Maternal Phenylketonuria

ABSTRACT. Elevated maternal phenylalanine levels during pregnancy are teratogenic and may result in growth retardation, significant psychomotor handicaps, and birth defects in the offspring of unmonitored and untreated pregnancies. Women of childbearing age with all forms of phenylketonuria, including mild variants such as hyperphenylalaninemia, should receive counseling concerning their risks for adverse fetal effects optimally before conceiving. The best outcomes occur when strict control of maternal phenylalanine levels is achieved before conception and continued throughout the pregnancy.

ABBREVIATIONS. PKU, phenylketonuria; Phe, phenylalanine; PAH, phenylalanine hydroxylase.

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism associated with deficient activity of phenylalanine hydroxylase (PAH) and elevated levels of Phe and Phe metabolites. Untreated, the disorder results in severe to profound psychomotor handicaps, seizures, autistic-like behaviors, microcephaly, rash, pigment dilution, and unusual body odors. Since the 1960s, newborn screening for PKU has allowed early detection and treatment of the disorder. Current treatment consists of dietary therapy that uses special medical foods that are devoid of or low in Phe and that are supplemented with tyrosine, the product of PAH activity. Depending on the degree of control during early childhood, most affected children have psychomotor development comparable to that of their peers at school entrance. Although dietary control is recommended for life, loss of dietary compliance frequently starts during mid childhood. By late adolescence, many affected persons, including females capable of reproduction, have stopped using special medical foods, and most have blood Phe levels above the current recommended therapeutic range. Although efforts have been made to identify and maintain contact with older patients with PKU, especially females, many of them have been lost to follow-up.

Elevated Phe levels during pregnancy are teratogenic. Abnormalities in the children of women with uncontrolled PKU during pregnancy were first reported by Dent in 1957 and Mabry et al in 1963. A subsequent survey of these women revealed significantly increased risk for spontaneous miscarriage (24%); in their offspring, risk was increased for intrauterine growth retardation (40%), microcephaly (73%), psychomotor retardation (92%), and congenital heart defects (10%). Postnatal growth retardation, abnormal neurologic findings, and mild craniofacial dysmorphic features also have been reported. The frequency of abnormalities seems to be directly related to the degree of elevation of maternal Phe levels during pregnancy. Abnormalities also were more likely to occur if there was lack of control of maternal Phe levels during critical periods of embryogenesis and organogenesis early in pregnancy.

The Maternal Phenylketonuria Collaborative Study, sponsored by the National Institute of Child Health and Human Development, was started in the United States in 1984 to determine the fetal outcomes with improved control of maternal Phe levels during pregnancy. This ongoing study has become an international effort with participating clinics in Canada and Germany since 1985 and 1991, respectively. The best observed outcomes occur when strict control of the maternal blood Phe level is instituted before conception and continued throughout pregnancy. The currently recommended Phe levels of control during pregnancy (120–360 μmol/L [2–6 mg/dL]; 60–250 μmol/L [1–4 mg/dL]) are at least as strict, if not more strict, than that currently recommended for PKU treatment during early childhood. Achieving this degree of control requires major commitment by the woman and support by the treating professionals. As levels of Phe are higher in the fetus compared with levels in the mother because of a placental gradient favoring the fetus, women with relatively mild elevations of Phe, such as women with mild forms of PKU, also may be at risk for adverse fetal effects in unmonitored and untreated pregnancies.

The effects of uncontrolled maternal PKU are analogous to those seen with fetal alcohol exposure and occur regardless of the genetic PKU status of the fetus. All offspring of PKU mothers will carry at least 1 abnormal gene at the PAH locus, which they inherit from their homozygous affected mother. Depending on the PKU carrier status of the father, approximately 1 in 120 offspring will inherit an abnormal PAH gene from both parents and also have PKU.

RECOMMENDATIONS

1. All girls and women of childbearing age with elevated Phe levels, including those with PKU and milder forms of hyperphenylalaninemia, should be identified and counseled concerning their risks for maternal PKU fetal effects with uncontrolled...
blood Phe levels during pregnancy. The pediatrician should include this information in anticipatory guidance counseling during adolescence for girls with PKU. The women and girls also should be referred to an experienced PKU treatment center for genetic and nutritional evaluation and counseling, optimally before contemplating pregnancy.

2. Women with hyperphenylalaninemia who are unable or unwilling to maintain blood Phe levels in the range for optimum pregnancy outcome should be assisted to obtain adequate means for birth control, including tubal ligation if requested.

3. Women with hyperphenylalaninemia who conceive with blood Phe levels greater than 250 to 360 μmol/L (4–6 mg/dL) should be counseled concerning the risks to the fetus and offered detailed ultrasonography to detect fetal abnormalities (eg, growth retardation, congenital heart defects). Termination of pregnancy may be considered by those who conceive with blood Phe levels that are known to be associated with a high fetal risk (>900 μmol/L [>14.9 mg/dL]).

4. Women who give birth to children with features of maternal PKU fetal effects without a known cause should undergo blood testing for hyperphenylalaninemia.

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