



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

# COMMITTEE OPINION

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(Replaces Committee Opinion Number 449, December 2009)

## Committee on Genetics

*This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

## Management of Women With Phenylketonuria

**ABSTRACT:** Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism characterized by deficient activity of the hepatic enzyme, phenylalanine hydroxylase. Increased blood Phe levels are toxic to a variety of tissues, particularly the developing fetal brain. The mainstay of treatment for PKU is the dietary restriction of Phe, which results in decreased blood Phe levels. Lifelong dietary restriction and therapy improves quality of life in patients with PKU and should be encouraged. Genetic counseling is recommended for all reproductive-aged women with PKU, and should include information on reproductive choices and family planning as well as management of maternal PKU. If possible, pregnant women with PKU or hyperphenylalaninemia should be monitored in consultation with practitioners from experienced PKU centers. Optimally, treatment of neonates diagnosed with PKU should be initiated within the first week of life. All unaffected children of women with PKU are carriers and should receive genetic counseling when they are able to understand the consequences. Consultation with a genetics professional to discuss reproductive options is recommended.

### Recommendations

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

- Lifelong dietary restriction and therapy improves quality of life in patients with phenylketonuria (PKU) and should be encouraged.
- Genetic counseling is recommended for all reproductive-aged women with PKU, and should include information on reproductive choices and family planning as well as management of maternal PKU.
- It is recommended that phenylalanine (Phe) levels less than 6 mg/dL be achieved for at least 3 months before conception and maintained at 2–6 mg/dL during pregnancy.
- Assessment of the early risk of osteopenia should be considered in affected individuals.
- Coordinated medical and nutritional care is important in the postpartum period.
- If possible, pregnant women with PKU or hyperphenylalaninemia should be monitored in consultation with practitioners from experienced PKU centers.
- Breastfeeding is safe for women with PKU as long as their infant does not have PKU.
- Despite the limited data, in women who are responsive to coenzyme tetrahydrobiopterin (BH<sub>4</sub>), sapropterin supplementation may be appropriate as an adjunct to dietary therapy.

### Introduction

The 2009 version of this Committee Opinion was revised because there have been advances in the understanding of maternal PKU. These include the importance of life-long treatment of patients with PKU, the acceptability of breastfeeding, and the potential benefit of supplementation with BH<sub>4</sub>.

Phenylketonuria is an autosomal recessive disorder of Phe metabolism characterized by deficient activity of the hepatic enzyme, phenylalanine hydroxylase (PAH). This enzyme is responsible for the conversion of Phe to tyrosine, and the lack of the enzyme causes elevated levels of Phe. The resultant increased blood Phe levels are toxic to a variety of tissues, particularly the developing fetal brain. More than 600 mutations of the PAH gene have been described (1). As many as 50% of patients with PKU

have a PAH variant whose activity may be improved by supplementation with BH<sub>4</sub> (1).

The mainstay of treatment for PKU is the dietary restriction of Phe, which results in decreased blood Phe levels. Because affected newborns with PKU appear normal at birth, newborn screening for PKU is mandated in all states and has facilitated early detection of newborns affected with PKU.

Optimally, treatment of neonates diagnosed with PKU should be initiated within the first week of life (1). Historically, children diagnosed with PKU were allowed to relax the dietary restriction of Phe in adolescence, however, it has been demonstrated that lifelong dietary therapy improves quality of life. Increased Phe levels in adulthood have been associated with significant adverse neurocognitive and psychiatric problems, including anxiety, depression, phobias, and deficits in executive functioning (1).

### **Lifelong Management Issues**

Lifelong dietary restriction and therapy improves quality of life in patients with PKU and should be encouraged. Genetic counseling is recommended for all reproductive-aged women with PKU, and should include information on reproductive choices and family planning as well as management of maternal PKU (2). It is recommended that Phe levels less than 6 mg/dL be achieved for at least 3 months before conception and maintained at 2–6 mg/dL during pregnancy. Although evidence suggests that women with PKU will benefit from remaining on a Phe-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 Phe-free products. The failure of young women with PKU to adhere to dietary modification represents a significant public health challenge because of the significant fetal consequences of maternal hyperphenylalaninemia as well as the high rate of unplanned pregnancies in the United States. The challenge of identifying and educating women about dietary restriction before conception is highlighted by a study that found 64% of women failed to achieve blood Phe control by 8 weeks of gestation (3). Family planning and preconception counseling should be made available to all reproductive-aged women with PKU. The crucial role played by dietary restriction should be stressed in the patient with PKU, preferably 3 months before conception, to normalize the blood Phe levels and optimize developmental outcomes for the fetus.

Approximately 40% of young adults with PKU develop osteopenia (4). Although the etiology of the osteopenia is unclear, screening for abnormal bone mineralization may be considered. Optimal screening for treatment for osteopenia in these women has not been determined. Assessment of the early risk of osteopenia should be considered in affected individuals. Aspects

of PKU management that are particularly relevant to obstetrician–gynecologists or other obstetric providers include the prevention of fetal embryopathy associated with maternal hyperphenylalaninemia and PKU and the risk of genetic transmission of PKU.

### **Prevention of Fetal Embryopathy Associated With Maternal Hyperphenylalaninemia**

In the United States, the prevalence of PKU is approximately 1 per 15,000 births (5). The success of newborn screening and early treatment of girls with PKU has resulted in a significant number of women with PKU achieving reproductive age and pregnancy. The fetal brain and heart are particularly vulnerable to high concentrations of blood Phe. The levels of Phe in fetal blood are higher than would be expected based on the maternal blood levels because Phe crosses the placenta by an active transport process. Children born to women with PKU 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 (6).

If Phe levels are maintained at 2–6 mg/dL before conception or by 8 weeks of gestation, there is evidence to suggest a reduction in the fetal sequelae of hyperphenylalaninemia (7). Reduction of the maternal blood Phe level to 10 mg/dL or less decreased the incidence of microcephaly from 73% to 8% (8). Because the fetal heart develops by 8–10 weeks of gestation, metabolic control achieved later may not decrease the risk of congenital heart defects (1).

Coordinated medical and nutritional care is important in the postpartum period. If possible, pregnant women with PKU or hyperphenylalaninemia should be monitored in consultation with practitioners from experienced PKU centers. Although Phe levels are increased in the breast milk of patients with PKU, their breastfed infants have normal Phe levels. Breastfeeding is safe for women with PKU as long as the infant does not have PKU. If the infant is known to be affected and the patient desires breastfeeding, this should be done in consultation with their physician (9).

In some patients with some limited PAH enzyme activity, who are more mildly affected, supplementation with BH<sub>4</sub> will significantly reduce blood Phe levels. Furthermore, approximately 2% of patients that present with elevated Phe levels will have a primary BH<sub>4</sub> co-factor deficiency. Therefore, the use of sapropterin dihydrochloride (sapropterin), a biologically active synthetic form of BH<sub>4</sub> is a promising adjunct to diet in some patients with PKU. Published clinical data on the safety and efficacy of sapropterin use in pregnancy, however, are limited to a small number of patients at present (10). Despite the limited data, in women who are responsive to BH<sub>4</sub>, sapropterin supplementation may be appropriate as an adjunct to dietary therapy.

## Risk of Genetic Transmission of Phenylketonuria

All offspring of women with PKU will carry at least one abnormal gene for PKU, which is inherited from their homozygous-affected mother. The carrier frequency for PKU is approximately 1 in 60. Given an affected mother, approximately 1 in 120 children will inherit an abnormal *PAH* gene from both parents and will be affected with PKU. All unaffected children of women with PKU are carriers and should receive genetic counseling when they are able to understand the consequences. Consultation with a genetics professional to discuss reproductive options is recommended.

## Resources

*The following resources are for information purposes only. Referral to these sources and does not imply the endorsement of the American College of Obstetricians and Gynecologists. These resources are not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.*

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