Management of Women With Phenylalanine Hydroxylase Deficiency (Phenylketonuria)

ABSTRACT: Phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder of phenylalanine metabolism that is characterized by insufficient activity of PAH, a hepatic enzyme. Throughout this document, PAH deficiency is used instead of the older nomenclature of phenylketonuria, in order to reflect the spectrum of PAH deficiency and in accordance with the terminology established by the American College of Medical Genetics and Genomics. Aspects of PAH deficiency management that are particularly relevant to obstetrician–gynecologists or other obstetric care providers include the prevention of embryopathy associated with maternal hyperphenylalaninemia and PAH deficiency and the risk of genetic transmission of PAH deficiency. Family planning and prepregnancy counseling are recommended for all reproductive-aged women with PAH deficiency. The fetal brain and heart are particularly vulnerable to high maternal concentrations of phenylalanine. The crucial role played by maternal dietary restriction before and during pregnancy should be stressed in counseling patients with PAH deficiency; the goal should be to normalize blood phenylalanine levels (less than 6 mg/dL) for at least 3 months before becoming pregnant and to maintain at 2–6 mg/dL during pregnancy, in order to optimize developmental outcomes for the fetus. Although phenylalanine levels are increased in the breast milk of patients with PAH deficiency, breastfed infants who do not have PAH deficiency have normal enzyme levels and no dietary restriction. Breastfeeding is safe for infants born to women who have PAH deficiency provided the infants do not have PAH deficiency. Coordinated medical and nutritional care, as well as follow-up with the patient’s metabolic geneticist or specialist, are important in the postpartum period. Because newborns with PAH deficiency appear normal at birth and early detection can improve developmental outcomes for children, newborn screening for PAH deficiency is mandated in all states. This Committee Opinion has been revised to include updates on advances in the understanding and management of women with PAH deficiency and recommendations on prepregnancy counseling, serial fetal growth assessments, and fetal echocardiography.

Recommendations

The American College of Obstetricians and Gynecologists makes the following recommendations:

- Lifelong dietary restriction and therapy improve quality of life in patients with phenylalanine hydroxylase (PAH) deficiency and should be encouraged.
- Prepregnancy consultation with a maternal–fetal medicine specialist and genetic counseling, as well as co-management with a metabolic geneticist or specialist involved in the patient’s care, are recommended for all reproductive-aged women with PAH deficiency and should include information on reproductive options and family planning as well as management of maternal PAH deficiency before, during, and after pregnancy.
- It is recommended that phenylalanine levels less than 6 mg/dL be achieved for at least 3 months before becoming pregnant and maintained at 2–6 mg/dL during pregnancy.
Pregnant women with PAH deficiency or hyperphenylalaninemia should be monitored in consultation with physicians familiar with PAH deficiency, with close follow-up with a metabolic geneticist and health care providers with experience in managing high-risk pregnancy.

- A detailed anatomic survey and fetal growth assessments are recommended for the detection of fetal anomalies and growth restriction in a pregnant woman with PAH deficiency.

- Fetal echocardiography is indicated to evaluate for congenital heart defects for those pregnancies of a woman with PAH deficiency.

- Breastfeeding is safe for infants born to women who have PAH deficiency provided the infants do not have PAH deficiency.

**Introduction**

This Committee Opinion has been revised to include updates on advances in the understanding and management of women with PAH deficiency and recommendations on prepregnancy counseling, serial fetal growth assessments, and fetal echocardiography. Throughout this document, PAH deficiency is used instead of the older nomenclature of phenylketonuria, in order to reflect the spectrum of PAH deficiency and in accordance with the terminology established by the American College of Medical Genetics and Genomics (1).

Phenylalanine hydroxylase deficiency is an autosomal recessive disorder of phenylalanine metabolism that is characterized by insufficient activity of PAH, a hepatic enzyme. This enzyme is responsible for the conversion of phenylalanine to tyrosine, and the lack of the enzyme causes elevated levels of phenylalanine, which produces a spectrum of disorders that range from classic presentation (formerly referred to as phenylketonuria) to mild hyperphenylalaninemia. As a result, individuals with PAH deficiency cannot tolerate typical dietary intake of phenylalanine. If excessive phenylalanine is consumed, the resultant increased blood phenylalanine levels are toxic to a variety of tissues, particularly the developing fetal brain and heart. More than 600 variants in the PAH gene have been described (1). As many as 50% of patients with PAH deficiency have a PAH gene variant whose activity may be improved by supplementation with tetrahydrobiopterin (BH4) (1). This would be evaluated in the course of PAH deficiency diagnosis and alternative treatments, which are beyond the scope of this document. The range of clinically significant outcomes depends on the degree of PAH deficiency. The mainstay of treatment for PAH deficiency is the dietary restriction of phenylalanine, which results in decreased blood phenylalanine levels.

Because newborns with PAH deficiency appear normal at birth and early detection can improve developmental outcomes for children, newborn screening for PAH deficiency is mandated in all states. Optimally, treatment of neonates diagnosed with classic PAH deficiency should be initiated within the first week of life (1). Historically, children diagnosed with classic PAH deficiency were allowed to relax their dietary restriction of phenylalanine in adolescence. This is no longer recommended for patients with classic PAH deficiency because it has been demonstrated that lifelong dietary therapy improves quality of life (1). Increased phenylalanine levels in adulthood have been associated with significant adverse neurocognitive and psychiatric problems, including anxiety, depression, phobias, and deficits in executive functioning (1).

Aspects of PAH deficiency management that are particularly relevant to obstetrician–gynecologists or other obstetric care providers include the prevention of embryopathy associated with maternal hyperphenylalaninemia and PAH deficiency and the risk of genetic transmission of PAH deficiency. The challenge of identifying and educating women about dietary restriction before pregnancy is highlighted by a study that found 64% of women at risk for embryopathy were unable to achieve blood phenylalanine control by 8 weeks of gestation (2). Family planning and prepregnancy counseling are recommended for all reproductive-aged women with PAH deficiency. The crucial role played by maternal dietary restriction before and during pregnancy should be stressed in counseling patients with PAH deficiency; the goal should be to normalize blood phenylalanine levels (less than 6 mg/dL) for at least 3 months before becoming pregnant, and to maintain at 2–6 mg/dL during pregnancy, in order to optimize developmental outcomes for the fetus.

**Lifelong Management Issues**

Lifelong dietary restriction and therapy improve quality of life in patients with PAH deficiency and should be encouraged (1). Although evidence suggests that women with PAH deficiency will benefit from remaining on a phenylalanine-free diet throughout their lives, many patients find the diet difficult to adhere to because of a variety of socioeconomic factors, as well as the unpalatable nature of many phenylalanine-free products.

The barriers women face in adhering to dietary modification as well as the high rate of unplanned pregnancies in the United States represent an important public health challenge due to the significant adverse fetal consequences of maternal hyperphenylalaninemia.

Prepregnancy consultation with a maternal–fetal medicine specialist and genetic counseling, as well as co-management with a metabolic geneticist or specialist involved in the patient’s care, are recommended for all reproductive-aged women with PAH deficiency and should include information on reproductive options and family planning as well as management of maternal PAH deficiency before, during, and after pregnancy. It is recommended that phenylalanine levels less than 6 mg/dL be achieved for at least 3 months before becoming pregnant and maintained at 2–6 mg/dL during pregnancy.
Approximately 40% of young adults with PAH deficiency develop osteopenia (3). Although the etiology of the osteopenia is unclear, screening for abnormal bone mineralization may be considered.

**Prevention of Embryopathy Associated With Maternal Hyperphenylalaninemia**

The success of newborn screening and early treatment of PAH deficiency has resulted in a substantial number of women with PAH deficiency achieving reproductive age and pregnancy. The fetal brain and heart are particularly vulnerable to high maternal concentrations of phenylalanine. The levels of phenylalanine in fetal blood are higher than would be expected based on the maternal blood levels because phenylalanine crosses the placenta by an active transport process. Children born to women who have PAH deficiency on unrestricted diets have a 92% risk of developmental delays, a 73% risk of microcephaly, and a 12% risk of congenital heart defects as well as growth delay and seizures (4).

Pregnant women with PAH deficiency or hyperphenylalaninemia should be monitored in consultation with physicians familiar with PAH deficiency, with close follow-up with a metabolic geneticist and health care providers with experience in managing high-risk pregnancy. Prepregnancy carrier screening of the partner and prenatal genetic testing should be made available. If phenylalanine levels are maintained at 2–6 mg/dL before pregnancy or by 8 weeks of gestation, there is evidence to suggest a reduction in the fetal sequelae of hyperphenylalaninemia (5). Because the fetal heart develops by 8–10 weeks of gestation, metabolic control achieved later may not decrease the risk of cardiac malformations (1). Reduction of the maternal blood phenylalanine level to 10 mg/dL or less decreases the incidence of microcephaly from 73% to 8% (6). In addition to complications with excessive phenylalanine, there are data to suggest that markedly low maternal phenylalanine levels, especially during the second and third trimesters, may be associated with intrauterine growth restriction (7). Therefore, a detailed anatomic survey and fetal growth assessments are recommended for the detection of fetal anomalies and growth restriction in a pregnant woman with PAH deficiency. Fetal echocardiography is indicated to evaluate for congenital heart defects for those pregnancies of a woman with PAH deficiency. Fetal echocardiography is indicated to evaluate for congenital heart defects for those pregnancies of a woman with PAH deficiency. If an infant is known to have PAH deficiency, breastfeeding should be recommended only in consultation with a pediatrician who has expertise caring for children with PAH deficiency (8).

**Risk of Genetic Transmission of Phenylalanine Hydroxylase Deficiency**

The incidence of PAH deficiency in a population is reported to vary by ethnicity and ranges from 1 in 2,600 (Turkey) to 1 in 10,000 (Northern European origin) and 1 in 200,000 (Finnish) (9). Phenylalanine hydroxylase deficiency is an autosomal recessive disorder and the carrier frequency for PAH deficiency depends on ethnicity but is approximately 1 in 50 in those of Northern European descent (9). All offspring of women with PAH deficiency will minimally be obligate carriers. Prepregnancy carrier screening is recommended for the partner of a patient with PAH deficiency. With both parental and maternal genotype, accurate risk for offspring can be determined. Many of the expanded carrier screening panels include screening for PAH deficiency (although they will not detect all of the PAH gene variants), and consultation with a health care provider with genetic expertise is recommended. Patients with a family member with PAH deficiency should be offered genetic counseling to discuss reproductive risk and appropriate testing options. Prenatal and prepregnancy genetic testing is available if familial mutations are known. Detection of fetal PAH variants in cell-free DNA is not recommended (10). Phenylalanine hydroxylase deficiency is included on statewide newborn screening panels in all 50 states.

**References**


5. Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia. An international survey of the outcome


