Pregnancy Experiences in the Woman With Mild Hyperphenylalaninemia

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ABSTRACT. Objective. A major issue in maternal phenylketonuria (MPKU) has been whether maternal non-PKU mild hyperphenylalaninemia (MHP) is teratogenic. Such untreated pregnancies and their outcomes are presented on this report.

Methods. Enrolled pregnancies in which the untreated prepregnancy assigned phenylalanine level (APL) was no more than 600 µmol/L were included in the Maternal PKU Collaborative Study and were followed according to protocol.

Results. Forty-eight enrolled women with non-PKU MHP had mean APL 408 ± 114 µmol/L. They had a total of 58 pregnancies that resulted in live births. Fifty were untreated. Maternal phenylalanine (Phe) levels in the untreated pregnancies decreased during pregnancy for average Phe exposure of 270 ± 84 µmol/L, virtually identical to the level of 269 ± 136 µmol/L in the 8 treated pregnancies. Birth measurements in the 50 offspring from untreated pregnancies were within normal limits with z scores of −0.25 for weight, 0.28 for length, and −0.63 for head circumference, although birth head circumference was negatively correlated with maternal APL (r = −0.30). Only 1 offspring had congenital heart disease. Offspring IQ was 102 ± 15 compared with 96 ± 14 in the mothers with untreated pregnancies and with 109 ± 21 in control offspring.

Conclusion. Maternal non-PKU MHP no more than 600 µmol/L does not require dietary therapy. The naturally lower Phe level during pregnancy seems to protect against teratogenesis. Pediatrics 2003;112:1548–1552; maternal phenylalanine, genotype, offspring, birth weight, birth length, birth head circumference, IQ.

ABBREVIATIONS. MPKU, maternal phenylketonuria; Phe, phenylalanine; CHD, congenital heart disease; MHP, mild hyperphenylalaninemia; HPA, hyperphenylalaninemia; MPKUCS, Maternal PKU Collaborative Study; APL, assigned blood phenylalanine level; PAH, phenylalanine hydroxylase; SD, standard deviation.

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Among teratogenic factors, maternal phenylketonuria (MPKU) is one of the most potent. More than 90% of the offspring from untreated pregnancies of women with classic PKU, ie, blood phenylalanine (Phe) level ≥1200 µmol/L, have microcephaly and mental retardation, 40% have intrauterine growth retardation, and 12% to 15% have congenital heart disease (CHD).1 When the woman has mild PKU with a blood Phe level in the range of 600 to 1200 µmol/L, however, these teratogenic effects are less frequent,1,2 and when dietary treatment lowers the maternal blood Phe level to the range of 120 to 360 µmol/L, the offspring may be normal.3 This relationship between the maternal blood Phe level and teratogenesis supports the concept of a dose response in MPKU.2

A particular question is whether maternal non-PKU mild hyperphenylalaninemia (MHP), in which the ambient maternal blood Phe level is in the range of 180 to 600 µmol/L, represents a threat to the fetus. A combined retrospective-prospective study of families identified through routine cord blood screening, thus unbiased as to offspring outcome, indicated that mothers with normal blood Phe levels in the MHP range had normal children.4 A subsequent retrospective international survey of untreated maternal MHP concluded that this entity did not have serious consequences for the fetus, although the birth measurements and IQ scores were slightly lower in offspring when maternal blood Phe was >400 µmol/L than when it was <400 µmol/L.5

If maternal MHP threatens optimal fetal development, then there is cause for concern. At least 30% of the infants with hyperphenylalaninemia (HPA) identified by newborn screening have MHP.5 Most of them remain untreated because MHP is generally considered to be benign.6–8 Consequently, dietary intervention during pregnancy in women with MHP would be a major challenge because most of these women will never have been exposed to the relatively unpalatable Phe-free medical product essential for metabolic control.9 The nutritional and social support required to meet this challenge would likely be greater than that required for the successful treatment of MPKU.5 Attempts to treat maternal MHP with less support are unsuccessful.

To further determine whether maternal MHP is teratogenic, the Maternal PKU Collaborative Study (MPKUCS) included these women as well. This report documents the results of these pregnancies and the status of the offspring.
TABLE 1. Data on Pregnancies in Women With Maternal MHP and in Non-PKU Control Subjects in the MPKUCS

<table>
<thead>
<tr>
<th></th>
<th>Maternal MHP Untreated Pregnancies (n = 50)*</th>
<th>Treated Pregnancies (n = 8)</th>
<th>Controls (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Phe (μmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td>390 ± 102 (40)</td>
<td>516 ± 108 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Trimester 1</td>
<td>310 ± 88 (28)</td>
<td>255 ± 161 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Trimester 2</td>
<td>261 ± 85 (50)</td>
<td>245 ± 145 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Trimester 3</td>
<td>234 ± 73 (47)</td>
<td>235 ± 98 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Average Phe exposure</td>
<td>270 ± 84 (50)</td>
<td>269 ± 136 (8)</td>
<td>—</td>
</tr>
<tr>
<td>WAIS-R IQ</td>
<td>96 ± 14 (34)</td>
<td>93 ± 16 (7)</td>
<td>103 ± 13</td>
</tr>
</tbody>
</table>

Data are mean ± SD; n in parentheses. WAIS-R indicates Wechsler Adult Intelligence Scale–Revised.

* Ten women in this group had 2 pregnancies each.

METHODS

The MPKUCS study protocol has been described. Participants included all women who had HPA and were known or reported to the study and were planning a pregnancy or were already pregnant. Control pregnancies in normal women who were known to the participating centers were also enrolled. Specific areas of the protocol relevant to the results that we describe include determination of the biochemical phenotype on the basis of a basal or assigned blood Phe level (APL), selected as the highest of 2 or 3 plasma Phe levels on an unrestricted diet measured by the amino acid analyzer or the fluorometric method when the subject was not pregnant; the average level of blood Phe during pregnancy (average Phe exposure); Phe hydroxylase (PAH) genotypes in the mother and offspring; and medical examinations of the offspring at birth, 6 months of age, and annually thereafter through childhood. Z scores for measurements of weight, length, and head circumference were calculated relative to population norms for sex and age. Developmental and cognitive assessments of the offspring were conducted according to protocol and included the Bayley Scales of Infant Development, the McCarthy Scales of Children’s Abilities, the Wechsler Intelligence Scale for Children–Revised, and the Wechsler Adult Intelligence Scale–Revised.

RESULTS

Mothers

Forty-eight of the women who had HPA and were enrolled in the MPKUCS had 1 or more pregnancies resulting in liveborn infants. Their APL was 40 ± 114 μmol/L with a range of 198 to 600 μmol/L. Cognitive testing was performed on 41 of these women, yielding a mean IQ of 95 ± 15 (range: 58–130). Their socioeconomic status was 3.8 ± 1.0 (range: 1–5; 1 = highest, 5 = lowest). Thirty-four different PAH mutations were detected in the 35 mothers who were genotyped. Using the Danish system for genotype-biochemical phenotype classification, the most frequent MHP mutations were A300S and A403V each in 7 mothers, E390G in 4 mothers, and V245A in 2 mothers. Other MHP mutations, each in 1 mother, included T92I, D145V, V177L, E178G, R241C, T380M, E390G, A395G, and D415N. The other allele in each of the mothers harbored a PKU mutation.

Table 1 provides data on untreated and treated pregnancies in women with MHP. The APL among the 40 mothers who had 50 untreated pregnancies was 390 ± 102 μmol/L, whereas that among the 8 mothers with treated pregnancies was higher at 516 ± 108 μmol/L. However, exposure to blood Phe during pregnancy was lower than before pregnancy and essentially the same between the 2 groups with a mean overall Phe exposure of 270 ± 84 μmol/L in mothers with untreated pregnancies and 269 ± 136 μmol/L in those with treated pregnancies. Thus, even without therapy, the maternal blood Phe levels decreased during pregnancy, with consistent declines through the trimesters (Table 1). The IQ of the 34 mothers who had untreated pregnancies and had IQ testing was 96 ± 14 (range: 58–130) and was 93 ± 16 (range: 73–115) among the 7 tested mothers with treated pregnancies. IQ among the control mothers was 103 ± 13 (range: 75–130).

Untreated Pregnancies

A total of 55 maternal MHP pregnancies in which no dietary therapy was given occurred during the study. These pregnancies resulted in 2 spontaneous abortions, 3 terminations, and 50 liveborn offspring. No complications were reported in any of the pregnancies except for the 2 spontaneous abortions.

Offspring

Table 2 presents birth data on the offspring of maternal MHP as compared with control subject in the MPKUCS. The mean gestational age of the 50

TABLE 2. Birth Data on Offspring From Untreated Maternal MPH and Non-PKU Control Pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Maternal MHP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age (wk)</strong></td>
<td>40 ± 1.5 (50)</td>
<td>39 ± 1.7 (100)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3329 ± 436 (49)</td>
<td>3404 ± 646 (94)</td>
</tr>
<tr>
<td>z score</td>
<td>−0.25</td>
<td>0.16</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>50.6 ± 1.9 (49)</td>
<td>51.0 ± 3.1 (90)</td>
</tr>
<tr>
<td>z score</td>
<td>0.28</td>
<td>0.75</td>
</tr>
<tr>
<td>Birth head circumference (cm)</td>
<td>33.6 ± 1.3 (48)</td>
<td>34.6 ± 1.6 (82)</td>
</tr>
<tr>
<td>z score</td>
<td>−0.63</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Data are means ± SD; n in parentheses.
offspring from the untreated pregnancies was normal at 40 ± 1.5 weeks (range: 35–42 weeks). Their mean birth measurements included weight 3329 ± 436 g (range: 2500–4621 g) yielding a composite Z score of −0.25, length 50.6 ± 1.9 cm (range: 46–53.5 cm) yielding a composite z score of 0.28, and head circumference 33.6 ± 1.3 cm (range: 31.5–36.5 cm) yielding a composite z score of −0.63. Thus, their birth weight was slightly below and their birth length slightly above the expected, but their birth head circumference was considerably below expected yet within 1 standard deviation (SD) of the mean. Mean z scores for all of the measurements, however, were significantly lower than those in the control offspring (Table 2). Perinatal complications included only cleft palate in 1 offspring and jaundice of unknown cause in a second offspring.

Figure 1 depicts the relationship between maternal APL and offspring birth head circumference. The higher the APL, the smaller the head circumference (r = −0.30; P = .035).

Postnatal follow-up has disclosed CHD in 1 offspring (2%) as previously reported.20 This consists of a bicuspid aortic valve with mild aortic stenosis and insufficiency along with a small patent ductus arteriosus. The heart lesions were discovered at 8 years of age, when he developed chest discomfort on exercise and an electrocardiogram revealed left ventricular hypertrophy. He had previously been classified as being healthy with no heart murmur or other sign of heart disease. The 2% frequency of CHD is similar to the CHD frequency of 1% in the control subjects.

As noted in Table 3, postnatal growth has been within normal limits, but, as with birth measurements, the values were lower than those of the control subjects and head circumference was significantly lower. At the most recent examination before 36 months of age (the latest age for which head circumference norms were available), their z scores were −0.16 for weight, −0.47 for length, and −0.45 for head circumference. As compared with the z scores of the birth measurements, growth had somewhat lagged but head circumference improved. Two of the offspring have received a diagnosis of attention-deficit/hyperactive disorder, and 1 of these offspring also has visual and speech problems as well as scoliosis.

Wechsler Intelligence Scale for Children–Revised IQ was measured in 40 of the offspring from untreated pregnancies (Table 3). The mean full-scale IQ of these offspring was 102 ± 15 (range: 65–125). This is slightly lower but not significantly different (P = .07) from control Wechsler Intelligence Scale for Children–Revised full-scale IQ of 109 ± 21 (range: 35–147). Figure 2 depicts the relationship between maternal APL and offspring IQ. There was no correlation between the 2 variables (r = 0.13; P = .44). In 5 offspring for whom the McCarthy Scales of Children’s Abilities assessment was the latest test administered, the mean General Cognitive Index was

<table>
<thead>
<tr>
<th>TABLE 3. Postnatal Growth Measurements and IQ in Offspring From Untreated Maternal MHP Pregnanacies and Non-PKU Control Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal MHP</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Age (mo)</td>
</tr>
<tr>
<td>z scores</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Height</td>
</tr>
<tr>
<td>Head circumference</td>
</tr>
<tr>
<td>WISC-R IQ</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

Data are means ± SD; n in parentheses.
86 ± 9 (range: 76–98). In 2 offspring who had only the Bayley Scales of Infant Development, the Mental Development Index was 140 and 93. Three offspring had no developmental or IQ testing.

Birth measurements and IQ were compared between offspring from the 29 pregnancies with maternal APL ≤400 μmol/L and from the 21 pregnancies with maternal APL >400 μmol/L (Table 4). There were no significant differences in the birth measurements between these 2 groups. There was also no difference in IQ with a mean of 102 ± 13 (range: 76–125) in the offspring from pregnancies when the mother had APL ≤400 μmol/L and IQ 101 ± 19 (range: 65–125) when the mother had APL >400 μmol/L, both mean scores higher than the corresponding maternal IQ scores. In the 5 offspring who had only a McCarthy Scales of Children’s Abilities cognitive assessment, the mean General Cognitive Index for the 2 whose mothers had an APL <400 μmol/L was 87, whereas the 3 offspring whose mothers had APL >400 μmol/L had a mean General Cognitive Index of 85.

Because every mother with complete genotyping was heterozygous for both an MHP and a PKU PAH mutation, each offspring would have inherited one or the other of these 2 mutations. Consequently, we compared the IQ of offspring who inherited an MHP mutation with those who inherited a PKU mutation. The mean IQ of the 17 offspring who inherited an MHP mutation was 104 ± 14, whereas the mean IQ of the 12 offspring who inherited a PKU mutation was 107 ± 12 (Table 5). When we examined the maternal IQ in these 2 cohorts, we also found no difference. The IQ among mothers whose children inherited an MHP mutation was 95 ± 15, whereas the IQ was 97 ± 13 among the mothers whose children inherited a PKU mutation. Thus, the IQ among the 2 types of offspring was comparable and exceeded maternal IQ by a comparable amount and would seem to be unrelated to whether an MHP or PKU mutation was inherited.

### Treated Pregnancies

All of the 8 treated pregnancies resulted in live-born offspring. Table 6 presents mean birth measurement z scores and IQ of offspring from 8 treated pregnancies as compared with those in offspring from the 50 untreated pregnancies. The scores for weight and head circumference tended to be lower in offspring from the treated pregnancies, and their length tended to be greater. As in the untreated pregnancies, all of the z scores were lower than in control offspring. Sample sizes of the untreated group were too small for statistical testing. Nevertheless, the mean IQ of 109 ± 17 among the treated offspring was slightly higher than that of the untreated offspring.

### Table 5. IQ in Offspring and Mothers Relative to Inheritance of MHP or PKU Mutation by Offspring

<table>
<thead>
<tr>
<th>Offspring Mutation</th>
<th>MHP (n = 17)</th>
<th>PKU (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring IQ</td>
<td>104 ± 14</td>
<td>107 ± 12</td>
</tr>
<tr>
<td>Maternal IQ</td>
<td>95 ± 15</td>
<td>97 ± 13</td>
</tr>
<tr>
<td>Maternal Phe (μmol/L)</td>
<td>6.0 ± 1.6</td>
<td>6.7 ± 2.1</td>
</tr>
<tr>
<td>APL</td>
<td>4.1 ± 1.3</td>
<td>4.5 ± 1.6</td>
</tr>
</tbody>
</table>

Data are means ± SD.

### Table 6. Birth Measurement z scores and IQ in Offspring From Treated Pregnancies Compared With Offspring From Untreated Pregnancies

<table>
<thead>
<tr>
<th>Offspring</th>
<th>Treated Preganacies</th>
<th>Untreated Preganacies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth measurement z scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>−0.74</td>
<td>−0.25</td>
</tr>
<tr>
<td>Length</td>
<td>0.48</td>
<td>0.28</td>
</tr>
<tr>
<td>Head circumference</td>
<td>−0.78</td>
<td>−0.63</td>
</tr>
<tr>
<td>WISC-R IQ</td>
<td>109 ± 17 (6)</td>
<td>102 ± 15 (40)</td>
</tr>
<tr>
<td>Range</td>
<td>84–128</td>
<td>65–125</td>
</tr>
</tbody>
</table>

Data are means ± SD; n in parentheses.
treated offspring (Table 6) and identical to the mean IQ of 109 ± 21 in the control subjects (Table 3).

**DISCUSSION**

This prospective examination of maternal MHP in the MPKUCS provides no compelling evidence that this natural degree of HPA during pregnancy has substantial teratogenic effects. Notably, the presence of a congenital heart defect in 1 offspring, representing only a 2% frequency of CHD, is not significantly different from the 1% frequency of CHD in the control population (P > .99) or from the 0.8% frequency in general populations. The IQ of the offspring from the untreated MHP pregnancies was 102 ± 15, well within normal limits and not significantly below the IQ of 109 ± 21 in the control offspring.

There might be a slight lowering of birth measurements in offspring from maternal MHP. This is most noticeable in birth head circumference. The mean birth head circumference of 33.6 ± 1.3 that we found is between the 10th and 25th percentiles for full-term infants and is virtually identical to the mean birth head circumference of 33.8 ± 1.0 among full-term infants from untreated MHP pregnancies in the retrospective study of Levy and Waisbren. The reduced offspring birth head circumference in the current prospective study that we report was negatively correlated with the APL in the mother and was consistent with the findings of Drogari et al., who reported an incremental reduction in birth head circumference of 0.5 cm for every 200-μmol/L increase in the maternal blood Phe level in treated MPKU. In addition to finding a normal mean IQ in the offspring from untreated MHP pregnancies, we found no correlation between offspring IQ and the maternal Phe levels from 200 μmol/L to 590 μmol/L.

The Phe tolerance in the untreated MHP pregnancies increased consistently during the pregnancies, beginning in the first trimester. This resulted in lower maternal Phe levels during pregnancy than before conception. A similar phenomenon of increased Phe tolerance has been observed in treated MPKU wherein by the third trimester a substantially greater amount of Phe must be added to the diet to maintain an optimal blood Phe level. It is possible that this natural reduction in maternal HPA during pregnancy offers protection against teratogenicity.

**CONCLUSION**

Maternal MHP with blood Phe no more than 600 μmol/L does not seem to be overtly teratogenic or to require dietary therapy. The naturally lower Phe level during pregnancy may protect against teratogenesis in these pregnancies.

**ACKNOWLEDGEMENTS**

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This study would not have been possible without the unfailing cooperation of the many participating metabolic centers throughout the United States, Canada, and Germany. Deborah Lobbregt, Coordinator of the Northeast Region of the MPKUCS, was invaluable in all phases of this and other aspects of the MPKUCS.

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