ABSTRACT. Objective. The maternal phenylketonuria (PKU) syndrome is caused by high blood phenylalanine (Phe) levels during pregnancy, leading to a host of birth defects, especially microcephaly and congenital heart disease (CHD). For finding whether the maternal PKU syndrome could be prevented, an international collaborative study was organized to evaluate treatment with a Phe-restricted diet. Blood Phe levels, maternal weight gain, and nutrient intakes during pregnancy were evaluated as to their effect on the rate of microcephaly and CHD in the offspring.

Methods. The study was a prospective, longitudinal effort aimed at lowering blood Phe during pregnancy. Women were enrolled at time of referral for pregnancy. Nutrient intake analysis, which serves as the basis for this report, was available from 251 pregnancies. Subjects were stratified by blood Phe control of ≤600 μmol/L by 8 weeks gestation or >600 μmol/L by 8 weeks gestation. Outcome of these pregnancies was correlated to blood Phe levels, weight gain, and nutrient intake.

Results. The study goal was to attain blood Phe levels of 120 to 360 μmol/L 3 months preconception; however, this goal was achieved by only a limited number of patients. Therefore, the data presented were based on blood Phe control ≤600 μmol/L or >600 μmol/L by 8 weeks of gestation. Blood Phe control of ≤600 μmol/L by 8 weeks of gestation was attained by 86 (34.3%) of the 251 women in this study, whereas the other 165 women had blood Phe control >600 μmol/L by 8 weeks of gestation. Of the 251 offspring, 166 were born with normal head circumference and 85 were born with microcephaly (<2 standard deviations below normal). Women with blood Phe >600 μmol/L at 8 weeks of gestation included 78 (92%) of the 85 infants with microcephaly compared with 8% in the group of women who had blood Phe levels ≤600 μmol/L. Weight gain during pregnancy was related to the rate of microcephaly. The highest occurrence of microcephaly (58%) was found in the pregnant women who gained <70% of recommended weight gain. Stepwise logistic regression analysis was used to determine factors associated with microcephaly. Significant factors included higher blood Phe levels when off diet, higher average Phe exposure during the pregnancy, lower Phe intake during pregnancy, lower weight gain during the pregnancy, and lower intake of protein and higher iron intake during the pregnancy. Infants with CHD were found only in the group of women who had blood Phe levels >600 μmol/L by 8 weeks of gestation. There was a higher rate of CHD in the offspring who were born to women who consumed <50% of the recommended intake of protein in the first trimester. The main source of protein for women with PKU is the medical food; therefore, when protein intake was low, vitamin and mineral intakes were also inadequate.

Conclusions. The data indicate that blood Phe control and how soon it is attained during pregnancy with PKU is important. Normal pregnancy weight gain should be encouraged to reduce microcephaly. Adequate protein and vitamin intakes early in pregnancy may have a protective effect for the prevention of CHD, even if blood Phe is elevated. The rate of microcephaly and CHD may be reduced if nutrient intake is optimal while attempting to control blood Phe levels. Pediatrics 2003;112:1534–1536; maternal PKU, congenital heart defects, microcephaly, nutrition.

ABBREVIATIONS. PKU, phenylketonuria; Phe, phenylalanine; CHD, congenital heart disease; HC, head circumference.

Phenylketonuria (PKU) is caused by a defect in the hydroxylation of phenylalanine (Phe) to tyrosine usually detected through newborn screening programs and treated early in life. As these individuals get older, dietary adherence erodes and blood Phe levels rise above the therapeutic goal of 120 to 360 μmol/L. Many women with PKU are at risk of having offspring with microcephaly, congenital heart disease (CHD), and low birth weight because of the diet discontinuation policies practiced in the United States. In an effort to prevent the effects of high blood Phe levels on pregnancy outcome, the Maternal PKU Collaborative Study was undertaken. Diet records were available from 251 of the women enrolled. The offspring of these women were studied for physical growth and CHD. The effects of blood Phe levels, maternal weight gain, and nutrient intakes were evaluated.

METHODS

A total of 251 women with classical PKU and diet analyses were included in this report. Although the treatment plan consisted of nutrition counseling before conception, most women were enrolled when pregnancy was established. A Phe-free medical food supplemented with low-protein foods to supply essential Phe to meet the needs of pregnant women was prescribed. The diets were analyzed for macro- and micronutrients. In most cases, prenatal vitamins were not prescribed because the medical food, ingested in adequate amounts, provided adequate vitamins and minerals. Three-day diet records were collected weekly, and nutrients were calculated. The 3-day diet intakes were collapsed into daily means for 19 nutrients using the software program Amino Acid Analyzer (Ross Laboratories, Columbus, OH). Dietary intake was assessed monthly, and results were incorporated into the study database. Weight status before pregnancy was noted, and monthly weight was recorded. Women were considered to be in dietary control when a blood Phe level of ≤600 μmol/L was achieved and no Phe...
levels exceeded 600 µmol/L for the remainder of the pregnancy. The 251 women were grouped according to blood Phe ≤600 µmol/L or >600 µmol/L at 8 weeks’ gestation. Newborn head circumference (HC) and the presence or absence of CHD were recorded, and factors that influenced pregnancy outcome were analyzed. For the purposes of this study, a child was classified in the microcephaly group when birth HC was in the microcephalic range and did not improve at later evaluations or when the last HC before 3 years of age was microcephalic. Normative data from the Swedish reference standards were used for birth measurements, and those from the National Center for Health Statistics were used for postnatal measurements.

Simple contingency table analysis was done by χ² and Fisher exact test for comparison of the 2 groups on overall proportions and frequency distributions of categorical variables. P < .05 was accepted as significant. Stepwise logistic regression analysis was used to determine factors that independently predicted offspring microcephaly. Variables were added to the model provided that the P value for improvement was <.15. Statistical analyses were performed using SAS/STAT Software, version 8 of the SAS system for UNIX.

RESULTS

Microcephaly

Women were divided into 2 groups: those who had blood Phe ≤600 µmol/L by 8 weeks’ gestation and those who had blood Phe >600 µmol/L by 8 weeks’ gestation. Eighty-six (34.3%) women maintained blood Phe control ≤600 µmol/L by 8 weeks’ gestation, whereas the remaining 165 women had levels >600 µmol/L by 8 weeks’ gestation. Of the 251 offspring, 85 (33.9%) were born with microcephaly. Of the 85 microcephalic offspring, 78 were born to women with blood Phe >600 µmol/L by 8 weeks’ gestation and represented 47% of this group, whereas only 7 (8.1%) were born to women who had blood Phe ≤600 µmol/L (P < .0001; Table 1).

Weight gain data for 237 of the 251 women were evaluated. Normal weight gain during pregnancy was considered to be 70% to 134% of recommended weight gain, inadequate weight gain was considered to be 70% of recommended weight gain, and excess weight gain was >134% of recommended weight gain. Overall, 57 women had low weight gain (Table 2). Of these 57 women, 33 (58%) had offspring with microcephaly. Eighty women who had adequate weight gain had a lower rate of offspring with microcephaly (24 [30%]), even with blood Phe >600 µmol/L. Surprising is that women with >134% of recommended weight gain had the lowest number of microcephalic infants (19 of 100 [19%]).

Stepwise logistic regression analysis showed that higher average blood Phe exposure during the pregnancy, higher off-diet blood Phe level, low prepregnancy weight, poor weight gain during pregnancy, and low protein and high iron intakes during pregnancy were found to be associated with microcephaly in their offspring (Table 3).

CHD

The 251 women with PKU who had nutrient analysis had 22 (8.8%) offspring with major cardiac malformations. None of the women who had blood Phe levels ≤600 µmol/L by 8 weeks’ gestation had offspring with CHD. Of the women with blood Phe >600 µmol/L by 8 weeks’ gestation, 36 ingested <50% of the recommended protein intake for pregnancy. Offspring of 11 (30.6%) of these 36 pregnancies had CHD compared with 11 (8.3%) of 132 offspring for whom mother’s protein intake was >50% of the recommended dietary allowance (P < .0013). In a previous report, stepwise discriminant analysis using first-trimester variables to discriminate CHD offspring identified protein intake, 4 to 8 weeks of blood Phe, fat intake, off-diet blood Phe level, and reduced vitamin B₁₂ intake as significant in development of CHD. Seven (53.9%) of 13 women with low vitamin B₁₂ intake had offspring with CHD, whereas only 7 of 106 women who had adequate B₁₂ intake had infants with CHD (odds ratio: 16.5; 95% confidence interval: 4.4–62.6; P = .0001).

DISCUSSION

The data presented confirm the deleterious effect of high blood Phe on brain growth, microcephaly, and CHD. The study also underscores the difficulty in achieving blood Phe ≤360 µmol/L or even ≤600 µmol/L. Nutrition factors other than high blood Phe levels play a role in preventing some of the deleterious effects of PKU during pregnancy. Unfortunately, blood folate levels were unavailable. The data presented show that microcephaly significantly decreased when weight gain was adequate. Similarly, CHD was dramatically decreased with adequate protein intake despite high blood Phe levels. These dietary components, often overlooked in the treatment

| TABLE 1. | HC of 251 Infants Born to Women Who Had PKU and Blood Phe ≤600 µmol/L by 8 Weeks’ Gestation |

<table>
<thead>
<tr>
<th>Blood Phe ≤600 µmol/L</th>
<th>Blood Phe &gt;600 µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normal HC</td>
<td>79</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
</tr>
</tbody>
</table>

Fisher exact P < .0001.

| TABLE 2. | Percentage of Recommended Weight Gain in 237 Women With PKU During Pregnancy and Offspring HC |

<table>
<thead>
<tr>
<th>Percentage of Recommended Weight Gain</th>
<th>(n)</th>
<th></th>
<th>(n)</th>
<th></th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>24</td>
<td>56</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70%–134%</td>
<td>33</td>
<td>24</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;134%</td>
<td>57</td>
<td>80</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% with microcephaly: 58% 30% 19%.

χ² = 25.4, df = 2, P = .001.

| TABLE 3. | Stepwise Logistic Regression Analysis to Determine Factors Associated With Offspring Microcephaly (n = 237) |

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average blood Phe exposure</td>
<td>.0001</td>
</tr>
<tr>
<td>Off-diet blood Phe</td>
<td>.0008</td>
</tr>
<tr>
<td>Pre-pregnancy weight</td>
<td>.0035</td>
</tr>
<tr>
<td>% recommended weight gain</td>
<td>.0241</td>
</tr>
<tr>
<td>Iron intake</td>
<td>.1094</td>
</tr>
<tr>
<td>Protein intake</td>
<td>.1002</td>
</tr>
</tbody>
</table>
of a PKU pregnancy, may alleviate some of the difficulties associated with high blood Phe levels.20–22

The data show the overall percentage of microcephaly in this group (85 of 251) to be 33.9% and the percentage of CHD (22 of 251) to be 8.8%. Although this is improved from untreated maternal PKU, 73% microcephaly and 12% CHD, the rates would have been lower if diet were started earlier in the pregnancy. The need for preconception education of women with PKU is indicated by the fact that 64% of the women entered the study after conception and failed to achieve blood Phe control by 8 weeks’ gestation.23 Efforts should be made by the primary care provider or obstetrician and nutrition counselor for education, reinforcement, and frequent follow-up to ensure compliance and adequate protein, energy, and fat intake. Prenatal vitamins should be prescribed.

The difficulty of controlling blood Phe levels as patients with PKU get older is now a widely recognized problem,3 which brings new challenges to the treatment of PKU. New therapeutic modalities need to be developed for treatment of maternal PKU to eliminate the high rate of CHD and microcephaly.

ACKNOWLEDGMENTS

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