Maternal Phenylketonuria

Committee on Genetics

ABSTRACT

Elevated maternal phenylalanine concentrations during pregnancy are teratogenic and may result in growth retardation, microcephaly, significant developmental delays, and birth defects in the offspring of women with poorly controlled phenylketonuria during pregnancy. Women of childbearing age with all forms of phenylketonuria, including mild variants such as mild hyperphenylalaninemia, should receive counseling concerning their risks for adverse fetal effects, optimally before conceiving. The best outcomes occur when strict control of maternal phenylalanine concentration is achieved before conception and continued throughout pregnancy. Included are brief descriptions of novel treatments for phenylketonuria. Pediatrics 2008;122:445–449

BACKGROUND

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism associated with deficient activity of Phe hydroxylase (PAH) and elevated concentrations of Phe and Phe metabolites. Untreated PKU is characterized by severe to profound intellectual disability, seizures, autistic-like behaviors, microcephaly, rashes, hypopigmentation, and a musty body odor (phenylacetic acid). Hyperphenylalaninemia may be defined as having a blood Phe concentration above the reference range (31–110 μmol/L [0.51–1.8 mg/dL], depending on age). Different schemes exist for classifying subtypes of PKU on the basis of the severity of the clinical or biochemical and/or molecular phenotype.1–4 Patients have been classified as having mild hyperphenylalaninemia if their blood Phe concentration without dietary therapy is elevated but less than 600 μmol/L (10 mg/dL).2 Classic PKU is characterized by a Phe concentration higher than 1200 μmol/L (20 mg/dL) while receiving a normal dietary intake of protein.3 “Variant” or “atypical” forms of PKU (600–1200 μmol/L [10–20 mg/dL] that do not fit the mild or classic descriptions also exist, although there is not yet a universally accepted definition of these variant forms. In rare cases, an elevated blood Phe concentration may be caused by inherited disorders of the biosynthesis or recycling of tetrahydrobiopterin (BH4), a cofactor in the PAH reaction.

Since the 1960s, newborn screening for PKU has allowed early detection and treatment of the disorder, preventing untoward consequences. Standard current treatment consists of selectively restricting intake of Phe and supplementing tyrosine (the product of normal PAH activity) by using special medical foods that are devoid of or low in Phe while providing enough additional protein, vitamins, and minerals to support normal growth. With good control of Phe concentrations during early childhood, most affected children have normal development measured at 5 years of age. Recommendations for dietary therapy have evolved as experience with different regimens and durations of therapy have accumulated. In earlier therapeutic protocols, treatment was only continued through the first few years of life, theoretically corresponding to the age at which brain myelination is complete. As developmental data accumulated, it became evident that treatment throughout childhood and adolescence was the best course for preserving intelligence. In more recent studies, it has been shown that brain MRI abnormalities and electrophysiologic testing abnormalities referable to the central nervous system are observed in adults who are on unrestricted Phe intake. Accordingly, it is reasonable to continue treatment into adulthood, and most centers recommend lifelong treatment. Strict adherence to the PKU diet is especially important for women during their reproductive years because of the risks to the fetus.

Adults with classic PKU who had good control as children typically have normal intelligence or mild degrees of intellectual deficit. Careful psychometric testing of well-treated individuals has detected instances and degrees of impairment in visual motor skills, abstract reasoning, problem solving, specific aspects of executive control, attention, verbal memory, expressive naming, and verbal fluency,3 although overall IQ may still be within the reference range. One possible explanation for these neuropsychologic impairments invokes mid-dorsolateral prefrontal cortex dys-
function caused by abnormal catecholamine concentrations. Another theory suggests that abnormal brain myelinization and deficiency of brain large neutral amino acids may play a role in impaired cognition.

In addition, emotional disorders (depression, anxiety, phobias), as well as hyperactive behaviors, are encountered more frequently in individuals treated for classic PKU than in the general population. However, people with untreated mild hyperphenylalaninemia do not seem to be at risk of developing neuropsychologic impairment.

Poor dietary adherence leads to blood Phe concentrations above the current recommended therapeutic range. High blood Phe concentrations in people who have discontinued their special diets often result in a decrease in IQ, learning disabilities, behavioral problems, and even neurologic complications. White matter abnormalities may develop in people with PKU who have poor dietary control. MRI of the brain may detect dysmyelination, especially T2 enhancement in the periventricular white matter in individuals with PKU who are under poor dietary control. Abnormal areas of white matter may also demonstrate restricted diffusion of water, possibly indicative of increased myelin turnover. These findings are potentially reversible once proper dietary therapy is reinstituted.

During pregnancy, Phe crosses the placenta by active transport, resulting in 70% to 80% increased fetal concentration of Phe compared with maternal concentration. An elevated Phe concentration is toxic and teratogenic to a developing fetus. Abnormalities in the children of women with uncontrolled PKU during pregnancy were first reported by Dent in 1957 and Mabry et al in 1963. The international survey of women with PKU, the results of which were published in 1980, documented an increased risk of spontaneous miscarriage (24%), intrauterine growth retardation (40%), microcephaly (73%), global developmental delays (92%), and congenital heart defects (12%) in their offspring. Postnatal growth retardation, abnormal neurologic findings, and mild craniofacial dysmorphic features also have been reported. The frequency of abnormalities seems to be directly correlated with maternal Phe concentration during pregnancy. Poor fetal growth, microcephaly, and structural heart defects also are more likely to occur if there was “lack of control” of maternal Phe concentrations during critical periods of embryogenesis early in pregnancy.

The Maternal Phenylketonuria Collaborative Study, sponsored by the National Institute of Child Health and Human Development, began in the United States in 1984 to determine fetal outcomes with improved control of maternal Phe concentrations during pregnancy. This study became an international effort with participating clinics in Canada and Germany since 1985 and 1991, respectively. The National Institutes of Health consensus conference on PKU in 2000 emphasized the importance of dietary control before conception. This international effort was completed in 2002 and culminated with the International Conference on Maternal Phenylketonuria in April 2002, which provided clear guidelines for the management of pregnancy in women with PKU. The study has provided essential information regarding the effective treatment of women with PKU. This information is now available for clinicians to impart to their patients with PKU to ensure that women with PKU know their risk and how they may be able to have healthy children with timely and appropriate intervention.

The effects of uncontrolled maternal PKU occur regardless of whether the fetus has PKU. The best observed outcomes occur when strict control of maternal blood Phe concentration is instituted before pregnancy or by 8 weeks of gestation at the latest. Women with PKU who have their blood Phe concentration in good control before conception have an excellent chance for normal pregnancies and neonatal outcome. The achievement of preconceptional and periconceptional dietary control with a Phe-restricted diet significantly decreases the risk of microcephaly, intrauterine growth retardation, congenital heart disease, and developmental delays in the offspring of women with hyperphenylalaninemia.

Normal pregnancy and neonatal outcome have been achieved in women with PKU who have blood Phe concentrations between 120 and 360 μmol/L before conception or by 8 weeks of gestation at the latest.

Before conception, counseling and early entrance into a prenatal care program are essential for achieving optimal fetal outcome for women with PKU, variant PKU, and mild hyperphenylalaninemia. It is acknowledged that reinstitution of a Phe-restricted diet and supplements is difficult. Because many pregnancies are unintended, dietary control throughout the childbearing years is essential for preventing an adverse effect on the fetus. The currently recommended Phe concentrations during pregnancy (120–360 μmol/L [2–6 mg/dL] in the United States) are consistent with those currently recommended for PKU treatment during early childhood. Achieving this degree of control requires a major commitment by the woman and support by her treating professionals. The recommendations for maternal control are based on maternal Phe concentration, as opposed to the genotype or severity of the mother’s metabolic condition. In 1 study, the IQs of offspring exposed to high concentrations of maternal Phe during pregnancy (>750 μmol/L) were low (mean IQ: 56) and similar whether the mother had PKU or hyperphenylalaninemia and regardless of the genotype, whereas offspring had normal cognitive development (mean IQ: 105) when their average exposure to Phe concentration during pregnancy was less than 360 μmol/L.

Dietary control for adults with PKU is challenging. Although low-Phe flour, pastas, cookies, and nutrition bars have increased dietary options for patients, the PKU diet remains bland, so poor dietary adherence continues to be a major problem. In addition to considerations about the palatability of the PKU diet, economic and health care system issues may contribute to barriers to dietary control. In 1 study that examined impediments to successful dietary control, women with private insurance identified infrequent assistance with the cost of medical food and beverages and low-protein foods as a...
barrier, despite the existence of US public law defining the formula as medical foods.\textsuperscript{26} Public assistance programs provided more coverage for the cost of the medical foods, clinic visits, and low-protein foods.\textsuperscript{26} However, these women were less likely to achieve metabolic control before 10 weeks’ gestation. Brown et al\textsuperscript{26} believed this may reflect that many women enrolled in public assistance programs were younger and less educated, which are factors associated with late control. Adolescent girls with PKU who become pregnant are at particular risk of not having dietary control until late in their pregnancy, given their young age and the higher risk of unplanned pregnancy.

The National Institutes of Health consensus guidelines recommend that pregnant women with PKU have their Phe concentrations monitored twice weekly.\textsuperscript{1} Frequent visits to clinicians who specialize in treating PKU are also recommended for pregnant women with PKU. However, given the limited number of specialist centers, especially centers skilled at caring for adults, there may be a need to travel relatively long distances to obtain appropriate management. Such barriers to access challenge patients to comply with the frequency recommendations for PKU monitoring. In addition, psychosocial, emotional, and social factors contribute to the barriers for successful control of PKU during pregnancy.\textsuperscript{26}

All offspring of mothers with PKU will inherit at least 1 abnormal allele at the \textit{PAH} locus from the affected mother. Affected mothers have 2 \textit{PAH} mutations, either in a homozygous (2 identical mutations) or compound heterozygous (2 different mutations) state. Depending on the \textit{PAH} carrier status of the father, approximately 1 in 120 offspring will also inherit an abnormal \textit{PAH} gene from the father and will have PKU.

A number of novel therapies are being developed for treatment of PKU, including large neutral amino acid supplementation, BH\textsubscript{4} administration, and enzyme therapy using Phe ammonia lyase (PAL). Large neutral amino acids compete with Phe for transport across the blood-brain barrier by the \textit{l}-type amino acid carrier and consequently decrease the concentration of Phe in the central nervous system.\textsuperscript{27} Decreased brain Phe concentration, as measured by proton magnetic resonance spectroscopy, and increased blood concentrations of tyrosine and tryptophan (the respective precursors for dopamine and serotonin) were noted in 1 clinical trial using large neutral amino acid supplements.\textsuperscript{28} Oral BH\textsubscript{4}, the naturally occurring cofactor to the PAH reaction, has been shown to decrease serum Phe concentrations, especially in patients with mild hyperphenylalaninemia.\textsuperscript{29,30} Response to BH\textsubscript{4} has also been documented in patients with classic or variant PKU.\textsuperscript{30,31} Another novel therapeutic approach uses the nonmammalian enzyme PAL. PAL converts Phe to transcinnamic acid, a harmless compound, and has been shown to reduce hyperphenylalaninemia in animal models of PKU.\textsuperscript{32} PAL therapy has the theoretic potential to increase dietary Phe tolerance, but significant practical hurdles need to be overcome (PAL is destroyed by gastric acidic pH and intestinal proteolysis). Although these are exciting developments, they are not currently approved for use during pregnancy, so the role that such therapies may play in reducing the risk of maternal PKU syndrome is still to be determined.

**RECOMMENDATIONS**

The recommendations of the American Academy of Pediatrics reflect the guidelines of the Maternal Phenylketonuria Collaborative Study of the National Institutes of Health.\textsuperscript{3,19} These recommendations are to be applied to individual patients and their particular care plan with the guidance of their primary care physician in coordination with the patient’s metabolic expert physician.

1. All girls and women of childbearing age with elevated Phe concentrations, including those with PKU and milder forms of hyperphenylalaninemia, should be counseled concerning their risks of having an adverse fetal outcome if they have uncontrolled blood Phe concentrations during pregnancy. Education regarding the risks of maternal PKU should begin when an infant is diagnosed with PKU in the newborn period. We recommend that the pediatrician include this information again in anticipatory guidance counseling during preadolescence and adolescence for girls with PKU. All individuals, particularly women and girls of childbearing age, should be referred to an experienced PKU treatment center for genetic and nutritional evaluation and counseling throughout their lifetime.

2. Women with hyperphenylalaninemia who are unable or unwilling to maintain blood Phe concentrations in the range for optimum pregnancy outcome should be counseled before conception regarding the risk of microcephaly, mental retardation, and fetal anomalies in their offspring. Emphasis should also be placed on the education that structural defects, such as congenital heart disease, are associated with poor control early in pregnancy. Dietary therapy should be in place before conception to ensure optimal outcome for the fetus. It is important that these women receive assistance to obtain adequate means for access to reproductive services.

3. Genetic counseling should be offered for all women with PKU before and after conception. Pregnant women with hyperphenylalaninemia should be counseled concerning the risks to the fetus and offered detailed ultrasonographic examinations and fetal echocardiography to detect fetal abnormalities (eg, growth retardation, congenital heart defects). Consideration should be given to maternal Phe concentrations during critical time periods of organogenesis. It is equally important that these women obtain assistance in locating centers with skilled clinicians who are able to provide medical care for pregnant women with PKU.

4. Mothers who give birth to children with features suggestive of maternal PKU, such as congenital heart disease, microcephaly, and suggestive facial dysmorphic features without a known cause, should undergo blood testing for hyperphenylalaninemia. The Phe level of a newborn of a mother with PKU is usually
normal. Consideration should also be given to other teratogenic causes, such as maternal diabetes mellitus, alcohol abuse, or use of isotretinoin. In addition, mothers should be considered for PKU testing if their infants have an initial elevation of Phe concentration on newborn screening that resolves.

5. Pediatricians should work with the families of people with PKU to ensure access to social services, medical foods, and routine reliable visits to a center with expertise in caring for people with metabolic disorders.

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Pediatrics 2008;122;445
DOI: 10.1542/peds.2008-1485

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*Pediatrics* 2008;122;445
DOI: 10.1542/peds.2008-1485

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