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Psychosocial issues and outcomes in maternal PKU ☆

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ABSTRACT

Elevated phenylalanine (Phe) levels in pregnant women with PKU are teratogenic. Fetal damage due to elevated maternal Phe levels during pregnancy is known as maternal phenylketonuria (MPKU). The risk of birth defects in MPKU, including global developmental delays, microcephaly, congenital heart disease, and low birth weight, can be dramatically reduced by controlling Phe levels during pregnancy (metabolic control). Phe levels should be maintained in the range of 120–360 μmol/L, ideally starting before pregnancy begins (i.e., when planning a pregnancy). If control is not achieved before pregnancy (e.g., if the pregnancy was unplanned), good outcomes are still possible if metabolic control is established by 8 weeks of pregnancy. Unfortunately, metabolic control before and during pregnancy can be poor. As well, many mothers stop treatment after pregnancy, which can decrease the mother's ability to focus on her child and increase her risk of behavioral and psychological problems. This can have a negative effect on the home environment. Many factors affect adherence to the strict diet used to control Phe levels, including poor access to medical care, lack of reimbursement for medical foods (in some regions, such as parts of the United States), practical difficulties with implementing the diet, financial constraints, demographics, and psychosocial issues. A comprehensive treatment approach that begins prior to pregnancy and continues after the infant is born may help to improve the management of MPKU. This approach should include education of girls about MPKU at an early age, interventions to prevent unplanned pregnancies, psychosocial support, improved treatment access and reimbursement for medical foods, and treatment guidelines. Treatments such as sapropterin may also have a role in improving metabolic control during pregnancy.

Introduction

Phenylketonuria (PKU[1]; OMIM 261600 and 261630) is an inherited metabolic disorder associated with a deficiency in phenylalanine hydroxylase (PAH; EC 1.14.16.1), the enzyme that metabolizes phenylalanine (Phe) to tyrosine. PKU causes elevated Phe levels which, if left uncontrolled, can lead to intellectual disability, seizures, microcephaly, autistic-like behaviors, musty body odor, and eczema-like skin problems. Phe levels can be controlled with a Phe-restricted (low natural protein) diet supplemented with a special formula containing all the amino acids in natural protein, except for Phe.

Phe is actively transported across the placenta, reaching fetal concentrations that are 1.25–2.5 times greater than maternal concentrations [1]. Elevated Phe levels in a pregnant woman with PKU are teratogenic [2]. Fetal damage due to elevated maternal Phe levels during pregnancy is known as maternal phenylketonuria (MPKU) [3]. The problem of MPKU was originally described by Charles Dent [4] in the 1957 report of the 23rd Ross Conference. An international survey by Lenke and Levy [5] in 1980 reported that children of women with PKU had a high rate of birth defects, including global developmental delay (92%), microcephaly (73%), congenital heart disease (CHD, 12%), and low birth weight (40%). Other features of MPKU include postnatal growth retardation, mild craniofacial dysmorphism, and neurological abnormalities [2]. Prenatal Phe exposure, as with MPKU, is also associated with

☆ *References to electronic databases:* Phenylketonuria, OMIM 261600 and 261630. Phenylalanine hydroxylase, EC 1.14.16.1.
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[1] *Abbreviations used:* PKU, phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; MPKU, maternal PKU; CHD, congenital heart disease; ADHD, attention deficit hyperactivity disorder; ADD, attention deficit disorder inattentive-type; HOME, Home Observation for Measurement of the Environment; MPKUCS, Maternal PKU Collaborative Study; WAMPKUP, Western Australian Maternal PKU Program; IQ, intelligence quotient; CBCL, Child Behavior Checklist; DQ, developmental quotient; WISC-R, Wechsler Intelligence Scale for Children – Revised; MHP, mild hyperphenylalaninemia; FAS, fetal alcohol syndrome; BH_4, tetrahydrobiopterin; PAL, Phe ammonia lyase.

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hyperactive or impulsive-type symptoms of attention deficit hyperactivity disorder (ADHD) while postnatal exposure, as with PKU, is more likely to cause attention deficit disorder inattentive-type (ADD). This suggests that the timing of Phe exposure affects outcomes, which may be explained by the fact that different brain areas develop at different times [6,7].

The study by Lenke and Levy [5] stimulated the publication of studies in the United Kingdom by the Charles Dent Metabolic unit review of the PKU Registry [8] and the report of the United Kingdom Registry [9] as well as the efforts by the National Institutes of Health in the United States (US) [10] and by the Heidelberg group [11] headed by Horst Bickel in Germany. Recommendations of these three studies varied, but all highlighted improved outcome of maternal PKU pregnancies as an important public health issue.

The Maternal PKU Collaborative Study (MPKUCS) found that achieving early control of blood Phe levels dramatically reduced the risk of cognitive problems, microcephaly, and low birth weight. CHDs occurred in 2% of pregnancies among women who achieved metabolic control by 10 weeks of gestation compared to an overall study rate of 7%. One percent of pregnancies in non-PKU women result in CHD [12].

Ideally, to achieve optimal pregnancy outcome, women with PKU need to plan their pregnancies, attain metabolic control prior to pregnancy, and maintain their blood Phe levels within the recommended range of 120–360 μmol/L (2–6 mg/dL) throughout pregnancy [12].

While there is some difference of opinion as to what the exact range of blood Phe should be in the early weeks of pregnancy, there is no disagreement among professionals that maternal blood Phe levels greater than 360 μmol/L increase the risk of CHD and/or microcephaly in the offspring.

Delays in achieving metabolic control: relationship to worsening outcomes

The Western Australian Maternal PKU Program (WAMPKUP) studied 30 pregnancies and 16 live births. There were seven spontaneous abortions and seven elective terminations. In all 16 live births, mothers did not achieve metabolic control (Phe < 360 μmol/L) prior to pregnancy or even by 10 weeks of gestation. Only three women achieved control by 13 weeks, and four women by 26 weeks. The authors do not state when the others achieved metabolic control, only that they did not achieve control by 26 weeks of pregnancy. Therefore, they either did not achieve control at all or achieved control later than 26 weeks of pregnancy. There was a linear relationship between time to metabolic control and lower intelligence quotient (IQ) in the offspring, with a significant correlation between lower IQ scores and delayed metabolic control. Pregnancies with delayed control were also significantly more likely to result in offspring with behavioral problems (clinically significant behavior issues as rated by the Achenbach Child Behavior Checklist [CBCL]) [13].

Maillot et al. [14] conducted a retrospective review of outcomes in 105 children born to mothers with PKU in the United Kingdom (UK). They found that IQ and developmental quotient (DQ) at age 1 and age 8 were higher in children whose mothers started a Phe-restricted diet before pregnancy compared with those whose mothers started the diet after pregnancy began, at a mean gestational age of 10 weeks. Starting the diet before the beginning of pregnancy also reduced the risk of CHD (0% for the prior-to-pregnancy diet group vs. 12.5% for the group initiating diet 10 weeks after pregnancy began). Interestingly, they also found that variations in Phe level control (measured by the standard deviation of Phe values) had a strong negative correlation with IQ at 4, 8, and 14 years of age. This suggests that Phe levels should not only be controlled early, but also be controlled consistently throughout the pregnancy, avoiding fluctuations [14]. In the 572 pregnancies studied by the MPKUCS (an international study with a large number of American centers) [15], outcomes in terms of IQ, birth length, birth weight, and head circumference were similar between infants born to mothers who attained control prior to pregnancy and those who achieved metabolic control by 10 weeks of pregnancy. The mean offspring IQ was 105 for women who attained control before pregnancy began. For women who attained Phe levels of 120–360 μmol/L in the first 10 weeks of pregnancy, the mean offspring IQ was 104. For those who reached Phe levels of 360–600 μmol/L by 10 weeks of pregnancy, the mean offspring IQ was 100. In women who attained control (Phe 120–600 μmol/L) by 10–20 weeks of pregnancy, the mean offspring IQ was 93. This score was better than expected. These data may be useful to consider during genetic counseling for women who have had an unplanned pregnancy. However, there was a linear relationship between each of these parameters (IQ, birth length, birth weight, and head circumference) in the offspring and the number of weeks to metabolic control in the mother [12]. In a subset of 251 MPKUCS patients with diet analyses available, there were 85 infants born with microcephaly. Seventy-eight (92%) of these infants were born to women with blood Phe greater than 600 μmol/L at 8 weeks of gestation, while 7 (8%) of them were born to women with blood Phe levels less than 600 μmol/L at 8 weeks of pregnancy [16].

Tests of cognitive outcomes and behavior in children from the MPKUCS at 7 years of age showed that a variety of cognitive outcomes were negatively affected by delays in achieving metabolic control. These included memory, language, behavior, visual motor skills, and achievement. Children born to mothers with delayed control (after the first 10 weeks of pregnancy) had behavioral problems such as aggression, hyperactivity, and poor impulse control. Significantly more women in the group who attained control after 10 weeks of pregnancy compared to women who attained metabolic control earlier scored in the lowest quartile of the Home Observation for Measurement of the Environment (HOME) scale, measuring level of support and stimulation in the child's home [17,18]. The child's developmental outcome as measured by the WISC-R (Wechsler Intelligence Scale for Children – Revised) was correlated with weeks to maternal metabolic control ($r = -0.61$, $P < 0.0001$) [17].

Adequacy of a Phe-restricted diet for optimal fetal development – effects of Phe "spikes in early pregnancy

Temporarily high Phe levels ("spikes") and nutrition both play a role in MPKU [12]. In the MPKUCS, all infants with CHD were born to mothers with Phe levels >600 μmol/L in the first 8 weeks of pregnancy [19]. In these infants, CHD risk was significantly higher when the mother had an inadequate protein intake (less than 50% of the recommended daily allowance), compared to cases where the mother had an adequate protein intake [19]. Low protein intake was mainly due to a low intake of medical food [19,20]. Inadequate intakes of vitamin B_{12} and fat were also associated with a significantly increased CHD risk [19]. Compared to women who achieved metabolic control later than 10 weeks of pregnancy, women who achieved metabolic control (Phe < 360 μmol/L) in the first 10 weeks of pregnancy tended to have higher intakes of protein, fat, and energy. Increasing protein, fat, and energy intake may help to control Phe levels in cases where control is difficult to attain [21].

A substudy of the MPKUCS was conducted to evaluate the effect of the quality of dietary treatment and to investigate whether Phe spikes could pose a risk to the fetus during the first 20 weeks of

pregnancy even in well-treated mothers [22]. Data from 72 well-treated mothers (who were treated before pregnancy occurred and who achieved Phe levels of <10 mg/dL [600 μmol/L] during the first 5 weeks of gestation) were analyzed. Women were classified into three groups based on cluster analysis of median Phe levels: group 1 (excellent Phe control; average Phe exposure during pregnancy = 3.27 mg/dL, largest Phe spike = 5.96 mg/dL), group 2 (moderately good Phe control; average Phe exposure during pregnancy = 5.07 mg/dL, largest Phe spike = 11.84 mg/dL), and group 3 (poorest Phe control; average Phe exposure = 6.98 mg/dL, largest Phe spike = 14.89 mg/dL). All groups showed spikes in Phe levels at about 6–10 weeks of gestation. The spikes were most pronounced in group 3. Pregnancy weight gain was lowest in group 3 and highest in group 1. Groups 1 and 2 consumed more calories from fat than group 3 (the difference was small but statistically significant). Babies in groups 1 and 2 were significantly longer than those in group 3. Babies in group 1 had significantly larger head circumference measurements than those in groups 2 and 3. DQ (Bayley Mental Development Index) was significantly higher in group 1 vs. group 3, and IQ at 4 and 6 years (McCarthy for 4 years, WISC-R for 6 years) was significantly higher in groups 1 and 2 vs. group 3. The mother's IQ was the most significant predictor of IQ at age 6, followed by maternal Phe levels from 5 to 8 weeks of gestation (which is around the same period of time as the Phe spikes occur). The authors concluded that better quality dietary treatment in the first 20 weeks of pregnancy helps improve fetal outcomes, that spikes in Phe levels occur around 6–10 weeks of gestation even in the best controlled and most adherent mothers, and that there should be a focus on providing optimal nutrition and preventing weight loss during the first trimester, particularly for women with a low IQ [22].

Tyrosine supplementation in MPKU

PKU interferes with the metabolism of Phe to tyrosine, resulting in lower blood tyrosine levels. It has been proposed that some of the birth defects seen in MPKU may be related to low tyrosine levels, and that tyrosine supplementation during pregnancy may help improve fetal outcomes [23]. Tyrosine supplementation during pregnancy raises maternal tyrosine levels above the recommended minimum concentration (45 μmol/L) [23]. However, the MPKUCS found no relationship between offspring outcomes and maternal blood tyrosine levels before and during pregnancy [12]. Also, the safety of tyrosine supplementation during pregnancy has not been extensively studied. Tyrosine supplementation is not recommended as a substitute for a Phe-restricted diet [23,24].

Relationship between mother's PKU severity and offspring outcomes

In the MPKUCS, 62% of women had severe PKU, 19% had mild PKU, and 19% had mild hyperphenylalaninemia (MHP) [25]. Offspring of women with severe PKU may be at risk for poorer outcomes [26]. This is partly because it is more difficult for these women to achieve metabolic control during pregnancy [26,27]. They also experience more fluctuations in Phe levels (Phe "spikes") during pregnancy [27]. As discussed above, Phe "spikes" have a strong negative correlation with IQ [14].

Guttler et al. [25] found that, in the MPKUCS, the severity of PKU only became an issue for fetal outcomes when metabolic control before and during pregnancy was poor. With mild PKU, offspring IQ was significantly related to maternal IQ but not to Phe levels during pregnancy (which were all less than 750 μmol/L). In severe PKU, cognitive outcomes in the offspring were related to Phe control during pregnancy: if Phe levels were <360 μmol/L, cognitive outcome was normal (mean IQ:105); at Phe levels between 360 and 750 μmol/L, IQ depended on both Phe levels and mother's IQ; at Phe levels >750 μmol/L, IQ was severely depressed (mean IQ: 56) regardless of the mother's IQ [25].

Challenges in controlling maternal Phe levels

The UK PKU Registry found that, in 56% of pregnancies, women were not following a Phe-restricted diet at the time pregnancy began [28]. Early on, the MPKUCS reported that only 26% of pregnancies began while women were on a Phe-restricted diet [12], and only 10% of women achieved metabolic control by 10 weeks of gestation (with only about half of them, or 5% of the total study group, gaining control prior to pregnancy) [29]. More recent American studies of women with PKU reported that approximately one-third started diet prior to pregnancy, and 55% attained control of Phe levels before 10 weeks of gestation [30,31]. Compared to the US, Germany has reported higher rates of early metabolic control. In the German MPKU study, 46% of women achieved control prior to pregnancy, with a further 33% in control by 10 weeks of gestation [32]. Germany contributed 43 early and well-treated pregnancies to the MPKUCS [personal communication, Dr. F. Trefz].

Many women with PKU are well-informed about the risks of MPKU [31], but there are a number of barriers to achieving metabolic control before and during pregnancy. These include the effects of discontinuing the Phe-restricted diet in childhood, poor access to medical care, practical difficulties with implementing the strict PKU diet, financial constraints, demographics, and psychosocial issues.

In the past, it was believed that the threat of elevated Phe levels to neurological development was restricted to the period of early brain development, so Phe-restricted diets were often discontinued in middle childhood. It is now recognized that elevated Phe levels continue to contribute to intellectual disability and behavioral issues throughout the lifespan, and it is now recommended that the Phe-restricted diet be continued for life [30]. However, many women of childbearing age today have not returned to their diet. This, combined with the fact that women with PKU are at risk for unplanned pregnancies, contributes to the large number of women from the US and UK who are not on a Phe-restricted diet when they become pregnant [28,33]. So far there are no systematic data on unplanned PKU pregnancies in Germany because PKU registries are not currently available there [personal communication, Dr. F. Trefz].

Poor access to medical care is another barrier to metabolic control. Some women face long travel times to reach the metabolic clinic. Brown et al. [30] reported that, in the US, the average travel time to a metabolic clinic was 1.75 h, with a range of 15 min to 5 h. Another challenge is the need to take unpaid time off work to attend the clinic. Lee et al. [28] states that, in the UK, limited availability of medical services for adults with metabolic disorders also plays a role in poor metabolic control during pregnancy. In Germany, more centers in a smaller country make clinic visits easier (maximum distances to centers are less than 150 miles) [personal communication, Dr. F. Trefz]. This may help explain why women in Germany are more likely to attain early metabolic control during pregnancy.

Practical concerns are also an issue. The Phe-restricted diet can be challenging to follow. Women may find the medical foods unpalatable [30], especially when they have pregnancy-related nausea and vomiting [34,20]. The diet requires rigorous attention to nutrient intake, and women may find this lifestyle change difficult when they are also dealing with the challenges of pregnancy [31].

Financial issues can also be a factor. In the US, many women with PKU receive some form of financial assistance for pregnancy or treatment-related medical costs. The medical foods are expensive and may not be covered by insurers. Some insurers require proof of pregnancy, which can interfere with starting the diet before pregnancy begins. Following the Phe-restricted diet is time-intensive, and frequent medical appointments are required. This may interfere with a woman's job and reduce the time available for paid work [30]. In Germany, all patients have health insurance, which covers medical food (and in some cases also low-protein food) [personal communication, Dr. F. Trefz]. This is another factor that may contribute to Germany's higher rate of metabolic control early in pregnancy [32].

Demographic factors can also influence a woman's likelihood of attaining metabolic control. The MPKUCS found that women who had difficulty attaining metabolic control by 10 weeks of pregnancy were 3.5 times more likely to be single, more than 4 times as likely to be under 21 years of age, and twice as likely to have an IQ less than 85 [17]. Brown et al. [30] found that younger women (25 and under), those with less formal education (high school or less), and women using social assistance were less likely to adhere to the Phe-restricted diet [30]. Unfortunately, many women with PKU have intellectual disabilities, emotional disorders, or low socioeconomic status, all of which can interfere with adherence to the diet [35].

Psychosocial issues also play a role. Waisbren et al. [36] found that strong social support from family and medical providers greatly increased the chance that a woman would start treatment before pregnancy. This support was practical as well as emotional: women relied on assistance from others to prepare their medical formula (25%) and perform their blood tests (55%). Women with positive feelings about the diet were more likely to maintain metabolic control than those with negative feelings (53% vs. 26%). Women who felt they did not get adequate support from their health professionals and those who believed that their circumstances were controlled by chance were less likely to maintain control of their Phe levels. Despite the fact that family support helped women initiate the PKU diet, those who relied too heavily on parental involvement were less likely to maintain metabolic control [36].

Brown et al. [30] studied 24 women with PKU and found that 88% thought it would be helpful to talk to another woman with PKU. However, less than 50% were able to participate in a MPKU support program, often due to financial constraints or difficulty obtaining time off work.

Long-term effects of MPKU on behavior – similarities to fetal alcohol syndrome (FAS)

Untreated or poorly-treated MPKU has lasting effects on the behavior of the offspring. Shaw-Smith et al. [37] report three cases of significant learning disabilities and behavioral problems in children born to a mother with poorly controlled Phe levels during pregnancy. These problems persisted as long as the children were followed (into their teens and early adulthood).

Maillot et al. [14] studied patients from the MPKUCS, the UK PKU Registry, and a French MPKU survey. They found that DQ (which includes a behavioral component) and IQ (which correlates with behavior [17]) at 1 and 8 years of age correlated negatively with maternal Phe levels. There was also a negative correlation between variations in Phe levels and IQ at 1, 8, and 14 years of age [14].

The MPKUCS examined cognitive and behavioral outcomes at 4 and 7 years of age for children born to mothers with PKU. At 4 years of age, maternal PKU offspring displayed more aggression, "acting out" behaviors, attention problems, and difficulties developing social relationships. Delayed metabolic control (after 10 weeks of pregnancy) was associated with lower IQ and a higher incidence of behavior problems such as aggression, hyperactivity, and poor impulse control at age 7 [7].

Antshel and Waisbren [7] conducted detailed cognitive and behavioral analyses on 15 children with MPKU, ranging in age from 7 to 16 years. They found that the children showed features of ADHD, including attention problems, poor impulse control, and impulsivity. The authors also noted that there may be a mismatch between PKU parents and MPKU children: the PKU parent may have a slower cognitive tempo (associated with elevated Phe levels), whereas the MPKU child tends to be hyperactive and impulsive, which may lead to conflict and behavior management issues [7]. Many features of untreated MPKU, both physical and behavioral, are similar to FAS. Lipson et al. [38] studied 34 children born to mothers with untreated hyperphenylalaninemia and noted several parallels to FAS: global developmental delays, facial dysmorphisms, CHD, and an overall increase in major and minor malformations. Other similarities include microcephaly [39], intrauterine growth restriction, hyperactivity, and problems with language, memory, and attention [40]. In both syndromes, microcephaly, facial dysmorphisms, and growth delays generally improve over time. Both MPKU and FAS exhibit a dose–response relationship: the greater the exposure, the poorer the outcomes [39]. These similarities suggest that MPKU may be a generic response to a teratogen [40].

Impact of PKU treatment discontinuation on the home environment

Many women with PKU discontinue their Phe-restricted diet after pregnancy. The Centers for Disease Control (CDC) interviewed 30 women with PKU and found that 71% had stopped their diet, mainly because they found the medical foods unpalatable [41]. In the Resource Mothers Study, only 4 out of 44 women (9%) found that their opinion of medical foods (formula) was more positive after pregnancy than before pregnancy. Still, 91% of women discontinued the medical foods after pregnancy [31].

In women with PKU, diet discontinuation is associated with lower IQ [42] and an increased risk of thought and mood disorders [43]. It may also cause learning difficulties, mental processing abnormalities, personality disorders, anxiety [44], and behavioral problems [2]. These changes may impair a mother's parenting ability and decrease the quality of the home environment [31]. Sheard [45] reported a strong correlation between maternal IQ and HOME scores among women in the MPKUCS.

The home environment is a critical factor in offspring outcomes for MPKU. There is a strong relationship between HOME scores and a child's developmental outcomes [18]. In the MPKUCS, Phe levels, IQ and HOME scores were all strongly correlated to the General Cognitive Index (GCI), a measure of a child's cognitive, motor, and perceptual development [45]. The MPKUCS also found that the negative effects of elevated Phe levels on the offspring can be at least partially offset by a stimulating home environment [46]. Children with lower HOME scores did not perform as well at 1 year of age compared to children with more stimulating home environments, even though they had normal neurological ratings at birth. The home environment had a greater impact on DQ at 1 year of age than the timing of maternal metabolic control during pregnancy [47].

Optimizing management of maternal PKU: guidelines and treatment options

Management of MPKU varies between countries [48]. Comprehensive treatment guidelines based on current evidence; new

Table 1
MPKU guidelines.

MPKU issue/topic	American guidelines [2,49]	United Kingdom (UK) guidelines [50]	German guidelines [51]
Phe levels and timing	120–360 μmol/L (2–6 mg/dL) by 3 months before pregnancy begins and continuing throughout pregnancy	60–40 μmol/L (1–4 mg/dL), starting prior to pregnancy and continuing throughout pregnancy	60–240 μmol/L (1–4 mg/dL), starting prior to pregnancy (training phase) and continuing throughout pregnancy
Blood tests recommended during pregnancy	Blood Phe levels twice weekly (or at least once weekly) Reliable home-testing methods for Phe should be developed	Blood Phe levels at least once weekly throughout pregnancy Full amino acid profile, vitamins, minerals, trace elements, and full blood count monthly throughout pregnancy	Blood Phe levels twice weekly (or at least once weekly) Full amino acid profile, vitamins, minerals, trace elements, and full blood count every trimester (12, 24, 36 weeks of gestation)
Counseling, education, and support	Counsel all women of childbearing age on MPKU and family planning. Offer referral to an experienced PKU treatment center Provide equal access to medical foods, frequent monitoring, and psychosocial support Continue psychosocial support after the infant is born	Counsel girls on MPKU and family planning before transferring to the adult clinic, reinforce in adolescence, and, in the adult clinic, fully explain specific risks of MPKU	Counsel all women of childbearing age on MPKU and family planning. Offer referral to an experienced PKU treatment center Provide equal access to medical foods, frequent monitoring, and psychosocial support Continue psychosocial support after the infant is born
Nutrient intake (see also Tables 2 and 3)	Women should maintain adequate intakes of vitamins and other nutrients during pregnancy, particularly folic acid and vitamin B_{12}	Dieticians should counsel women on dietary protein restriction, including food lists and meal preparation, to ensure adequate nutrient intake	Dieticians should counsel women on dietary protein restriction, including food lists and meal preparation, to ensure adequate nutrient intake

treatment options; and programs to address psychosocial, practical, and financial issues are needed.

Table 1 summarizes MPKU guidelines in various countries.

Tables 2 and 3 describe nutrient intake recommendations during pregnancy for women with PKU.

The guidelines shown in Tables 1–3 provide some useful recommendations. However, there are still many areas for improvement in the management of MPKU. Adherence to the Phe-restricted diet remains poor, and many women with PKU do not achieve metabolic control soon enough to ensure optimal outcomes [28–31]. After their children are born, women often discontinue their Phe-restricted diet, leading to lower IQ [42] and an increased risk of psychological and behavioral problems [2,43]. These factors may reduce the quality of the home environment, which could have negative effects on the child's developmental outcomes [18,31]. Even well-treated women may have subtle cognitive deficits that could interfere with their parenting abilities [2].

There are a number of possible avenues to improve MPKU management, including treatments to improve Phe control (e.g., sapropterin, and, after approval by the Food and Drug Administration (FDA), pegylated Phe ammonia lyase (PAL) enzyme therapy), and programs for education and psychosocial support [2,52].

Sapropterin

Sapropterin is a synthetic form of tetrahydrobiopterin (BH_4), the cofactor of PAH, an enzyme that metabolizes Phe to tyrosine [53]. Sapropterin has been shown to reduce serum Phe levels in BH_4-responsive patients with MHP and in BH_4-responsive people with PKU [2]. Sapropterin may also be combined with a Phe-restricted diet to increase Phe tolerance and help avoid Phe "spikes" (temporarily high Phe levels) in people who are BH_4-responsive [54]. Phe control remains poor in many pregnancies [29–31], and even women who achieve good Phe control on diet experience Phe level

Table 2
Recommendations for nutrient intake in MPKU pregnancy.

Trimester	Protein (g/day)	Phenylalanine (mg/day)	Tyrosine (mg/day)[a]	Energy (kcal/kg/day)[b]
I	>74	200–600	7000	2155–3155
II	>74	200–800	7000	2155–3155
III	>74	300–1200	7000	2155–3155

Adapted from: F.K. Trefz, P. Funk-Wentzel, J. Heinemann, Maternale PKU, in: Erfahrungen und Behandlungsstrategien, SPS Verlagsgesellschaft, Heilbronn, 2005. ISBN 3-936145-20-2.

[a] Additional tyrosine intake recommended when plasma tyrosine <0.5 mg/dl.

[b] Dependent on age and physical activity (see Table 3).

Table 3
Nutrient recommendations for different age groups and physical activity levels.

Age	Physical activity level (PAL)			
	PAL 1.4[a] Low (kcal/day)	PAL 1.6[b] Normal (kcal/day)	PAL 1.8[c] More (kcal/day)	PAL 2.0[d] Increased (kcal/day)
<19 years	2255	2555	2855	3155
19 to <25 years	2155	2455	2755	3055
25 years and older	2155	2355	2655	2955

Adapted from: D-A-CH 2000: "Referenzwerte für die Nährstoffzufuhr 2008", Deutsche Gesellschaft für Ernährung e. V., Bonn.

[a] Profession with primarily sitting work.

[b] Profession which includes sitting and walking during work.

[c] Profession which includes mainly walking during work.

[d] Profession which requires hard physical work.

"spikes" at around 6–10 weeks of pregnancy [22]. Wide variations in Phe levels are associated with lower IQ in the offspring [14]. Thus, sapropterin is a potentially useful treatment for pregnant women with PKU [54].

In 2005, Koch et al. [55] reported the first case of sapropterin therapy in CJ, a 29-year-old pregnant woman with PKU. CJ was treated with Phe-restricted medical foods and sapropterin (40 mg per day in the first trimester, 60 mg per day in the second trimester, and 100 mg per day in the third trimester). CJ's Phe levels were in control (between 120 and 360 mmol/L) within 5 weeks of conception and remained well controlled for most of the pregnancy. The outcome of the pregnancy was normal, and the infant did not have CHD. No adverse fetal effects of sapropterin were observed [55]. At 4 years of age, the offspring had an IQ of 132 [56].

New data are available on the use of sapropterin in five pregnant women with PKU [57,58]. The women were treated with sapropterin in addition to a Phe-restricted diet. The sapropterin dose ranged from 40 to 400 mg per day in the first trimester, 80 to 600 mg per day in the second trimester, and 100 to 600 mg per day in the third trimester. No adverse effects of sapropterin on the infants were observed. Phe levels were reasonably well controlled in most pregnancies. The infants were free of microcephaly, cardiac or neurological problems, and other symptoms of the MPKU [57,58], and have developed normally on follow-up [unpublished data].

Cunningham et al. [59] describe the use of sapropterin during pregnancy in a 29-year-old PKU patient. The patient's Phe levels "off diet" were 612 μmol/L (10.2 mg/dL). The patient was able to initiate only moderate dietary restriction, reaching Phe levels of 522 μmol/L (8.7 mg/dL). With sapropterin therapy, she was able to achieve a mean Phe level of 162 μmol/L (2.7 mg/dL), starting 10 weeks before her pregnancy began and continuing throughout pregnancy. During the first trimester, the patient had a reduced caloric intake due to nausea and anorexia, but her Phe levels remained within the range of 120–240 μmol/L (2–4 mg/dL). The infant showed normal physical and neurological development at birth. Normal development has continued throughout the first year of life.

These case reports suggest that further study of sapropterin is warranted. Future research could provide more information on its safety and efficacy during pregnancy, longer-term outcomes in the offspring, and optimal dosing [54].

Pegylated PAL enzyme therapy

Pegylated PAL has been explored in animal models as an alternative therapy for PKU. It breaks down Phe into transcinnamic acid, and has been shown to lower Phe levels in animals. However, its safety and efficacy have not been studied in humans [52].

Outreach, education, and psychosocial support programs

Psychosocial support, education, and outreach programs are critical to ensure optimal fetal outcomes. These programs help women with PKU understand the importance of metabolic control, achieve control prior to pregnancy, maintain control during pregnancy, and receive support after birth to ensure ongoing metabolic control and a stable and stimulating home environment [36,49].

The Resource Mothers Program for MPKU matched pregnant women with PKU with a "resource mother": a mother of children with PKU. The resource mothers met with the pregnant women for approximately twenty 2-h sessions, where they educated them about MPKU and assisted them with shopping, meal planning, preparing for the baby, and coping with pregnancy. On average, women who had a resource mother achieved control of their Phe levels 8 weeks earlier than those who did not. In this relatively small sample, 31% of women with a resource mother attained metabolic control, vs. 11% of women without a resource mother [35].

MPKU camps are another way to offer education and psychosocial support. Waisbren et al. [60] describe the results of a 6-day summer camp for 25 young women with PKU. The camp offered education on blood drawing, low-protein food preparation, food flavoring, contraception and pregnancy, and MPKU research. Phe levels on the last day of camp were 37% lower than levels taken on the first day of camp, a statistically significant reduction. The vast majority of campers (96%) were able to reduce their Phe levels. Campers' knowledge of MPKU and the Phe-restricted diet was significantly increased, as measured by questionnaires designed to test knowledge in these areas. Campers were also significantly more likely to feel that other people wanted them to use birth control if they were sexually active. However, there were no significant changes in other attitudes towards birth control, marriage, and pregnancy, or in their perceived ability to cope with PKU [60]. Singh et al. [61] report on a week-long metabolic camp for 13 adolescent girls with PKU aged 11–18 years. The camp provided comprehensive education about PKU and dietary treatment. One component of the education program focused on MPKU, offering information on reproductive development and the importance of dietary compliance. At the end of the camp, plasma Phe levels were significantly decreased, participants felt significantly less isolated, and their knowledge of PKU and dietary treatment was significantly increased. One year after the camp, the improvements in knowledge of PKU and dietary treatment remained. However, plasma Phe levels had returned to pre-camp levels.

Waisbren et al. [36] have also developed a MPKU life cycle model that divides MPKU into four stages: prevention of unplanned pregnancy, reproductive decision making, treatment initiation, and treatment continuation. They have identified psychosocial issues that affect women at each stage in the life cycle, including attitudes, knowledge, social support, and personality issues. Each stage has a specific treatment goal: consistent birth control use to prevent unplanned pregnancy, formation of a reproductive decision, timing of treatment initiation, and adequacy of treatment during pregnancy. This research may be used to help to develop programs targeted to each stage in the model.

Conclusions

With the development of newborn screening for PKU [62], various products for maintaining a Phe-restricted diet, and the availability of sapropterin [54,55], we should be able to reduce the rate of CHD and microcephaly to that seen in the offspring of non-PKU pregnancies, which is 1–2% [12,63]. This is also true of developmental delay, which occurs at a rate of about 4–5% in non-PKU pregnancies [12].

To optimize the management of MPKU, we need a comprehensive approach that addresses all stages of the MPKU life cycle (prevention of unplanned pregnancy, reproductive decision making, treatment initiation before pregnancy begins, and treatment continuation). This approach should involve education, updated treatment guidelines, better access to medical foods and pharmaceutical therapies, and psychosocial support. Pharmaceutical therapies such as sapropterin may help increase Phe tolerance, reduce Phe "spikes," and improve metabolic control during pregnancy. Women with PKU should plan their pregnancies and attain metabolic control before pregnancy begins. If this is not possible (e.g., if the pregnancy was unplanned), it is not too late to achieve a good pregnancy outcome as long as control is attained in the first 8 weeks of pregnancy [12]. The outlook for MPKU is positive, but the need remains for careful tracking of all women with PKU of childbearing age, continued educational efforts, and removal of barriers to early and continued maternal metabolic control.

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