Prevention of Fetal Damage Through Dietary Control of Maternal Hyperphenylalaninemia

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Maternal phenylketonuria (PKU) has become one of the concerns of prenatal care. The high phenylalanine level of the pregnant woman with PKU is associated with serious adverse effects on the fetus. Offspring born to these mothers may manifest microcephaly, mental retardation, congenital heart disease, and low birth weight. Dietary treatment during pregnancy is the only means of preventing these fetal complications. It is essential, however, that this therapy begin before conception or at least early in pregnancy and that it is administered in cooperation with a PKU clinic. Thus, the control of maternal PKU represents a challenge of modern medicine in which obstetrics and biochemical genetics merge into a single cooperative entity for the benefit of the fetus and future generations.

Phenylketonuria
PKU was the first inborn error of amino acid metabolism to be clearly defined. In 1934 Fölling described 10 mentally re-
tarded children who excreted phenylpyruvic acid, a phenylalanine metabolite. Subsequently, he and others identified this disorder in many institutionalized mentally retarded individuals, and the enzymatic defect in the phenylalanine hydroxylase system was discovered (Fig. 1). As a result of this defect, phenylalanine accumulates in blood and other body fluids, and large amounts of phenylalanine and its metabolites are excreted in urine. It is the excretion of the phenylketone metabolite from which the same “phenylketonuria” derives. We know that PKU is an autosomal recessive genetic disorder with an incidence of 1:12,000 and that in classic PKU, mental retardation will always occur unless dietary treatment begins in early infancy. In addition to this type of PKU, other patients with generally milder degrees of hyperphenylalaninemia have been classified into related but distinct disorders (e.g., atypical PKU and mild hyperphenylalaninemia) (Table 1). The diagnostic criteria and natural history of these disorders have been described.

Identification of PKU in infants by screening is now a part of routine newborn care in most of the world. This identification leads to phenylalanine-restricted dietary treatment and the prevention of mental retardation from PKU. Until recently this diet was usually discontinued at the age of 5 or 6 years, but now most children remain on the diet at least until adolescence. However, women with PKU entering childbearing age are currently on a normal diet.

**The Challenge of Maternal PKU**

The biochemical abnormalities of PKU in the mother cross the placenta and affect the fetus of a phenylketonuric woman. When the woman has classic PKU with an untreated blood phenylalanine level of at least 1,200 μM (20 mg/dl), the frequency of mental retardation among offspring is 92%, and the frequency of microcephaly among offspring is 73%. Congenital heart disease and low birth weight are also frequent in offspring at this level of maternal phenylalanine. As shown in Table 2, the frequencies of adverse effects seem to correlate with the degree of hyperphenylalaninemia in the mother. For instance, studies of offspring of women with mild hyperphenylalaninemia or atypical PKU indicated that these degrees of hyperphenylalaninemia are less likely to damage the fetus.

Several reports have described families in which spontaneous abortion was frequent among those with PKU. Most notable among these is the report by Huntley and Stevenson. In contrast, a survey of untreated pregnancies in maternal PKU concluded that there was little or no increase in

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**TABLE 1. Metabolic Disorders Associated with Hyperphenylalaninemia**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Blood Phenylalanine (μM)</th>
<th>Phenylalanine Hydroxylase Activity (%)</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>PKU</td>
<td>≥1,200</td>
<td>&lt;1</td>
<td>Diet</td>
</tr>
<tr>
<td>Atypical PKU</td>
<td>720–1,100</td>
<td>2–3</td>
<td>Diet</td>
</tr>
<tr>
<td>Mild hyperphenylalaninemia</td>
<td>130–700</td>
<td>2–5</td>
<td>None</td>
</tr>
<tr>
<td>Normal</td>
<td>≤120</td>
<td>100</td>
<td>—</td>
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**FIG. 1. Pathway of phenylalanine hydroxylation. The enzyme defect in PKU is in the apoenzyme phenylalanine hydroxylase (1).** Tetrahydrobiopterin (BH₄) is necessary as a cofactor for phenylalanine hydroxylase activity. Defects in biopterin synthesis (2) or QBH₂ reduction (3) have not been reported in maternal PKU.
spontaneous abortion. Certainly most maternal PKU pregnancies result in liveborn offspring.

**Public Health Implications of Maternal PKU**

Until recently maternal PKU was rare, since most women with PKU were mentally retarded and not in a social setting compatible with pregnancy. Newborn screening and dietary treatment of PKU have changed this picture dramatically, since women with PKU of childbearing age are now intellectually normal. PKU does not limit female fertility. Thus, unless there is treatment that will protect the fetus from the effects of maternal PKU, these offspring will be mentally retarded and may replace in the current generation those with PKU in the previous generation in whom mental retardation was prevented by newborn screening and dietary therapy.

**Pathogenesis**

The mechanism of fetal damage in maternal PKU is unknown. Undoubtedly, the biochemical abnormalities of PKU in the mother are the major elements, since in the untreated maternal PKU, the fetus that does not have PKU is as severely damaged as one that is phenylketonuric. Furthermore, treatment with a low phenylalanine diet that controls the biochemical abnormalities during pregnancy lessens or prevents the adverse fetal effects. Thus the fetus is harmed by an abnormal biochemical environment produced by a genetically abnormal mother.

Animal studies have attempted to mimic maternal PKU in order to identify the offending agent. The lack of a natural animal model for PKU is a major limiting factor. Some investigators have induced PKU in pregnant animals by feeding or injecting large amounts of phenylalanine, usually accompanied by an inhibitor of phenylalanine hydroxylase, or by administering one of the metabolites of phenylalanine. While this reproduces some of the biochemical features of human PKU, such as the high phenylalanine level, other features are quite different. For instance, the treated animals develop high levels of tyrosine in response to phenylalanine loading, in contrast with the low tyrosine levels in human PKU. Thus nonhuman animal models for maternal PKU are inherently limited.

No animal offspring have had all of the abnormalities noted in human maternal PKU offspring. Infant monkeys born to hyperphenylalaninemic mothers had normal head circumferences and no gross congenital anomalies, but their birth weights were low, and they had learning defects. Rats with hyperphenylalaninemia induced during pregnancy bore offspring with an impaired maze learning ability and low birth weight. Fetal body weights and brain weights were lower in hyperphenylalaninemic pregnancies. The hyperphenylalaninemia induced by administration of phenylalanine to preg-
nant animals is not only transferred to the fetus but magnified in the fetus. Phenylalanine levels in fetal brain are markedly elevated. In rat fetuses this excess phenylalanine in the brain is accompanied by an increased level of brain glycine, leading Brass et al. to propose that increased cerebral glycine mediates the effect of maternal hyperphenylalaninemia on fetal brain similar to the cerebral toxicity of glycine in nonketotic hyperglycinemia.

Other theories of pathogenesis of the fetal brain defect in maternal hyperphenylalaninemia include inadequate sources of energy, deficient fetal brain uptake of tyrosine and tryptophan, and reduced protein synthesis in fetal brain because of ribosomal disaggregation. No convincing explanation exists, however, for the pathogenesis of all the fetal effects of human maternal PKU.

Management of Maternal PKU

Reducing the maternal blood phenylalanine level by dietary treatment during pregnancy offers some protection to the fetus, especially if the diet begins before conception. Careful planning of pregnancy and compliance with this difficult diet, however, require an unusual degree of understanding and participation by the young woman with PKU and her family.

The first step in this process is education. This is best accomplished in a PKU clinic setting with a specific program devoted to maternal PKU. The names of appropriate centers can be obtained from the authors or by contacting Dr. Richard Koch, Director of the Maternal PKU Collaborative Study, Children's Hospital of Los Angeles, P.O. Box 54700, Los Angeles, CA 90054, (213) 669-2238. A proper educational program includes information about the dangers to the fetus from untreated maternal PKU and the fetal protection offered by specific dietary treatment beginning before conception and continuing throughout pregnancy. It must also include sex education and information about family planning and the early recognition of pregnancy.

Genetic information should also be included in this education. The woman should know that she has two genes for PKU and will therefore transmit one of these genes to the conceptus. Her offspring will have PKU only if he or she receives a second PKU gene from the father. Thus the father must be a carrier of the PKU gene, or less likely, have PKU if the offspring of a maternal PKU pregnancy is to have PKU. This necessarily limits the probability that the offspring will have PKU, perhaps to 10% or less. Most important, the young woman with PKU should understand that these considerations relate only to whether the offspring will have PKU and do not address the potential for fetal damage from maternal PKU, which is independent of fetal genotype.

The management of pregnancy in a woman with PKU includes not only routine prenatal care but also specific treatment for maternal PKU in collaboration with a PKU clinic. Prenatal vitamins should not be prescribed, since all except folic acid are provided in the special formula used to treat maternal PKU. Folic acid supplements must be provided separately.

The phenylalanine-restricted diet should begin as early as possible, preferably before conception. The purpose of this diet is to reduce the maternal blood phenylalanine concentration to a level considered safe for the fetus (240-600 μM; 4-10 mg/dl) and to eliminate urinary phenylketones and other phenylalanine metabolites. This diet combines low-protein foods, almost exclusively fruits and vegetables, and a special formula containing all amino

*Formulas available for the treatment of maternal PKU include: 1. PhenyI-Free (Mead Johnson Nutritional Division, Evansville, Ind) 2. Maxamum xP (Scientific Hospital Supplies, Gaithersburg, Md) 3. Milupa PKU 3 (Milupa Corp., Darien, Conn)
acids except phenylalanine. Thus the phenylalanine intake is strictly controlled by limiting the protein content of the diet, but adequate intake of protein equivalents is maintained through the ingestion of amino acids in the formula. The protein and energy needs of pregnancy, as well as the vitamin and mineral requirements, can be met by this diet provided that it is appropriately administered and monitored by frequent biochemical testing. This must be conducted in collaboration with a PKU clinic because these clinics can provide biochemical analyses, nutritional support, and the formula required for the management of pregnancy in these patients. The Maternal PKU Collaborative Study can provide all the necessary information about maternal PKU pregnancies and their treatment.

**Results of Treated Maternal PKU Pregnancies**

Experience with dietary treatment of 54 maternal PKU pregnancies (Table 3) suggests that dietary treatment is effective in improving the outcome of these pregnancies. It appears that the fetus is best protected if the maternal biochemical abnormalities are controlled by diet beginning before conception and continuing through pregnancy.²

Whether treatment that begins after conception also protects the fetus is unclear. As noted in Table 3, treatment initiated during the first trimester seems to result in normal birth weight, but microcephaly and congenital heart disease may still occur in a relatively high percentage of these offspring. The mental status of offspring from maternal PKU pregnancies not treated until after conception is still undetermined.

**Summary**

Maternal phenylketonuria is a new entity in obstetrics. If unrecognized and for this or other reasons untreated, it produces a substantial risk for fetal damage. Our knowledge of the pathophysiology of the fetal complications in maternal PKU is very limited, but the degree of maternal hyperphenylalaninemia seems to be important. The management differs from the other high-risk pregnancies in the need for a special diet beginning before conception. An effective program of dietary therapy designed in collaboration with a PKU clinic will reduce the likelihood of fetal damage and improve pregnancy outcome.

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<table>
<thead>
<tr>
<th>TABLE 3. Results of Treated Maternal PKU Pregnancies²⁰²⁰</th>
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<tr>
<td><strong>Relation to Conception</strong></td>
</tr>
<tr>
<td><strong>Trimester</strong></td>
</tr>
<tr>
<td><strong>Before</strong></td>
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<tr>
<td>No. studies</td>
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<tr>
<td>IQ or DQ</td>
</tr>
<tr>
<td>Microcephaly</td>
</tr>
<tr>
<td>Congenital heart disease</td>
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<tr>
<td>BW &lt;2,500 g</td>
</tr>
</tbody>
</table>

*One offspring was stillborn.
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