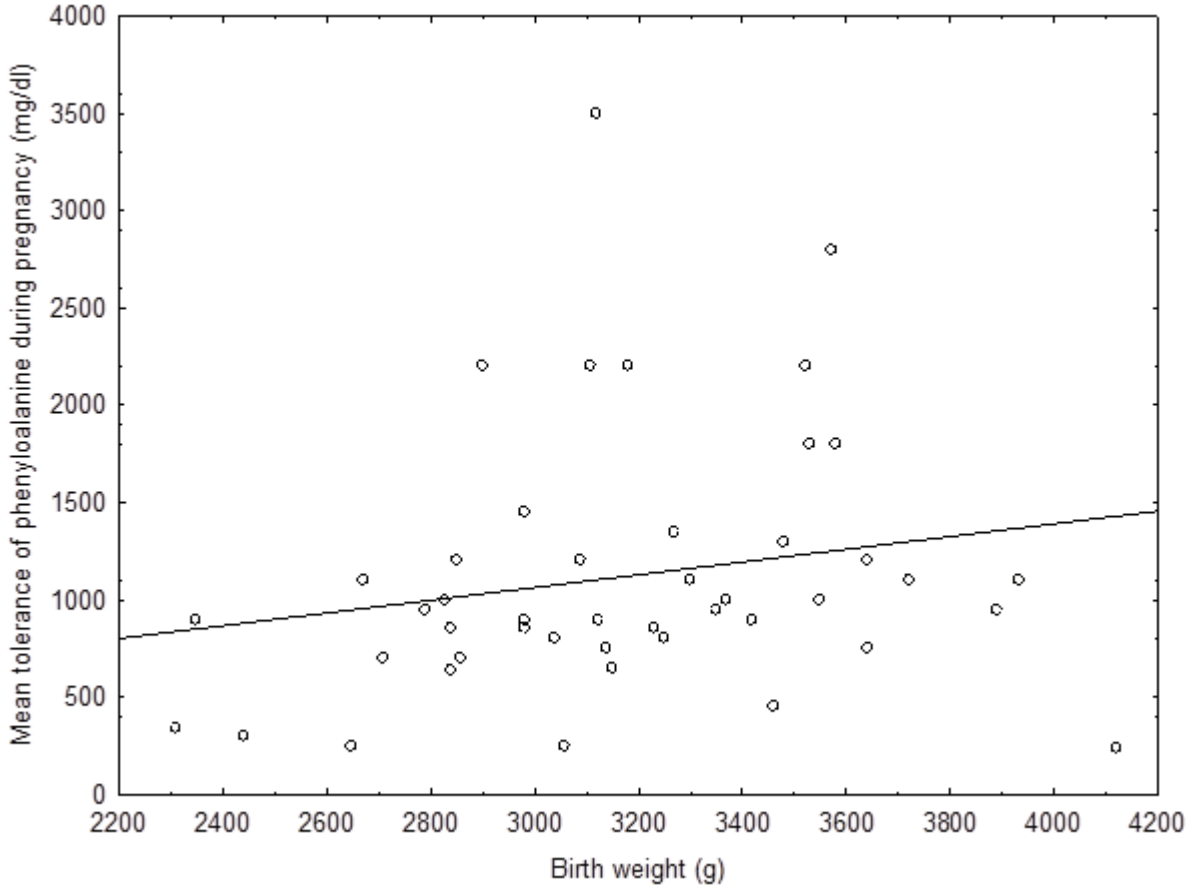

Figure 1. Relationship between the mean tolerance of phenylalanine during pregnancy (mg/dl) and the birth weight (g).

Table 3. Differences in perinatal parameters and in Phe concentration during pregnancy, by use of tyrosine supplementation

	Tyrosine supplementation used in the period prior to conception?		
	Yes (n[1] = 30)	**No (n = 15)**	**p-value[2]**
Birth weight (g)	3163 ± 468	3180 ± 375	NS
Head circumference (cm)	33.6 ± 2.23	35.1 ± 4.1	NS
Phe concentration (mg/dl) in trimester 1 of pregnancy	6.05 ± 4.49	6.52 ± 4.32	NS
Phe concentration (mg/dl) in trimester 2 of pregnancy	4.1 ± 3.05	4.72 ± 3.22	NS
Phe concentration (mg/dl) in trimester 3 of pregnancy	2.83 ± 3.51	3.36 ± 4.37	NS
Mean tolerance of Phe during pregnancy (mg/dl)	1119.4 ± 717.5	1121.3 ± 661.5	NS

[1] *n, number of children*

[2] *p-value, Mann–Whitney U-test*

link between phenylalanine concentrations in women with PKU from Poland, pregnancies outcomes and development characteristics of the children.

The basis of nutrition therapy for women with PKU is regular monitoring of Phe concentration (once per week when planning for pregnancy and twice per week during pregnancy, according to the European PKU Guidelines), accompanied by dietary modification to ensure a low intake of Phe (1). In this study, as many as 13% of women stated that they did not follow the low-phenylalanine diet during the period prior to conception. Common reasons for this were that they were not planning a pregnancy, or that they had problems achieving metabolic control of their PKU at that time. Unfortunately, women also abandoned the low-phenylalanine diet under the mistaken assumption that childhood and adolescence were the best time for therapy. In fact, every four-week delay in beginning treatment in newborns has been shown to lead to an average drop of four IQ points , which emphasizes that neurological damage begins early after birth. Many studies indicated that treatment in the early years of life has more impact than treatment in later years (1, 7, 8). Most importantly, there is currently no strong evidence that it is safe to discontinue dietary treatment in adults: treatment for life is recommended, even though it is acknowledged that dietary management is associated with a significant burden on patient (1). This is a clear signal that it is necessary increase awareness among patients with PKU that the need for a low-phenylalanine diet applies throughout life. This is important, not only in terms of maternal PKU syndrome, but for all patients with PKU, as has been demonstrated many times. Adults with PKU who have discontinued the low-phenylalanine diet during adolescence have been reported to show significantly slower reaction times than adults following dietary restrictions and control groups, as well as subtle differences in inhibition, attention, and working memory (9, 10). The older group (> 32 y) in the study of Weglage et al.(11) performed slower in terms of information processing, which might be related to their early relaxation of the diet. Koch et al. (12) concluded that dietary discontinuation during adolescence was associated with poorer outcomes in adulthood in terms of intellectual ability and test scores, and with increased rates of medical and behavioral problems (1).

Once pregnancy had been confirmed, all the women followed the recommended low-phenylalanine diet, and thus returned to using low-phenylalanine preparations. Many patients with PKU (not only women) have reported that their reason for abandoning low-phenylalanine medical preparations (thus increasing the supply of phenylalanine in the diet) was that they had unacceptable tastes (2, 13). Moreover, both in our study and in that of Yildiz et al. (2) women reported an increased feeling of nausea and gastrointestinal discomfort. It has been reported that drinking the preparation in smaller portions more often leads not only to better tolerance, but may also be an additional factor in improving tolerance of phenylalanine in the longer term (13).

The results confirm the importance of diet during the period prior to conception: the women who employed the low-phenylalanine diet both before pregnancy and during each trimester showed significantly lower levels of phenylalanine and a higher tolerance of it, and their children were born with a larger head circumferences and greater body weight. The average head circumference of the children of women not following the low-phenylalanine diet was 30.8 ± 1.9 cm, compared with 35.0 ± 3.4 cm among the women using the low-phenylalanine diet. Prick et al. (14) indicate that head circumference of neonates born in term should be in the range of 33–38 cm. This criterion allows us to diagnose microcephaly (the primary birth pathology of children with maternal phenylketonuria syndrome) among the children of the women in our study who did not use the low-phenylalanine diet prior to pregnancy. Low birth weight is another common feature of this syndrome. The women who adhered to the dietary restrictions, who also had higher individual tolerances to phenylalanine, gave birth to children of significantly greater weight (3242 ± 380 g vs. 2723 ± 310 g), which was additionally evident in the correlation. In addition to the low birth weight and smaller head circumference, the women not using the low-phenylalanine

diet during the period prior to conception gave birth to significantly more children with defects typical of maternal PKU syndrome, such as cerebral palsy and increased muscle tone. This is further evidence for the importance of low phenylalanine intake, not only during pregnancy, but particularly during the period prior to it.

The medical preparations taken by patients (including XP Maxamum, Milupa Pku 3 tempora, Cooler express, PAM Maternal, and PKU Lophlex LQ) are not enriched with tyrosine, leading to a risk of deficiencies of this amino acid. Tyrosine supplementation seems to be particularly justified here. The literature indicates that some clinics added extra Tyr to Phefree L-amino acid supplements, in order to improve neuropsychological functioning (15). In this population, two thirds of women monitored their tyrosine levels, and only 40% supplemented with tyrosine. However, no significant differences were found between the perinatal parameters and maternal phenylalanine levels in the groups monitoring and not monitoring tyrosine. Tyrosine deficiency affects patients with PKU and may manifest as disorders of the thyroid gland, including hypothyroidism, a feeling of tiredness, or depressed mood. Our results suggest that it is necessary to monitor the parameters of operation of the thyroid in women with PKU. It can also be assumed that the complaints reported by the women—which included irritability, impaired concentration, problems in interpersonal relations, depression, tearfulness, and agitation—are also consequences of tyrosine deficiency. As medical preparations do not contain added tyrosine for patients with PKU, further research is needed in the Polish population to assess the frequency of tyrosine deficiency in women with PKU and its consequences. It is also important to spread awareness of the need for tyrosine supplementation by patients with PKU.

One limitation of our study was the use of self-report and mother-report instruments. The subgroup comparisons of on-diet versus off-diet women in the period prior to conception involved small sample sizes. Further research is needed in young women to increase awareness of the significance of low-phenylalanine diets in preventing development of maternal phenylketonuria syndrome.

Conclusion

The results follow the general pattern reported by other studies. We underline that the treatment of pregnant women with phenylketonuria is of great importance to prevent neonatal sequelae. We strongly recommend starting treatment prior to conception, as the deleterious effect of not using the low-phenylalanine diet in period prior to conception is very clear. Educational programs conducted in an appropriate way among young women with PKU are necessary.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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