Australasian consensus guidelines for the management of maternal phenylketonuria (PKU).

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ABSTRACT

Objective: To provide strategy for the consistent management of maternal phenylketonuria in response to request from the family metabolic support group, Metabolic Dietary Disorders of Australia (MDDA).

Methods: A working party was created by the Australian Society of Inborn Errors of Metabolism (ASIEM) with membership from each centre that manages maternal PKU (MPKU) within Australia and New Zealand (Australasia). The working party had representation consisting of consultant metabolic physicians, metabolic fellow in training, metabolic nurse practitioner candidate and metabolic dietitians.

Results: A review of all literature, current and historical, was undertaken on the management of MPKU. The results were summarised and formed the basis of discussion for this published guideline/recommendation.

Conclusion: There is little evidence to direct practice; only one systematic review of MPKU management has been published. These guidelines are based on published literature and the available International recommendations from the United Kingdom, Scotland, Europe and Northern America. Further research is required to determine best management practices for the outcomes of infants whose mother has PKU.

Key words

maternal phenylketonuria; maternal PKU; MPKU; clinical practice guideline;

ABREVIATIONS

ACMG, American College of Medical Genetics

DQ, developmental quotient

HPA, hyperphenylalaninaemia

IQ, intellectual quotient

MPKU, maternal phenylketonuria

MPKUCS, Maternal Phenylketonuria Collaborative Study

NHMRC, National Health and Medical Research Council

PHE, phenylalanine

PKU, phenylketonuria

RCPA, The Royal College of Pathologists of Australasia

RACP, Royal Australasian College of Physicians

RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists

SSIEM, Society for the Study of Inborn Errors of Metabolism

SIMD, Society for Inherited Metabolic Disorders

INTRODUCTION

Phenylketonuria (PKU); OMIM 261600 and 261630) is an autosomal recessive inborn error of metabolism resulting from a deficiency in the enzyme phenylalanine hydroxylase (PAH), and characterised by elevated serum phenylalanine (PHE) level[1]. The overall incidence in Caucasian populations is around 1:10,000[1,2].

As newborn screening for PKU has been available in Australasia since the mid to late 1960's, the cohort of women who are currently in their child bearing years and planning pregnancies are expected to have been diagnosed through a screening program been managed by an Australasian specialist metabolic unit with the philosophy of diet for life. Usual practice in Australasia is a co-ordinated and structured multi-disciplinary team approach with access to qualified metabolic consultants, dietitians, metabolic specialist nurses as well as psychosocial support. . It is possible that some women with PKU who were born overseas or who have been lost to follow up may not be known to and managed in a specialist centre.

Adequate phenylalanine control for the duration of the pregnancy is expected to result in children of PKU mothers having normal intelligence and social development[3]. High levels of phenylalanine are teratogenic to the unborn foetus[4], it is therefore well documented that tight control of PKU during pregnancy must be achieved for best infant outcomes. Unsatisfactory phenylalanine control in pregnancy can result in serious birth defects such as microcephaly, congenital heart disease, intra-uterine growth retardation, facial dysmorphia and intellectual impairment in the infant from a mother with PKU[5].

METHODS

At the request of the Metabolic Dietary Disorders of Australia (MDDA) to the Australian Society of Inborn Errors of Metabolism (ASIEM), a working party was created following expressions of interest from ASIEM members where management of maternal PKU was within their patient group responsibility. The working party had multidisciplinary team representation consisting of metabolic physicians (MT, DM, JF), metabolic nurse specialist (AI) and metabolic dietitians (AE, PS, RA, JP, MW) with representation from each Australian state/territory and New Zealand.

The Working party performed a non-systematic literature review, then drafted group clinical guidelines for the management of MPKU for the Australian and New Zealand population. The working party was divided into two groups determined by professional stream. Group 1 (AI, DM, MT, JF) consisted of medical and nursing health professionals who focused on biomarkers and monitoring. Group 2 (JP, RA, AE, PS, MW) consisted of dietetic health professionals whose task focused on the dietary management of MPKU.

The draft guideline was released for consultation to the Australasian adult metabolic units and revisions were made based on these comments. The approved guideline was sent to the Royal Australia and New Zealand College of Obstetrics and Gynaecology (RANZCOG), Royal College of Pathologists of Australasia (RCPA), Royal Australasian College of Physicians (RACP), Australian College of Midwives and New Zealand College of Midwives.

REVIEW OF LITERATURE

Recommendations are assigned a level of evidence. These levels of evidence were adapted from the National Health and Medical Research Council (NHMRC) evidence hierarchy[6].

Table 1. NHMRC Levels of evidence[6]

Level	Level of Evidence
1	Systematic review of evidence
2	Single experimental studies (e.g. randomised control trial)
3	Quasi-experimental studies (e.g. pseudorandomised trial, cohort study, single arm study)
4	Non-experimental studies (e.g. case report and case series)
5	Opinion of respected authorities

NB: N of 1 trial may be experimental, quasi-experimental or non-experimental depending on design.

BIOMARKERS

The teratogenicity of PKU is generally thought to relate to elevated, toxic levels of PHE[7] but not to metabolites of PHE[8] nor due to deficiency of downstream metabolites, including tyrosine. Clinical monitoring has therefore focused on measurement of phenylalanine.

There has been relatively little discussion on the role of tyrosine deficiency in MPKU. A recent systematic review by the Cochrane Collaboration reviewed the evidence for

tyrosine supplementation in phenylketonuria[9]. 56 patients from 3 trials were included in the review but whilst plasma tyrosine levels were clearly different between intervention and control groups, there were no differences in other outcomes. There have been no reports of studies of plasma tyrosine levels in pregnancy, nor other biomarkers (serum melatonin and urine 6-sulfatoxymelatonin and dopamine levels).

Pre-conception

The Agency for Healthcare Research and Quality (AHRQ) of the US Department of Health and Human Services published a systematic review of evidence in PKU in 2012[10]. This report reviewed the evidence for plasma PHE target ranges, including levels in MPKU and identified only 1 study which provides evidence for plasma PHE levels in MPKU[10]. Interpretation of this report, and others in the field, are hindered by inconsistent and sometimes erroneous use of terms[10]. For instance, the AHRQ report uses a definition of low IQ as being those with an IQ <85, therefore not utilising the standard diagnostic categories or ranges used by Wechsler Intelligence Scale for Children or the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[10].

The “Maternal Phenylketonuria Collaborative Study (MPKUCS)” involved 414 offspring from 515 pregnancies and 100 controls, recruited from metabolic clinics in the United States and Canada between 1984 and 2002, with Germany, Austria, and Switzerland being added in 1992[5,11]. This study is the only study that provides evidence for specific levels in pregnancy, though two other studies confirmed the relationship between maternal PHE and child outcomes first observed in MPKUCS[5,11]. Results from this study suggested that reaching metabolic control

earlier in pregnancy is associated with higher IQ and that pre-conception control was better than control in early pregnancy and that control throughout pregnancy was better than for only a part[22]. The reports of MPKUCS are numerous, including approximately 20 publications[10-32], meaning that the results are cumulative and iterative.

UK MRC guidelines recommend not conceiving until metabolic control has been obtained[29], US guidelines recommend maintaining PHE levels <6 mg/dL (334 µmol/L) for at least 3 months prior to pregnancy[32].

RECOMMENDATIONS

1. PKU pregnancies have best outcomes if planned (level of evidence (LOE 3)
2. Consultation with a metabolic MPKU trained multidisciplinary team is highly desirable at least 4 months before conception (LOE 5)
3. Monitor plasma PHE levels at least weekly during the pre-conception phase (LOE 5)
4. Maintain plasma PHE levels between 70 – 250 µmol/L for 3 months prior to conception (LOE 3)
5. Monitor nutritional markers pre-conception (LOE 3)

RECOMMENDATIONS (Appendix 1)

Control during pregnancy

The MPKUCS demonstrated a linear relationship between maternal PHE levels >360µmol/L throughout gestation and lower IQ of the developing foetus[33]. There is a high degree of variation between international recommendations for maternal PHE control. US guidelines suggest an upper limit of 360 µmol/L though the most recent ACMG guideline acknowledged an upper level of 240 µmol/L in International guidelines[1]. Previous US guidelines recommended a target range of 2-6 mg/dL (111-334 umol/L) [1]. French PKU guidelines cite a recommended upper limit of 5 mg/dL (278 µmol/L)[34], UK guidelines cite a target range of 60-250 µmol/L and 60-240 µmol/L[25], the Dutch guideline cites an upper limit of 240 µmol/L[35], the West of Scotland Management Guidelines for Maternal Phenylketonuria recommend a target range of 100-250 µmol/L[36]. We were unable to identify any evidence supporting an upper limit of 240 µmol/L, nor for any specific lower limit.

Although tyrosine supplementation can effectively bring levels into the normal range in women with PKU[37], the MPKUCS found no relationship between offspring outcomes and maternal blood tyrosine levels before and during pregnancy[38].

With the current available literature we advocate PHE levels between 70 - 250 µmol/L. We make no specific recommendations regarding tyrosine levels.

Monitoring biochemical control

Regular monitoring of PHE levels before, during and after the pregnancy is essential for best outcome for the infant and mother. It is recommended that at least weekly monitoring of PHE either by tandem mass spectroscopy (blood spot) or formal

plasma amino acid quantification. Baseline biochemical screens should include electrolytes, liver function tests (LFT), albumin, iron studies, vitamin B12, vitamin D, copper, selenium and zinc, with minimum monthly monitoring of electrolytes and plasma amino acids, and minimum trimesterly monitoring of RBC folate, homocysteine, cholesterol and essential fatty acids[4,2,39].

Frequency of PHE monitoring

There are no studies addressing this question. A systematic review accompanying the ACMG PKU guidelines recommended measuring phenylalanine levels weekly to twice weekly, with no preference made for measurement in plasma, serum or whole blood[2]. The UK MRC guidelines recommend twice weekly levels[29]. The West of Scotland Management Guidelines for MPKU recommend 2-3 measurements per week[36].

RECOMMENDATIONS

1. Maintain plasma PHE levels between 70 – 250 µmol/L
2. Monitor plasma PHE levels at least weekly
3. Monitor plasma PHE levels at the same time each day after a minimum 3 hour fast
4. Monitor during pregnancy nutritional markers that were abnormal prior to conception

NOTE: ***Pregnancy monitoring***

Women with PKU should be managed by standard perinatal protocols and offered routine screening tests.

Consideration should be given to referral to a specialist high risk pregnancy or materno-fetal medicine service Given the high risk of fetal problems in maternal PKU, high resolution second trimester morphology scanning by ultrasound, should be performed, preferably in a tertiary hospital.

Follow up scans may be indicated where there are concerns about fetal growth.

Fetal cardiac echo is recommended.

RECOMMENDATIONS

1. Refer to a high risk pregnancy specialist obstetric service
2. Perform detailed second trimester fetal morphology ultrasound and fetal cardiac echocardiogram

RECOMMENDATIONS (Appendix 1)

DIETARY RECOMMENDATIONS

Establishing a preconception diet

Ideally women with PKU who wish to become pregnant should do so in a planned way in order to ensure safe plasma phenylalanine (PHE) levels prior to conception[23]. To achieve PHE levels within the acceptable preconception range, the vast majority of patients (with the exception of those with mild hyperphenylalaninaemia) will be required to exclude all high protein foods including meat, poultry, seafood, dairy, egg, tofu, legumes and nuts from their diet.

Dietitians must titrate each patient's natural protein allowance to plasma PHE[2], and generally the following measures will be required[41]:

1. The exclusion of high protein foods including meat, poultry, seafood, dairy, egg, tofu, legumes and nuts.
2. Administration of phenylalanine-free (PHE-free) amino acid supplement to meet total protein requirements.
3. An allowance of a measured quantity of PHE in the form of grams or units of protein, or phenylalanine exchanges.
4. Substitution of regular bread, pasta, rice and flour-based products with specialised low protein medical foods.
5. Additional vitamins and minerals.

Patients who are already maintaining a low phenylalanine diet and demonstrate good metabolic control prior to the preconception period typically require only modest adjustments to their diet to achieve safe pregnancy PHE levels. Those with poor metabolic control and who are not "on diet" prior to the preconception period will

require significant dietary intervention, and may cope better if changes are implemented in a stepwise fashion. Women who become pregnant without appropriate PHE control will require intensive dietary intervention, possibly in an inpatient setting, to attain safe PHE levels within a timely fashion[1]. In some centres it is standard clinical practice to exclude all natural protein from the diet in unplanned pregnancies until phe levels are in the desired range[42].

RECOMMENDATIONS

1. Best infant outcomes occurs with planned pregnancies (LOE 3)
2. ASIEM endorsed the use of the following low protein counting tool - Women's' & Children's Hospital Low Protein Diet for phenylketonuria (PKU) available from (LOE5) http://www.wch.sa.gov.au/services/az/other/nutrition/documents/Low_Protein_Diet_for_PKU_2013.pdf
3. Pre-conception diet planning should include a protein restricted, nutritionally adequate diet with PHE-free amino acid supplementation (+/- supplementation with tyrosine) (LOE 3)
4. Level of protein restriction will be determined by the plasma PHE levels (LOE 2)
5. If conception occurs prior to the establishment of such a diet, intensive intervention including hospital admission may be required to rapidly achieve
6. If conception occurs prior to the establishment of such a diet, intensive intervention including hospital admission may be required to rapidly achieve safe PHE control. (LOE 3)

RECOMMENDATIONS (Appendix 1)

Nutritional management in pregnancy

The below recommendations apply to the nutritional management of pregnancy in phenylketonuria where it differs from standard pregnancy care. Local pregnancy guidelines including recommendations for alcohol, food safety and micronutrient intake should be referred to in conjunction with this guideline.

Weight

Nutrition related elements other than raised blood PHE levels play a role in ameliorating some of the detrimental effects of PKU during pregnancy including microcephaly[41] and congenital heart defects[39], and optimising outcomes such as birth length, weight and head circumference[44].

One such nutrition related parameter is weight. Matalon et al. found that low pre-pregnancy weight and poor weight gain throughout pregnancy were significant risk factors for microcephaly, and that the highest rate of microcephaly (58%) was observed in the offspring of women who had gained less than 70% of the recommended gestational weight gain[43]. Furthermore, microcephaly significantly decreased when weight gain was adequate. Birth length, weight and head circumference has also been shown to be positively influenced by weight gain of the mother[44].

Whilst an increase in weight can improve the utilisation of dietary PHE and may improve maternal PHE tolerance[45], it is not usually desirable to gain weight in excess of the recommendations during pregnancy because of associated complications that may occur during delivery[45, 47]. Additional weight gain during pregnancy may also be

difficult to lose, increasing the risk of complications in future pregnancies[47] in addition to other health issues[45, 48]. There is therefore no evidence to suggest that maternal weight gain in PKU should differ from usual pregnancy recommendations.

Current weight gain recommendations in pregnancy

Recommended total weight gain in pregnancy is based on pre- conception body mass index (BMI). For women with a BMI of less than 18 kg/m² the recommended weight gain for a singleton pregnancy is 12.5-18 kg; at BMI 18.5-24.9 kg/m² weight gain should be 11.5-16 kg; at BMI 25-29.9 kg/m² weight gain should be 7-11.5 kg and for those with a BMI > 30 kg/m² weight gain should be 5-9 kg[49]. All women would be expected to gain approximately 1-2 kg in the first trimester with the majority of weight gain to occur in the second and third trimesters.

Weight monitoring

There is no consensus on how frequently weight should be monitored in maternal PKU with recommendations varying from weekly[3], to a minimum of monthly[2] to every clinic visit which should occur monthly to per trimester[2].

RECOMMENDATIONS

1. Where possible, women should be counselled on achieving a healthy weight prior to conception (LOE 5)
2. Weight gain during pregnancy should be in accordance with normal weight gain requirements in pregnancy which is dependent on preconception (LOE 5)

RECOMMENDATIONS (Appendix 1)

Energy intake

Adequate energy intake is essential throughout the duration of pregnancy to prevent catabolism and support foetal growth[4]. The MPKU study found that women who achieved metabolic control defined as PHE <360µmol within the first 10 weeks of pregnancy tended to have higher protein, fat and energy intakes[45], thus women who have difficulty lowering their plasma PHE concentrations should increase their protein intake from PHE-free amino acid supplement, as well as increase fat and energy intake. Pregnancy-related nausea and vomiting may make nutritional adequacy difficult to achieve particularly in the first trimester[40]. Additionally, over-restriction of energy intake may occur inadvertently through the reduction in protein allowance required in the preconception and pregnancy period, and can contribute to increased maternal PHE levels by promoting catabolism [1].

Modified low protein food products such as pasta, breads, biscuits and flour are valuable sources of energy in the diets of pregnant women with PKU. Carbohydrate- and fat-based energy supplements can be considered as a protein-free source of additional energy if adequacy cannot be achieved with regular food, such as in hyperemesis gravidarum.

The available evidence suggests that energy requirements are not increased in PKU[2, 50], thus, as in women without PKU, energy needs during pregnancy should be calculated using weight-based predictive equations such as the Schofield equations. The average additional energy requirement is nil in the first trimester, 1.4MJ/day in the second trimester and 1.9MJ/day in the third trimester of pregnancy[50], however these can vary widely and should be individualised according to the mother's age,

physical activity pre-pregnancy weight status[52], and adjusted as required to achieve appropriate weight gain. Maillot et al. recommend a 10% increase in energy intake if weight gain during pregnancy is below the recommendations[3].

Protein intake (natural and synthetic)

Total Protein

Achieving adequate protein intake for the duration of pregnancy is essential in women with PKU. The MPKU study found that inadequate intake of total protein throughout pregnancy negatively correlated with plasma PHE concentrations and may contribute to poor reproductive outcomes, with a mean protein intake greater than the recommended dietary allowance (RDA) producing the best outcomes in this group[27]. Insufficient total protein intake in MPKU appears to be an independent risk factor for the development of congenital heart defects (CHD), irrespective of first trimester plasma PHE levels[39]. Matalon et al 2003 also reported a higher rate of CHD in the offspring who were born to women who consumed <50% of the recommended intake of protein in the first trimester[43].

Australian and New Zealand dietary reference values for the general population suggest protein requirements increase by 0.2g/kg in the second and third trimester of pregnancy to enable an increase in body weight and growth of the foetus, however it may be prudent to aim above this target in PKU based on the evidence presented above. Recommendations for protein intake in pregnant women with PKU vary in the literature. Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening Collaborative (SERC) estimate total protein requirements for women consuming PHE-free amino acid supplement as part of their protein source

at ≥ 70g per day of protein throughout pregnancy, with PHE requirements of 265-770mg in the first trimester, 400-1650mg in the second trimester and 700-2,275mg in the third trimester and throughout lactation depending on patient tolerance with slightly higher recommendations for pregnant women ≤ 19 years of age[53]. Total protein intake in pregnant women with PKU will need to be derived from a natural protein target, titrated to plasma PHE levels, with the deficit provided by PHE-free amino acid supplement.

Natural Protein (Phenylalanine)

Throughout pregnancy maternal PHE requirements alter substantially requiring frequent blood PHE analysis and diet modification[1]. A PHE tolerance that remains low in the third trimester may be indicative of foetal PKU[54]. In the MPKU study, maternal genotype appeared to have little influence on PHE requirements during the first trimester[44]. Low plasma PHE and dietary PHE intake in pregnancy have been linked to poorer outcomes, thus the avoidance of over-restriction of natural protein is important. In a retrospective analysis of PHE intake in pregnant women with PKU, Teissier et al 2012 reported lower PHE intake from the 5th to the 8th month of pregnancy in the mothers of offspring with intrauterine growth restriction (IUGR) and concluded that the duration of time spent with PHE levels < 120µmol/L during pregnancy was associated with a higher risk of IUGR[55].

Synthetic Protein (PHE-free amino acid supplement)

Given the significant restriction of natural protein (dietary PHE) in pregnant women with PKU, the majority of protein intake will need to be derived from PHE-free amino acid supplements[4]. Women with low protein intake secondary to inadequate

consumption of PHE-free amino acid supplement have been found to have a low overall nutrient intake and a higher incidence of congenital anomalies in their offspring[56], and data from the Maternal PKU Collaborative Study (MPKUCS) revealed a higher PHE level and lower levels of seven amino acids in mothers of infants with congenital heart defects, indicating insufficient synthetic protein consumption[39]. Literature suggests that protein targets based on L-amino acid mixtures should be 120-140% of the RDI as L-amino acids found in the majority of PHE-free amino acid substitutes are absorbed and oxidised more rapidly than intact natural protein sources[2].

Glycomacropeptide (GMP) is a protein derived from whey, a natural by-product of cheese production, which has very low natural PHE content, and has been utilised as the protein source in several PKU medical food products[58]. While GMP is low in PHE, it also contains insufficient amounts of histidine, leucine, tryptophan and tyrosine that must be supplemented in the medical food. Threonine and isoleucine content is two to three times higher than other natural protein sources[58]. As an intact protein, GMP may increase palatability and satiety compared with amino acid-based medical foods, however there is currently little data available on its long-term use and no studies of GMP in MPKU[4]. Current commercially available GMP products contain a small amount of PHE in the order of 2.5-5mg per gram of protein[59], which must be taken into account when included in a low PHE diet[4].

Large Neutral Amino Acids (LNAA), which compete with PHE for absorption in the intestine and at the blood-brain barrier, are not recommended for use during pregnancy due to limited knowledge regarding their effects on the developing foetus[1].

RECOMMENDATIONS

1. Adequate protein in the form of a combination of natural protein and PHE-free amino acid substitute for the duration of pregnancy is essential to optimise fetal outcomes (LOE 3)
2. Actual protein intake varies, however the best outcomes have been shown in offspring of women who consumed greater than the recommended dietary allowance (RDA). Protein targets based on L-amino acids mixtures should be set at 120-140% of RDA to account for differences in absorption and utilization. (LOE 3)
3. There is currently no available data on the safety of Glycomacropeptide (GMP) products in pregnancy. If utilized, the small phenylalanine content should be taken into consideration. (LOE 5)
4. Large Neutral Amino Acids (LNAAs) are not recommended (LOE 5)

RECOMMENDATIONS (see appendix 1)

Micronutrients

As in women without PKU, ensuring micronutrient adequacy prior to conception is essential. Because foods naturally high in protein also contain other essential nutrients, it is important to ensure a diet modified for PKU remains nutritionally

complete. Inadequate vitamin B12, folate, copper and niacin have been shown to be associated with birth defects, spontaneous abortion and preterm birth in individuals without PKU, and a higher incidence of congenital cardiac defects observed in women with PKU who have inadequate B12 intake[4].

When the prescribed amount of PHE-free amino acid supplement does not contain adequate amounts of micronutrients, or an individual's intake is inadequate, a vitamin and mineral supplement should be provided[2]. Iron deficiency has been reported among individuals with PAH deficiency, and routine evaluation of iron status is recommended[59]. Periconceptionally, 5 mg folic acid is recommended for all PKU patients in order to reduce the risk of neural tube defects, and should be continued throughout pregnancy[60]. There is a risk of vitamin A toxicity if medical formula is prescribed in large volumes, or combined with a standard multivitamin, therefore a pregnancy multivitamin excluding vitamin A is advised, and the total vitamin A intake should be compared against the published Upper Limit[1].

Individuals with PKU are at an increased risk of essential fatty acid deficiency due to an inherently low fat intake when following a restricted protein diet, and the minimal fat content of many PHE-free supplements[4]. As such, it is recommended that Dietitians ensure adequate intake of essential fatty acids, referring to the Australian

and New Zealand nutrient reference values, Docosahexaenoic acid (DHA) supplementation of 200-300mg/day should be provided to all pregnant PKU patients[52] and may come from the phe-free amino acid supplement or an over-the-counter fish-oil supplement[2].

RECOMMENDATIONS

1. Adequate micronutrient intake and the prevention of vitamin A toxicity throughout pregnancy is essential to reduce the risk of birth defects (LOE 4)
2. All pregnant women with PKU should receive folic acid and DHA supplementation (LOE 2)

RECOMMENDATIONS (Appendix 1)

Post-partum and lactation

Maternal phenylalanine requirements decrease in the post-partum period compared with the heightened anabolic requirements during the third trimester of pregnancy[1], and will depend on whether or not the mother chooses to breastfeed. Breastfeeding is encouraged regardless of whether the mother maintains strict PHE control post-partum, as infants unaffected by PAH deficiency are able to metabolise the slightly elevated phenylalanine levels in their mother's breast milk[59, 60].

Ongoing monitoring of plasma PHE and titration of natural protein intake is required to determine the mother's phenylalanine tolerance whilst she is breastfeeding her infant. For women without PKU, the Australasian nutrient reference values quote an additional 21 grams of protein per day during lactation[51], therefore a figure of 120-

140% of this (25-29 grams) is advised if a phe-free amino acid supplement is used to meet this requirement. A systematic review by Singh et al. recommends protein intake be derived from greater than or equal to 70 grams of protein per day from amino acid supplement and 700-2,275mg phenylalanine (as provided by 14 – 45.5g natural protein), depending on PHE tolerance[2]. Energy requirements are also raised throughout lactation, by approximately 2,000kJ per day dependent on activity level, stage of lactation and weight status[51].

Micronutrient requirements during lactation are the same for women with or without PKU, and include increased demand for all vitamins, calcium, phosphorous, zinc, and selenium. Most PHE-free amino acid supplements available in Australasia that provide added vitamins, minerals and trace elements will meet the Australian and New Zealand RDI for lactation when the amount of supplement providing 80g protein equivalent/day is consumed, provided the woman is also eating fruit and vegetables daily. Some preparations do not contain vitamins, minerals and trace elements and supplementation is necessary. Adherence to diet post-partum may be poorer than during pregnancy, therefore additional micronutrient supplementation may be required.

Long-term continuation of diet to maintain good PHE control following childbirth is strongly recommended for its beneficial effects on the health and development of offspring[39]. Diet discontinuation is associated with an increased risk of maternal thought and mood disorders[62], and behavioural problems[64], which may go on to compromise a mother's parenting ability and the quality of the home environment[37].

RECOMMENDATIONS

1. Mothers with PKU are encouraged to breastfeed (LOE 5)
2. Nutrient recommendations during lactation are similar to those of women without PKU (LOE 5)
3. Long-term continuation of a phenylalanine-restricted diet is recommended following pregnancy to maximise maternal and child health and wellbeing (LOE 5)

RECOMMENDATIONS (Appendix 1)

Frequency of Metabolic Clinic Review (face-to-face, teleconference, telephone)

There are no studies addressing this question. The US guidelines recommend dietitian contact weekly to twice weekly with monthly clinic visits. The West of Scotland Management Guidelines for Maternal Phenylketonuria recommend weekly contact with monthly clinic appointments until 36 weeks[36].

RECOMMENDATIONS

1. MPKU Pregnancies (including hyperphenylalanaemia) should be managed in consultation with a multi-disciplinary team of health professionals that include a specialist metabolic physician, a maternity team, metabolic trained dietitians, nurses and psychosocial support workers[4, 65-67] (LOE 5)
2. Review either face-to-face or teleconference should begin pre-conception and continue for the duration of the pregnancy at monthly intervals to ensure all aspects of the pregnancy and MPKU are closely assessed and provide the opportunity to identify any risks early so that interventions can be established. These consultations should review overall control, assess diet, monitor weight gain as well as a psychosocial assessment. (LOE 5)
3. Telephone contact between the dietitian and the patient should occur at least once per week or with each PHE result as available to provide adjustments to the diet to maintain optimum control. (LOE 5)

RECOMMENDATIONS (Appendix 1)

CONCLUSION

This guideline should be considered, as a guideline only and that there may be slight variations in practice where the same outcomes can be achieved.

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AI - Nil

DM - Nil

AE - Nil

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RA - Nil

JP - Nil

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JF - Nil

Contributions

AI – Working party lead, literature search, medical management write-up, amalgamation of the dietetic and medical document

DM– Literature search, clinical lead medical management write-up, amalgamation of the dietetic and medical document, final edit

AE - Dietetic write-up and final editor

PS – Dietetic write-up and final editor

RA - Dietetic write-up and final editor

JP– Literature search, clinical lead dietetic management write-up, amalgamation of the dietetic and medical document

MT – Literature search, final edit

MW – Literature search, final edit

JF – Literature search, final edit

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Appendix A – Australia and New Zealand Maternal PKU recommendations

Management component	Recommendation	Level of evidence
Pre-conception diet	A minimum of 3 months	3
Pre-conception and MPKU plasma PHE levels	70 - 250 µmol/L	5
Pre-conception and MPKU tyrosine levels	Upper limit of the normal range	5
Measurement of phenylalanine levels (blood spot or formal quantitation)	At least weekly	5
Measurement of full amino acid profile and nutritional bloods	Pre-conception then each trimester	5
Face-to-face or tele-health	1 – 2 Monthly	5

consultations		
Telephone contact	At least weekly and with each PHE results	5
Dietary management guidelines	As directed by a metabolic trained dietitian	5
Protein counting tool	ASIEM Low Protein Diet Chart for PKU http://www.wch.sa.gov.au/services/az/other/nutrition/documents/Low_Protein_Diet_for_PKU_2013.pdf	5