PKU

A Practical Guide to Maternal PKU

Vitaflo in Association With You

Supporting education in the dietary management of rare diseases

Vitaflo®

Innovation in Nutrition

A Nestlé Health Science Company

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Disclaimer

This guide should be **read in conjunction with national and local guidelines** for the dietary management of Phenylketonuria (PKU) and maternal PKU (mPKU). It is based on European and American guidelines for the management of PKU, as well as clinical experience and best practice recommendations for the management of mPKU.

It is **for use by healthcare professionals** working with individuals with PKU.

This guide is **not for use by individuals with PKU.**

It is for general information only and must not be used as a substitute for professional medical advice.

All product information was obtained from manufacturer's information available as of the date of publication and is subject to change.

For specific product information, please consult the manufacturer.

The term medical foods is used throughout this guide. Medical foods might also be known as medical formulas, protein substitutes or PKU protein supplements. The medical foods (PKU express, PKU cooler, PKU air, PKU sphere), and supplementary product (Tyrosine1000) discussed in this practical guide must be used under medical supervision.

Collaborators

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Abbreviations

BMI — Body mass index

DHA — Docosahexaenoic acid

Hyperphe — Hyperphenylalaninemia

IQ — Intelligence quotient

LCP — Long-chain polyunsaturated fatty acids

LP — Low protein

mPKU — Maternal PKU

PAH — Phenylalanine hydroxylase

PE — Protein equivalent

phe — Phenylalanine

PKU — Phenylketonuria

Practice on calculating phenylalanine intakes vary within North America between counting mg of phe, grams of protein or using 15 mg phe exchanges. Local procedure should be observed and adhered to when giving individuals advice.

Foreword

Dietary management of PKU during pregnancy is complex and demands a great deal of both the individual and healthcare professionals supporting them. Nutritional requirements differ at every stage of maternal PKU (preconception, throughout pregnancy and during lactation) and dietary recommendations must be tailored to suit each individual. Careful monitoring and specialist expertise is essential to ensure the best outcome for both mother and infant.

The Charles Dent Metabolic Unit (CDMU) at University College London Hospitals (UCLH) is one of the largest and longest established facilities for adolescents and adults with inherited metabolic diseases. The unit was founded by Charles Dent who was one of the first physicians to recognize the teratogenic effect of high maternal phe levels in 1956[1]. CDMU has now been managing mPKU for over 40 years with nearly 300 babies born to women with PKU attending the unit. All of these children are offered developmental follow up until adolescence, and outcomes are recorded in a database which was initiated in 1977. This cumulative data contributes to improved knowledge and research and helps to ensure all women with PKU and their children continue to be offered the best possible care.

This practical guide for the dietary management of mPKU has been created as an aid for healthcare professionals and offers realistic suggestions and ideas to help with some of the challenges faced. In addition, it illustrates how Vitaflo's PKU product range can be incorporated into the diet.

Charlotte Ellerton

Dedication

mPKU dietetic care has been influenced hugely by Maggie Lilburn who was the first metabolic dietitian at the CDMU. She was a pioneer in this field from 1970 until her retirement in 2004, continuing in research until 2007. Her dedication to supporting individuals throughout pregnancy continues to inspire so many.

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1.0 Introduction to mPKU dietary management

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Women with phenylketonuria (PKU) must optimize metabolic control when planning, and during, pregnancy. High blood phenylalanine (phe) concentrations (referred to as phe levels) are teratogenic and can result in maternal PKU syndrome: microcephaly, severe developmental delay, cardiac defects, and low birth weight (<2500g) in the offspring[2]. Tight control is necessary due to the positive amino acid gradient across the placenta, thereby exposing the fetus to higher phe concentrations than the mother[3].

Maternal PKU syndrome can be avoided with diligent dietary management prior to conception and during pregnancy[4–6]. The European and American Guidelines recommend maintaining phe levels between 120–360µmol/L prior to conception and throughout pregnancy[7-8]. This requires individuals with PKU to restrict their dietary phe intake and consume sufficient energy, protein, and micronutrients to meet nutritional requirements.

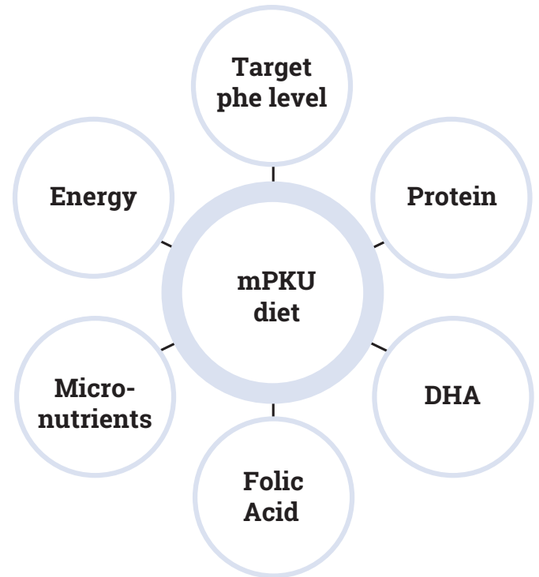
Best outcomes for children born to mothers with PKU are associated with achievement of metabolic control prior to conception[4-6]. Despite this knowledge, conception with uncontrolled phe levels (called an 'unplanned pregnancy') is common in PKU[9]. Unplanned pregnancies account for 30–60% of PKU pregnancies in large, specialist metabolic centers[10,11]. Dietary restriction should begin immediately in the event of an unplanned pregnancy, as evidence suggests that favorable birth outcomes can still occur when good metabolic control is achieved by 8–10 weeks gestation, and maintained throughout pregnancy[4].

Dietary management for a PKU pregnancy should be overseen in a specialist metabolic center experienced in the care of maternal PKU (mPKU)[12]. Care is required from the metabolic team including a physician, dietitian, and ideally, a psychologist who are all specialized in the management of adults with inborn errors of metabolism[7].

The aims of mPKU dietary management

1. **Reduce and maintain stable phe levels to within recommended target range**
   - The European and American PKU management guidelines recommend that phe levels are kept between 120 and 360 µmol/L preconception and throughout pregnancy[6,7].
2. **Ensure adequate nutritional intake to to support growth and development of the fetus**
   - Nutritional demands change throughout preconception, pregnancy and lactation. Each stage needs careful monitoring and frequent adjustment.
   - In addition to high blood phe, suboptimal intakes of energy, protein and vitamin B_{12} have been shown to have a negative impact on outcomes[13–15].

1.1 Priorities for mPKU dietary management

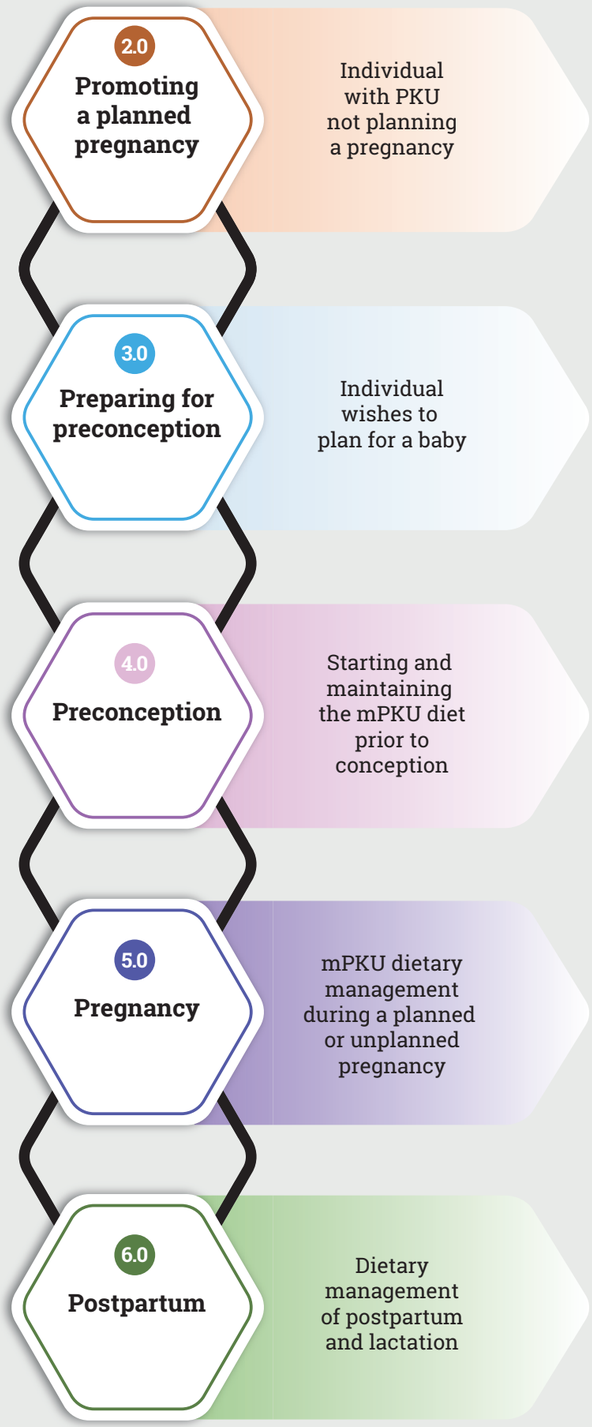


As well as managing PKU, important considerations for a healthy pregnancy include observing food safety, avoiding excessive vitamin A intakes and ensuring sufficient folic acid supplementation and DHA intakes.

The rest of this guide focuses on the practical management of mPKU. For further information on mPKU the following references are recommended:

- Acosta, P.B. and K. Matalon, Chapter 5: Nutrition management of individuals with inherited disorders of aromatic amino acid metabolism, in Nutrition management of individuals with inherited metabolic disorders, P.B. Acosta, Editor. 2010, Jones & Bartlett Publishers. p. 119–175.
- Acosta, P.B., et al., Intake of major nutrients by women in the Maternal Phenylketonuria (MPKU) Study and effects on plasma phenylalanine concentrations. The American journal of clinical nutrition, 2001. 73(4): p. 792–796.
- Koch, R., et al., The Maternal Phenylketonuria International Study: 1984-2002. Pediatrics, 2003. 112(6 Pt 2): p. 1523.
- Maillot, F., et al., A practical approach to maternal phenylketonuria management. Journal of inherited metabolic disease, 2007. 30(2): p. 198–201.
- Maillot, F., et al., Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine. The American journal of clinical nutrition, 2008. 88(3): p. 700–705.
- Matalon, K.M., P.B. Acosta, and C. Azen, Role of nutrition in pregnancy with phenylketonuria and birth defects. Pediatrics, 2003. 112(6 Pt 2): p. 1534–6.
- Lee, P., et al., Maternal phenylketonuria: report from the United Kingdom Registry 1978–97. Archives of disease in childhood, 2005. 90(2): p. 143–146.

mPKU dietary management stages



2.0 Promoting a planned pregnancy

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It is important to provide continuous education to regularly reinforce the message that pregnancies in PKU should be planned[7, 9]. Knowledge and experience of managing mPKU has evolved and some women with PKU may not be aware of current recommendations, especially if they have not been attending a metabolic clinic or are lost to follow up due to gaps in transition or scarcity in treatment centers.

At regular but appropriate time points individuals with PKU and hyperphenylalaninemia (hyperphe) should be counseled about:

Effective contraception and referral to family planning clinics, as appropriate

Consequences of high phe on pregnancy outcomes

Increased risk of heart defects, microcephaly, reduced intelligence quotient (IQ), behavioral problems[2, 4–6, 16–19].

Consequences of poor adherence to an adequate nutrient intake

For the individual: Nutritional deficiencies specifically protein, vitamin B_{12}, iron and DHA[20–22].
For a fetus: Nutritional deficiencies are associated with increased risk of poor growth, microcephaly, and heart defects[13–15].

Current target phe levels for pregnancy compared to adults on diet

When treatment recommendations are adhered to, the chances of a good outcome are comparable to the general population[7].

Offer encouragement by sharing that support is available from the metabolic clinic and peers, if desired, as well as family, friends or partner/spouse, as appropriate.

Educational messages on mPKU should be embedded into care programes at an early age[23,24]. European PKU guidelines suggest that these discussions begin prior to adolescence. Content should be tailored to the appropriate level for the individual and their family, taking into consideration cultural or religious background and any psychological and/or intellectual disability[7].

To reinforce positive health messages of a planned pregnancy in PKU, the inclusion of partners, family or friends in the discussion should be encouraged, while respecting the individual's right to confidentiality[9,25]. A study of psychosocial factors in mPKU[25] found that women with PKU had more unplanned pregnancies compared to women with type 1 diabetes. They also required more support from parents or partners to follow advice before and throughout the pregnancy[25].

If a woman with PKU becomes pregnant unexpectedly she should be encouraged to contact the metabolic center immediately to inform them of a suspected pregnacy. See **unplanned PKU pregnancy section 5.4** for more information.

All individuals should be encouraged to maintain up-to-date contact details with their metabolic center, including personal and emergency contact information. Clinic emergency contact information should also be provided to all individuals.

3.0 Preparing for preconception

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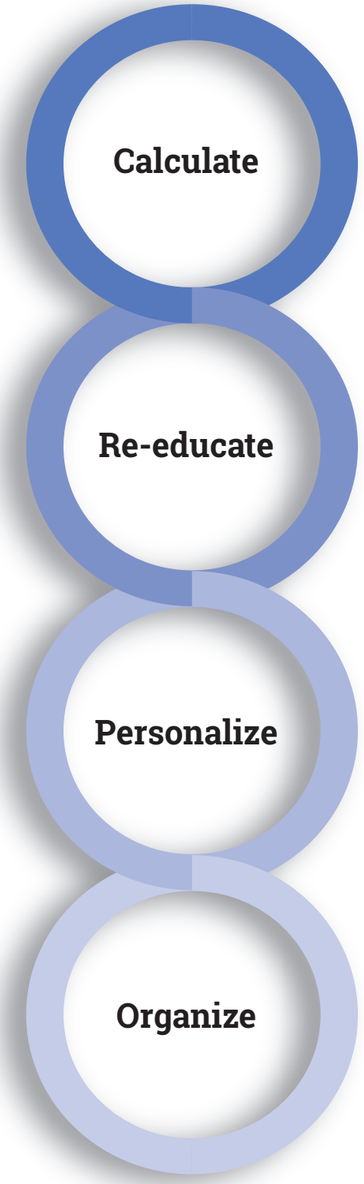
In an ideal case, an individual with PKU will inform the physician or dietitian that she is ready to plan for a pregnancy. This allows for preparation of the mPKU diet, which takes time. Individuals should be provided with a realistic time frame required to achieve phe levels in the target range. Preparing for preconception involves the following stages.



Phe, protein and other nutrient requirements will need to be calculated prior to starting the mPKU diet for preconception. Nutritional requirements differ at every stage of mPKU. The **Calculate section 7.0** illustrates requirements for preconception, during pregnancy and lactation.

Whether the individual is already on a phe-restricted diet, off diet or returning to care, she will need education to achieve stable phe levels within the recommended target range for preconception and pregnancy.

With any dietary intervention, personalized dietary advice will be the key to success.

Supporting the individual to plan and organize their diet will make it more manageable.

3.1 Re-educate

Individuals who adhere to the PKU diet should be offered re-education to ensure they are following the diet well enough to keep phe in the target range for preconception and pregnancy.

Intensive dietary education is required for those who struggle with adherence or who are off diet.

For an unplanned pregnancy, education is required urgently.

- Several days of education will be more difficult to provide at short notice.
- Education might need to be staged, initially focusing on establishing medical food and a very low phe, high calorie diet to reduce the phe level as quickly as possible.
- See the **unplanned PKU pregnancy section 5.4** for more information.

3.2 Personalize

Written information will be invaluable for individuals to take home with them.

For example, some individuals may prefer low protein food lists while others may benefit from an online calculator to track phe content/intake.

Consider different learning styles to help with understanding and retention of information.

Use visual and practical methods for education, such as written information, food models, food demonstrations and grocery store trips.

Identification of preferred medical food.

Individuals have different tastes. Being supported and encouraged to try all the appropriate presentations of medical foods will help to find the option most suited to each individual. To maximize adherence, some may wish to take a combination of products to suit their taste and lifestyle.

Changes in taste preferences are common throughout pregnancy. Maintaining optimal medical food and nutrient intake is a priority. Altering flavor and/or preparation of medical foods is common and should be encouraged if adherence is compromised.

There are many nutrients which need to be considered in mPKU, see section 7.0 Calculate. Some individuals may choose to take a medical food with a nutrient profile which meets recommendations, limiting the number of additional supplements they may need to take.

Tip: Remember that the individual might not wish to tell family, friends and work colleagues that she is planning a pregnancy or is pregnant. This may impact the diet (e.g. when and where foods are weighed or medical food is taken to maintain privacy).

Tip: Encourage the individual to consider her usual routine and how the medical food will be included alongside regularly spaced meals, and sufficient fluid. This includes; work, travelling, special occasions, weekends and meals with family.

Vitaflo's range of medical foods

- All PKU medical foods within the Vitaflo range are designed to be interchangeable, allowing flexibility.
- All are formulated with a comprehensive range of vitamins and minerals.
- All, except PKU express, contain DHA.

Once medical foods are selected, it is essential to review the total micronutrient intake from the full medical food prescription and recommend additional supplementation if required[10].

See **Vitaflo's range of medical foods section 8.0 for more information.**

Tip: Remember to not provide your own opinion on the taste of the medical food before the individual tries it. Everyone is different and should be allowed to form their own opinion when trying the product for themselves.

Tip: Check your body language. Make sure you are open and encouraging with both your verbal and non-verbal communication.

For the management of hyperphe/mild PKU, phe restriction and/or medical foods may not have been required since early childhood. These individuals may have been lost to follow up and may have limited understanding of PKU and the importance of dietary restriction during pregnancy.

Individuals with hyperphe, or those who have been off diet, are likely to find taking medical food daily very difficult as they may not have taken a medical foods regularly since their childhood[7,26]. For any individual who has not recently taken medical food routinely, it is advisable to increase the dose gradually over several days to promote tolerance and acceptance. Provide a larger sample supply of the preferred medical foods to take home.

Identification of preferred low protein foods

It is vital for the individual to taste a variety of LP foods, as these will likely provide the majority of the energy for the diet, especially during preconception and early stages of the pregnancy for individuals with a low phe tolerance. Variety is important to avoid taste fatigue and so that individuals will not be as tempted by restricted foods[27]. Providing a practical session where the individual can try and cook with the foods for themselves is invaluable.

Tip: Batch-cook LP meals and label with the date, name of dish and number of exchanges per portion before freezing. Remind patients to observe food hygiene precautions.

The individual will need enough LP foods while limiting waste. Help the individual to work through her usual week and when she would likely use staples such as bread, rice, or pasta as a base for meals.

Recipes ideas

It is useful for the individual to leave the dietary education session with at least 3 to 4 recipes for main meals which she would feel able to cook at home. Providing the necessary LP products for these recipes as samples will allow her to practice at home to build up confidence with LP cooking.

A range of delicious recipes are available from the Vitaflo Vitafriends PKU website: **www.vitafriendspku.com/us/recipes**. Some of these recipes require little or no specific LP products, making them especially useful when access to LP products is restricted.

3.3 Organize

Women who have been lost to follow up, have been off diet or have hyperphe may have never independently organized a LP diet before, especially if their parents/guardians managed the diet for them.

Medical food tips

A continuous supply of preferred medical food and LP foods needs to be set up and maintained.

Encourage the individual to set reminders to regularly review and rotate their stock at home to ensure adequate supply within the expiration.

Menu planning tips

Consolidating the education session with menu planning helps to bring all the information together. The individual can visualize what the mPKU diet will look like on a day to day basis. It also allows the dietitian to check their understanding of phe counting and energy intake.

Essential equipment: Digital weighing scales - lightweight scales are easier to transport.

Tip: You may wish to encourage some individuals to take their scales with them to accurately calculate phe while away from home e.g. vacation, weekends away.

Tips on eating out for the mPKU diet	Tips on eating over the holidays for the mPKU diet
Research menu options and nutritional information on restaurant websites.	Consider self-catering, as it offers flexibility.
Contact the restaurant in advance to see if they will use LP pasta, rice, pizza bases in their dishes.	When at a catered event, ask for information on the menu or whether adaptations can be made, and take advantage of the salad bar.
Ask for possible meal adaptations, such as removing high protein/phe containing ingredients or changing dressings.	Travel with a small supply of medical food and LP foods in carry-on luggage.
Gluten free alternatives to bread, pasta or pizza are usually lower in protein. Some food outlets may be able to adapt gluten-free options to provide a lower protein choice which could be counted into the individual's phe allowance.	Provide a customs letter for carry-on contents.
	Consider a short-term change to a powdered, light weight and easy to pack product such as PKU express.
	Recipes for common brands vary between countries. Encourage individuals to check the labels for aspartame, protein content and ingredients while abroad, as the product's recipe may be unsuitable in the country visited.

4.0 Preconception

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The best outcomes for children born to mothers with PKU are reported when phe level is controlled prior to conception and throughout pregnancy, referred to as a 'planned' pregnancy[2, 4, 12, 28].

Previous sections of this guide have covered best practices to promote a planned pregnancy, as well as preparation for preconception. Once these preparations have been completed and the individual has received sufficient supply of medical food and LP foods, they will be able to start the mPKU diet and the preconception stage.

Encourage continued use of contraception until phe levels have been stable in the target range for at least two (2) weeks[7] and the individual is confident with the diet.

Start mPKU diet.

Blood spot monitoring — minimum once weekly[7, 29].

Some centers recommend twice weekly[9] for more frequent feedback and to encourage the diet to be followed consistently throughout the week.

Blood spot results should be reported as quickly as possible[7].

Once to twice weekly telephone/email review[10].

Adjust the diet if phe level has not reduced into target range by 7–10 days after starting the diet (see Troubleshooting section 5.5).

Reassure that a rise in phe is expected around menstruation. No dietary change is required to anticipate this, as levels should reduce back into range afterwards (provided dietary intake remains stable).

Routine metabolic outpatient clinic appointment every 6–12 months[7, 29].

Full plasma amino acid and micronutrient profile.

3-day food diary or 24 hour dietary recall to assess phe exchanges, energy and medical food intake.

Review supply of medical food and LP foods and amend if additional LP foods are required for energy or variety.

Note: Referral to a fertility service should be considered for women who have maintained their phe level within the target range and have not conceived after 6 months of stopping contraception[7, 10].

5.0 Pregnancy

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Dietary management for an unplanned pregnancy requires some additional considerations which are covered in more detail in the **Unplanned PKU pregnancy section 5.4**.

Whether a planned or an unplanned pregnancy, the individuals should be encouraged to contact the metabolic clinic as soon as possible to report a positive pregnancy result. Additional monitoring for the mPKU diet during pregnancy is required.

Blood spot monitoring — minimum twice weekly[7].

Some centers request three times weekly blood spots[10].

Report result as soon as possible[7], ideally within 2 days of the blood spot being taken[10].

Consider adjusting the diet if phe is within 50µmol/L of the limit of target range.
See **Troubleshooting section 5.5** for more information.

Telephone/email review two[7,29] to three times weekly[10].

Encourage the individual to contact their dietitian between reviews with questions or symptoms affecting appetite or the ability to adhere to medical food or the phe-restricted diet.

Outpatient clinic review once per trimester[7, 10, 29].

Full plasma amino acid and micronutrient profile if indicated.

Nutrition visit in clinic including weight, 3-day food diary or 24-hour recall to assess phe, energy and medical food intake.

Review supply of medical food and LP food and adjust as indicated.

5.1 Maternity Care

A pregnancy is usually confirmed by a home pregnancy test or testing by a primary care physician or obstetrician. The individual should inform her primary care physician of pregnancy in order to initiate referral to conventional maternity services.

Maternal care highlights

All routine prenatal care is recommended for women with PKU throughout gestation[8].

Early pregnancy dating using ultrasound is recommended due to concerns about later development of intrauterine growth slowing and the possibility of microcephaly[8].

A level 2 screening ultrasound for fetal anomalies is also recommended. Fetal echocardiography should be performed at 18–22 weeks gestation[8].

Provided no obstetric concerns have been identified, no additional birthing plans or procedures are needed, women with PKU can deliver locally[30].

If concerns are raised during obstetric care monitoring, care and delivery plans may need to be guided by a high risk obstetrics group.

To provide clear communication, a monthly summary letter providing all the blood spot results and dietary advice given can be addressed to the individual and all professionals involved in their mPKU care. See **section 10.2 Example monthly summary letter** for more information.

Priorities for dietary management

First trimester 0 to 12 weeks of pregnancy

Good metabolic control in the early weeks of pregnancy is important for preventing fetal cardiac defects and protecting IQ[2, 6].

Dietary phe tolerance is low and therefore the diet will be the most restrictive during this time. Phe levels can be very sensitive.

Second and third trimester 13–40 weeks of pregnancy

After approximately 16 weeks' gestation phe tolerance can increase rapidly as fetal growth accelerates[10].

As the baby grows it is necessary to increase phe/natural protein significantly to prevent the phe level dropping below the lower limit of the target range[10]. Persistent low phe levels, below 100 µmol/L, have been associated with growth retardation[31].

Assess dietary adequacy. Increase dietary phe prescription by at least 1–2 g of protein/100 mg phe at a time when phe drops to below 150 µmol/L on 1–2 consecutive blood spots. At times, this increase may need to be more rapid, in line with growth, to prevent phe dropping below 120 µmol/L. For more information see **Troubleshooting section 5.5**.

Some women find increasing phe in their diet difficult and will require encouragement and inspiration. When dietary protein intake reaches approximately 15 g or above, higher protein foods can be included. Portions of 3–6 g protein can be useful[32].

Pregnancy associated nausea and vomiting, viruses, infections, and changes in appetite can have a detrimental effect on metabolic control[28] due to inability to meet energy and/or protein requirements. This can lead to catabolism and stimulate release of endogenous protein stores which contribute to elevated phe levels[13]. Managing catabolism during this time is essential, see **sections 5.3 Nausea and vomiting and 5.5 Troubleshooting** for more information.

Providing enough energy, protein and micro-nutrients is essential to support growth and development[14, 28].

Aim to maintain stable phe levels within the target range. Variation in phe level has been shown to be negatively associated with birth weight[28].

Gestational stages of development

10 weeks

The heart is fully formed by 10 weeks and has already started to beat.

12 weeks

By 12 weeks the organs of the fetus including the brain are formed. The fetus will be about the size of a lemon.

Most women will not know they are pregnant until they miss their first or second menses (period) which relates to the 4th or 8th week of pregnancy.

20 weeks

By 20 weeks the fetus is about the same length as a carrot.

30 weeks

By 30 weeks the fetus is about the size of a pineapple.

Pregnancy associated nausea and vomiting usually lessens after 12–16 weeks gestation[33], however, symptoms of indigestion, heart-burn, dizziness and constipation are more common after week 20.

5.3 Nausea and vomiting

Nausea and vomiting is common, affecting up to 85% of all pregnancies[33]. Symptoms typically subside between 12–16 weeks but for up to 15% of women the symptoms will persist beyond 16 weeks[33]. These symptoms can affect appetite[33] but women also often describe feelings of isolation, fatigue, helplessness, depression, anxiety, frustration, difficulty in coping and irritability[33].

For PKU, this can mean poor adherence to medical food, difficulty following a strict diet and/or inability to consume sufficient calories which can lead to catabolism[28]. This can result in increased phe levels as well as insufficient protein and micronutrient intakes. Symptoms of nausea and vomiting in mPKU need to be identified promptly and treated aggressively[7].

Advice from the obstetrician should be sought. Acid-reducing and anti-emetic medications are often discussed early and recommended at a low threshold[7]. Anti-emetic medications are more effective if used earlier[34] and effective use helps to regain metabolic control if it is compromised by nausea, vomiting and associated poor appetite.

In extreme cases, enteral tube feeding can be considered. Positive outcomes have been reported in two (2) cases where gastrostomy tube feeding was used for management of mPKU[35]. Gastrostomy tube placements during pregnancy are complicated by the potential risk of uterine and fetal injury[36]. Each case should be reviewed individually to assess benefit versus risk of each intervention.

If the individual vomits after taking her medical food she must take another dose as soon as possible to minimize any rise in phe level.

General tips for nausea in pregnancy[34]:	Practical tips to help adherence to medical food:
Small, frequent meals and drinks Eating a small meal or snack every 2–3 hours may be helpful. Remember, if portion sizes are smaller, extra calories need to be included elsewhere in the diet e.g. food fortification, high calorie drinks, or snacks.	**Avoid the smell** Use ready to drink resealable medical foods such as PKU cooler or PKU air. For PKU express and PKU sphere* use a container with a fitted lid and straw or cover the glass with plastic wrap and pierce with a straw.
Cold meals This is particularly useful if smells are triggering nausea. LP sandwiches, LP pasta or LP rice salad can be helpful.	**Take the medical food very cold** Make PKU express or PKU sphere* up with ice-cold water or keep PKU cooler or PKU air in the fridge. Mini cool packs can be useful to keep the medical food cold during the day while away from home.
Eat plain carbohydrate-rich foods 20 minutes before getting up in the morning Snacking on plain, carbohydrate-rich foods such as LP crackers or plain LP toast before getting up might help to reduce nausea.	**Try taking small amounts more frequently** Split into smaller doses more regularly through the day. This might be particularly useful if there is a certain time of the day when nausea is worse. Smaller pack sizes are available for certain medical foods so smaller doses can be carried and taken more conveniently.
Try ginger Many women say ginger can reduce nausea. In PKU suitable sources include fresh or crystallized ginger, ginger tea, non-alcoholic ginger beer (make sure the label is checked for protein or aspartame).	**Try a different dilution** Some women find a more dilute medical food easier to take and so, additional water or permitted drink could be added to PKU express. PKU express can be made with less fluid and taken as a 'shot', or 'mini drink' followed by a drink of water, or permitted juice.
Enough rest The need for sleep increases during early pregnancy, and being tired may exacerbate nausea and vomiting. Encourage the individual to let her family or friends know how they can help[37].	**Try a different flavor or medical food preparation** Sometimes a change in flavor or medical food is needed. Medical foods are available as ready to drink liquids, powders (in packets or containers), and as tablets.
	Try a GMP-based medical food GMP-based medical foods such as PKU sphere* are less acidic and have a lower osmolality than AA-based foods[38]. This may be beneficial for some women experiencing nausea or heartburn.

*PKU sphere contains phe and the additional phe must be accounted for when incorporating into the mPKU diet. Changes should be made gradually and closely monitored. It is suggested that dietary phe intake should be adjusted to account for the phe content from GMP-based medical food.

5.4 Unplanned PKU pregnancy

Dietary restriction should begin immediately in unplanned pregnancies, and women should be offered to be seen within 24 hours of informing the metabolic unit of the pregnancy[24]. This appointment should include a full physician's assessment and dietary education.

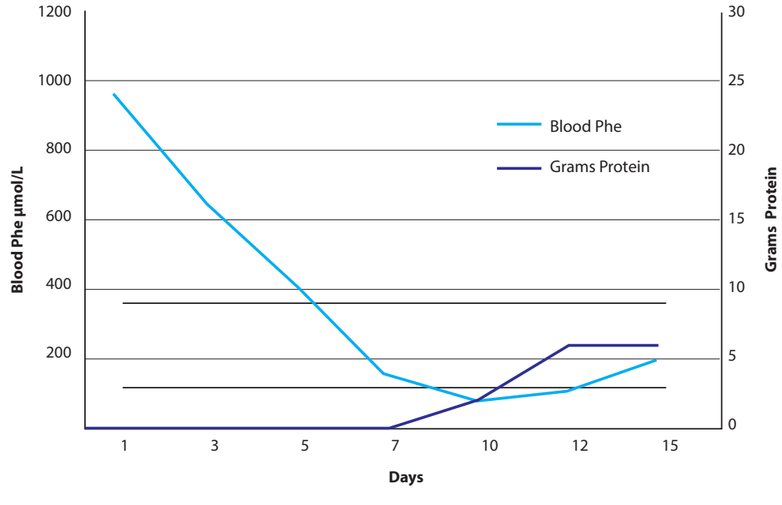
Where an individual is unable to attend an appointment, advice can be provided over the phone and/or email. You could use the **Information collection checklist** and **Dietary advice checklist** on the following pages to support this conversation.

In 'unplanned' pregnancies, evidence suggests that more favorable birth outcomes are reported if the phe level is between 120 and 360 µmol/L at the earliest possible point[12, 28].

Studies show that the later a woman with PKU gains control of her phe levels during pregnancy, the more likely it is that the child will have[2, 12, 28,39,40].
- microcephaly
- lower intelligence/IQ
- cardiac defects
- behavioral problems such as aggression and poor attention

Achieving metabolic control by 8–10 weeks gestation is critical[4]. If metabolic control is not achieved by 10 weeks' gestation the obstetrician may counsel the individual to discuss options around continuing the pregnancy[10].

When the individual is established on a low phe diet with sufficient medical food, the phe levels should reduce quickly into the target range (typically within 7 days). To prevent the phe level dropping below the lower limit of the target range phe/natural protein will need to be reintroduced. For individuals with milder PKU or hyperphe, the reintroduction of dietary phe might need to be rapid, possibly requiring an increase of up to 4–6 g protein/200–300 mg phe at a time.



Information collection check list

When the individual makes contact to report an unplanned pregnancy, collecting the information listed below can help to establish the best course of action until the individual can attend the metabolic clinic.

- [ ] **Date of last period**
- [ ] **Information about any previous pregnancies**
- [ ] **Grams natural protein/mg phe if on diet or when last on diet**
- [ ] **Stock of in-date medical food at home**
  - Exact brand and flavor
  - How much protein equivalent it provides
  - If it contains micronutrients and DHA
- [ ] **Last known phe level (might be several years ago)**
- [ ] **Center previously providing care, if known**
- [ ] **24-hour dietary recall to establish:**
  - Dietary pattern
  - Phe intake
  - Energy intake
  - Knowledge of counting phe/natural protein
- [ ] **Ability to take a blood spot on their own, supply of blood spot cards and lancets at home**
- [ ] **Partner or family who might be able to support with the diet/blood spots**
- [ ] **Contact details including:**
  - Current home address and phone number
  - Primary care physician
  - Emergency contact
  - Address suitable for delivery of samples and letters

Dietary advice check list

- [ ] **Establish medical food to provide at least 70–80 g protein equivalent (PE)**
  - This is critical to reduce phe level rapidly and to ensure to meet protein and micronutrient requirements (see **section 7.0 Calculate**)
  - Ideally, the individual will have sufficient supply at home
  - If the individual has no access to medical food and is unable to attend the metabolic center, urgent samples should be ordered as a priority, ideally with next or same day delivery
- [ ] **Minimize dietary sources of phe**
  - Try to guide the individual through each meal to suggest low protein (LP) alternatives to their current meals
  - Ideally, the individual will have sufficient supply of LP products at home
  - If the patient has no access to LP foods, samples can be ordered from manufacturers until a regular supply can be established.
- [ ] **Maintain sufficient energy**
  - Adequate energy intake is vital to promote anabolism which will help to reduce phe level
  - A phe-restricted diet, without sufficient LP foods, will be low in calories
  - Encourage fortification of meals, snacks and drinks with fats, oils and sugars
  - Supplementation with a glucose polymer or high fat supplements may be indicated
- [ ] **Establish blood spot monitoring**
  - Twice to three times weekly phe blood spots should be established as quickly as possible
  - Remind the individual to pay the appropriate postage when sending her blood spot
  - If the individual has no access to blood spot cards and lancets, provide a supply as quickly as possible
  - If the individual feels unable to take her own blood spot due to needle-phobia, encourage her to seek help from a relative/friend/partner who could help. There are demonstration videos on YouTube™ which you might feel are suitable to refer the individual to.

5.5 Troubleshooting

With frequent monitoring, it will be possible to see the phe level trending upward or downward within the target range. Always check for causes of high or low blood phe concentration before making changes to dietary recommendations. It is good practice to adjust medical food or phe/grams of protein after assessing two consecutive blood spot results. If blood phe is very high, very low or the patient has contacted to report onset of illness, immediate adjustments to phe/natural protein intake and medical food should be considered.

Table 1: High phe levels — Potential causes and corrective actions

Potential cause	Action
Inadequate medical food consumed	Explore reasons why intake has decreased (e.g. illness). Check correct medical food has been issued. Reiterate importance of medical foods (as well as phe control) to support growth. If the volume is too large consider using a powdered version (such PKU express) which can be concentrated, or split into more frequent, smaller doses. Offer a change in flavor or preparation of medical food. Encourage discussion of underlying anxieties.
Excess phe intake	Explore reasons why phe has increased (e.g. new foods or drinks which they may not realize contain phe). Review portion sizes. Food diaries can be a useful way to identify additional phe and counting accuracy. Check low protein food has not been confused with gluten-free. Encourage menu planning, aiming to spread phe/natural protein intake out during the day. Offer further dietary education on phe counting.
Catabolism Illness or infection. If nauseous see **Nausea and vomiting section**.	Reduce phe/natural protein intake. Increase energy intake (see below). Consider increasing medical food if not already maximized.
Poor energy intake or weight loss It can be difficult to meet energy requirements during preconception and early stages of pregnancy, especially when phe allowance is low	Utilize LP foods to increase variety and to prevent hunger or temptations. Increase energy in the diet by the addition of fats, oils, or sugar. Glucose polymers or high fat supplements may be required. Consider using permitted, high calorie fluids to make up PKU express or PKU sphere to increase energy content. Ask your Vitaflo representative for 'My PKU express recipes'. Consider increasing medical food if not already maximised.
Poor adherence	Encourage discussion. Provide practical tips to address cause (e.g. eating out or away from home, at work or over the holidays). Involve other professionals to provide additional support and encouragement. For those individuals who are struggling to adhere to L-AA medical foods during pregnancy, GMP-based medical foods, such as PKU Sphere*, offer an alternative choice and taste that might be preferred. Improved adherence to medical food, when intake was previously suboptimal, is likely to improve phe tolerance and metabolic control.

*PKU sphere contains phe and the additional phe must be accounted for when incorporating into the mPKU diet. Changes should be made gradually and closely monitored. It is suggested that dietary phe intake should be adjusted to account for the phe content from GMP-based medical food.

Table 2: Low phe levels — Potential causes and corrective actions

Potential cause	Action
Insufficient dietary phe intake	Check recommended phe/natural protein intake is being consumed. Suggest replacing low protein foods with protein containing sources (e.g. bread, pasta, rice, couscous). Recommend foods higher in protein as tolerated (e.g. beans, legumes, dairy products). Assess if the individual is overestimating phe/natural protein or basing calculation on uncooked or frozen foods.
Excess weight gain	Encourage healthy weight gain. Food diaries can be a very useful way to assess for excessive energy intake. Consider a lower sugar and calorie medical food if appropriate. Encourage use of phe allowance on staple foods or high protein foods to reduce overall calorie intake.
Rapid fetal growth From 16 weeks of pregnancy phe tolerance/ requirement increases alongside fetal growth.	At around 18–25 weeks phe/natural protein allowance may need to be increased significantly in a short period as growth accelerates. Increase dietary phe prescription by at least the equivalent of 1–2 g protein at a time when phe reduces to below 150 µmol/L on 2 consecutive blood spots. This increase may need to be more rapid in line with rapidly reducing phe levels to prevent phe dropping below 120 µmol/L. Recommend higher protein foods in 3–6 g protein portions once dietary phe reaches the equivalent of approximately 15 g protein[10].

Table 3: mg of phe/g of protein not increasing after 16–20 weeks' gestation — Potential causes and corrective actions

Potential cause	Action
Poor adherence As phe tolerance increases the individual may find she is able to consume more phe without adverse effects on phe control. It is important for both the dietitian and individual to know the mg phe/g protein being consumed so that accurate changes can be made if needed.	Ask the individual to complete a food diary with her actual intake. For example, the individual reports consuming 8 g protein, food diary reveals she is consuming 12 g protein, phe level is stable in target range, then encourage the individual to weigh and measure out 12 g protein.
Inadequate medical food consumed	Explore reasons why intake has decreased (e.g. illness, high volume). Check correct medical foods have been issued. Reiterate importance of medical foods to support growth as well as phe control. If the volume is too large consider using a powdered version (such PKU express or PKU sphere*) which can be concentrated, or split into more frequent, smaller doses. Encourage discussion of underlying anxieties.
Poor fetal growth If the baby's growth slows the phe tolerance can reduce and result in rising blood phe concentrations. Slowing of fetal growth at the very end of pregnancy is normal[41] and sometimes phe tolerance is lower.	Ensure to inform all healthcare professionals involved in their care of high phe levels, especially if there are already concerns of poor fetal growth.
Poor energy intake or weight loss	Utilize LP foods to increase energy intake. Ask if they have taste preference or cravings for certain foods and suggest new recipes. Increase energy in the diet by the addition of fats, oils, or sugar. Glucose polymers or high fat supplements may be required. Consider using permitted high calorie fluids to make up PKU express or PKU sphere* to increase energy content. Ask your Vitaflo representative for 'My PKU Express Recipes'. Consider increasing medical food if not already maximized.

*PKU sphere contains phe and the additional phe must be accounted for when incorporating into the mPKU diet. Changes should be made gradually and closely monitored. It is suggested that dietary phe intake should be adjusted to account for the phe content from GMP-based medical foods.

In the experience of the Charles Dent Metabolic Unit, individuals who have an uncontrolled phe during pregnancy should be:

- highlighted to the metabolic physician.
- offered a metabolic clinic appointment, further dietary education and/or a home visit to help identify factors affecting metabolic control.
- offered a hospital admission to supervise the phe restricted diet, intake of medical foods and blood spot monitoring as well as providing further advice and support from the dietitians, dietetic assistant, metabolic physician, or psychologist as required.

If phe levels remain high after 2 weeks of interventions:

- a multi-disciplinary team meeting should be called to discuss next actions including referral to appropriate services if there are safeguarding concerns.
- the outcome of the multi-disciplinary team meeting should be discussed with the individual.

In the Charles Dent Metabolic Unit experience safeguarding services have; reinforced the health messages from the metabolic team, offered additional support such as childcare, provided some financial support with attending appointments, and supported with posting of blood spots. The process of involving safeguarding services is lengthy and the multi-disciplinary team decision to refer is not taken lightly due to concern of breaking trust or rapport between the metabolic team and the individual.

6.0 Postpartum

6.0 Postpartum

Adherence to the PKU diet can be particularly challenging after the baby is born. The new baby will likely require much of the individual's time and attention.

Continuing the PKU diet

Some studies associate adults aiming for phe levels within the target range with positive outcomes on:

- sustained attention[42]
- mood[42]
- reaction times[43]
- cognitive ability[44]
- executive function[44]

Tip: Preparing and freezing LP meals as well as stocking up on LP foods before the baby arrives will help.

Tip: Recruit the partner or family members to support the individual with preparing and organizing the diet.

It is important to ensure her diet is adequate in calories, protein and micronutrients to support lactation. See **Calculate section 7.0** for more information.

Nutrient intake recommendations for lactation are the same as during the third trimester of pregnancy[29].

Dietary phe recommendations for lactation remain the same as requirement for the third trimester[29].

Tip: Encourage the individual to contact the metabolic center if she would like further support.

For the infant	For the mother
Record weight, length (if available) and head circumference at birth. Newborn screening as per national/local protocol. An echocardiogram is recommended for all infants where metabolic control was poor at conception or during the pregnancy[7]. Follow up care with psychometric assessments by a clinical psychologist at 1 year, 4 years and 8 years may be beneficial[10].	Restart contraception after birth. It has been observed that women with PKU who did not plan their pregnancy may be less likely to plan subsequent pregnancies[28]. Offer a metabolic outpatient clinic review 4–8 weeks postpartum [10, 29], and every 6 or 12 months thereafter as per routine clinical care[7, 29]. Usual follow up from primary care physician.

Exclusive breastfeeding for a baby's first 6 months of life, where appropriate, should be encouraged in line with WHO recommendations[45].

Mothers with PKU should be encouraged to breastfeed irrespective of their phe level postpartum[33, 42]. Infants born to women with PKU who do not inherit PKU are able to metabolize phe contained in their mother's breastmilk without difficulty[7,32,46].

Babies who do inherit PKU can still be breastfed by their mother, in conjunction with phe-free infant formula, with close monitoring[7,46].

Benefits of breastfeeding for the infant	Benefits of breastfeeding for the mother
• Providing ideal nutrition for healthy growth and development[45]. • Helping to build up a strong immune system[45]. • Encouraging a strong bond between mother and infant[45].	• Faster return to pre-pregnancy weight[45]. • Protection against certain diseases[45].

7.0 Calculate

7.0 Calculate

7.1 Phenylalanine

Phe is an essential amino acid so a small, measured amount needs to be provided from the diet. Phe requirement/ tolerance varies among individuals depending on their PAH enzyme activity level, and can also be affected by[13,47].

- Adequacy of medical food intake
- State of health (i.e. presence of nausea, vomiting or infection)
- Stage of pregnancy
- Weight changes
- Energy intake

The initial phe prescription provides a starting point for preconception. The aim is to maintain stable levels[28]. It is practice at the Charles Dent Metabolic Unit to aim for phe levels in the middle of the target range prior to conception and throughout pregnancy. After initiating the mPKU diet for preconception the phe level should reduce into the target range by the 7th to 10th day[32]. If not, then further dietary manipulation may be required, see **Troubleshooting section 5.5**.

Individuals with low phe tolerance

Dietary protein intake is severely restricted to control phe intake for individuals with a low phe tolerance (previously described as 'classical' PKU).

On diet	Off diet
A food diary might be useful to correlate current phe levels and phe intake and make the necessary adjustments to achieve target phe levels. In individuals who are on diet and maintaining phe levels 500–600 µmol/L in the experience of the Charles Dent Metabolic Unit, a good starting point is to reduce phe prescription by half. This is usually sufficient to bring the levels into the middle of the target range 120–360 µmol/L.	If an off diet blood phe level is available, it is useful for calculating the initial prescription for phe during preconception: **Table 4: suggested Phenylalanine prescription to achieve phe value 100–300 µmol/L in PKU. Adapted from Maillot, et al[10] and updated with Charles Dent Metabolic Unit experience.**

Blood phe concentration – off diet	mg phe (approximate g protein) to commence preconception diet
>2000 µmol/L	200 (4)
1600–2000 µmol/L	300 (6)
1200–1600 µmol/L	400 (8)
1000–1200 µmol/L	500–600 (10–12)
600–1000 µmol/L	600–700 (12–14)

Individuals with higher phe tolerance

Individuals with high phe tolerance (previously referred to as mild PKU) or hyperphe will require less dietary restriction, however they require the same level of monitoring and support to ensure phe levels remain in target range and their dietary intake is nutritionally adequate.

Prior to making dietary changes, a series of fasting blood spots (at least 3 to find an average) will be needed to estimate their phe tolerance. This average phe level can allow an estimation of their phe prescription using table 5.

Table 5: suggested Phenylalanine prescription to achieve phe value 100–300µmol/L in hyperphe *from the Charles Dent Metabolic Unit experience.

Blood phe concentration — off diet	Dietary recommendations
450–600 µmol/L	30–40 g dietary protein and additional medical food
300–450 µmol/L	Usual diet and additional medical food
<300 µmol/L	Usual diet and monitor blood phe levels

European guidelines state that untreated phe levels of less than 360 µmol/L do not require dietary management[7] but would benefit from monitoring of phe levels during pregnancy and outcome of the child to support future research.

Use of sapropterin in maternal PKU.

Although sapropterin therapy may support significant dietary liberalization, it seldom allows individuals to maintain appropriate blood phe without some phe restriction and medical food. Regular monitoring of blood phe, dietary adequacy, and nutritional status continue to be essential. Individualized patient counseling includes planning and calculating the diet with a higher phe or protein allowance, choosing appropriate natural protein sources, reading labels, distributing high-phe/intact protein foods throughout the day, meeting micronutrient/vitamin requirements when the medical food prescription is decreased, and understanding the importance of consistent sapropterin dosing. [29,48,49.]

There is limited published evidence on the use of saproperin in pregnancy[50–52], however this adjunct therapy should be considered when the effects of not using it outweigh potential adverse effects[8]. Guidelines suggest use of sapropterin should be evaluated during pregnancy on a case-by-case basis[29], and may be appropriate especially in women with moderate or mild forms of PKU who are not able to maintain blood phe levels in the recommended treatment range for pregnancy[53]. Given the known adverse effects of elevated maternal Phe on pregnancy outcomes, US guidelines recommend that women taking sapropterin who become pregnant should be offered the option of remaining on the medication, and women who may benefit from sapropterin be offered the option of using it during pregnancy[29]. Ideally, sapropterin response should be determined prior to pregnancy to avoid fluctuations in Phe levels or difficulty in interpretation of responsiveness[8].

It is essential to regularly monitor phe levels and individualize the diets of responders to sapropterin as described above. Particular attention should be given to assessing micronutrient intake dependent on medical food intake and natural protein tolerance, and supplementing where appropriate to meet specific recommendations during pregnancy.

7.2 Protein

Due to the restriction of dietary protein required to achieve target phe levels in mPKU, it is vital to ensure sufficient medical food is prescribed to meet protein requirements[13,15].

The role of medical food in dietary management of mPKU includes:

- Allowing to keep a low blood phe concentration[7,13]
- Providing a main source of protein and micronutrients which are essential for growth and cardiac development of the fetus[13–15,54].

To promote protein utilization and anabolism medical food should be consumed:

- At regular intervals in 3–4 doses spread throughout the day[55]
- With LP sources of energy[56]

Protein requirements increase in pregnancy and this usually complements an increase in phe tolerance. This increase in phe tolerance is therefore met by dietary protein rather than increasing medical food. As phe tolerance increases the individual can be encouraged to include higher protein options as tolerated[10,32].

Table 6: Calculation of protein requirements for mPKU

Reference	Calculation for Daily Protein Requirements (g/Day)				
	Non-pregnant adult	First trimester	Second trimester	Third trimester	Lactation (up to 6 months)
American PKU guidelines[29]	120–140% RDA for age	>70	>70	>70	>70

Twin pregnancy

For a woman with PKU carrying twins, one recommendation is that protein intake be increased by 10 g in the first trimester and then adjusted as blood Phe status is monitored. Another recommendation for multiple fetuses is to provide stated protein needs of 0.9 g/kg/day plus an additional 12 g/day, and energy needs at 700 kcal/day per fetus. Guidance for other nutritional requirements of pregnancy in women without PKU applies. Providing sufficient energy to promote adequate weight gain is essential, especially early in pregnancy when nutrient stores are laid down for the third trimester. In reported experience from two clinicians, phe tolerance increased from 300 to 1500 mg/d for one twin pregnancy, and from 550 to 1000 mg/day in another[57].

7.3 Energy

Providing enough energy helps to avoid catabolism and therefore helps to maintain a more stable phe level. Inadequate energy intake is linked with poor maternal weight gain, lower birth weight and poorer phe control[13, 15].

There are several reports which estimate the additional energy demands of pregnancy and lactation for the general population. No studies have determined energy requirements in pregnancy or lactation specifically for PKU.

Table 8: Energy requirement recommendations for pregnancy and lactation in the general population

Reference	Estimated Additional Energy Required (kcal/Day)			
	First trimester	Second trimester	Third trimester	Lactation (up to 6 months)
IOM 2005[58] for girls 14–18 and women 19–50 years	nil	+340	+454	+330
FAO/WHO/UNU 2001[59]	+85	+360	+475	+505

As rates of overweight and obesity in the general and PKU population are rising[60], it is important to also avoid excess weight gain during pregnancy. It is ideal for women to begin pregnancy at a healthy weight (BMI 18.5–24.9 kg/m²). Women who are underweight or overweight at the beginning of pregnancy are at risk of poor maternal and fetal outcomes. Women who are underweight benefit from greater weight gain during pregnancy. For women who are overweight and obese, the consequences of weight change during pregnancy are not completely understood. Due to this uncertainty, as a precaution weight loss during pregnancy is not advised[61].

Energy requirements in pregnancy vary, the best indicators of adequate energy intake are appropriate weight gain for BMI status and good metabolic control. Inadequate intakes of protein, fat and energy may result in elevated phe levels and may contribute to poor outcomes[13].

7.4 Micronutrients

Monitoring of nutritional status in pregnancy is essential. It is important to assess dietary intake of all key micronutrients and biochemical parameters to ensure nutrient adequacy. Other micronutients of note in addition to the below are vitamin A, D, selenium and zinc[29].

Folic Acid

400 µg per day[7]

Folic acid is essential for neural tube development. In mPKU, 400 µg is recommended during preconception and the first trimester in addition to folic acid contained in medical food[7]. In some countries 5 mg is recommended during pregnancy in obesity or with specific co-morbidities such as diabetes[62,63].

Vitamin B_{12} status should be monitored to ensure that high intake of folic acid does not mask B_{12} deficiency[7].

Long chain polyunsaturated fatty acids (LCPs)

200–300 mg DHA per day[29].

The phe restricted diet for PKU does not contain dietary sources of omega-3 LCPs. In PKU, DHA can be provided from; fortified medical foods or over-the-counter supplements. It is important to check if these supplements contain vitamin A, fish liver oil, or sources of protein or aspartame.

Iodine

Pregnancy and lactation:
200 µg per day[69]

Iodine is an essential nutrient, crucial for neurodevelopment[70].
In the general population there are concerns that women may not consume enough iodine in pregnancy[71,72]. Sources of dietary iodine are severely restricted in the mPKU diet. It was found that average intakes in PKU individuals who were not routinely taking medical food was 30 µg/day and individuals taking >120% protein recommendations from medical foods was 120 µg/day[65].

Not all medical foods contain sufficient iodine for pregnancy and lactation. It is important to consider appropriate supplementation to meet increased requirements.

Vitamin B_{12}

Pregnancy: 4.5 mg per day[60]

Lactation: 5.0 mg per day[60]

Patients with PKU are at risk of vitamin B^{12} deficiency[21, 61-63]. The vitamin B^{12} status (including functional marker plasma homocysteine and/or methylmalonic acid) for all individuals with PKU should be regularly reviewed and corrected if low[7].

In mPKU, insufficient vitamin B^{12} is associated with infant cardiac defects[15].

Tyrosine

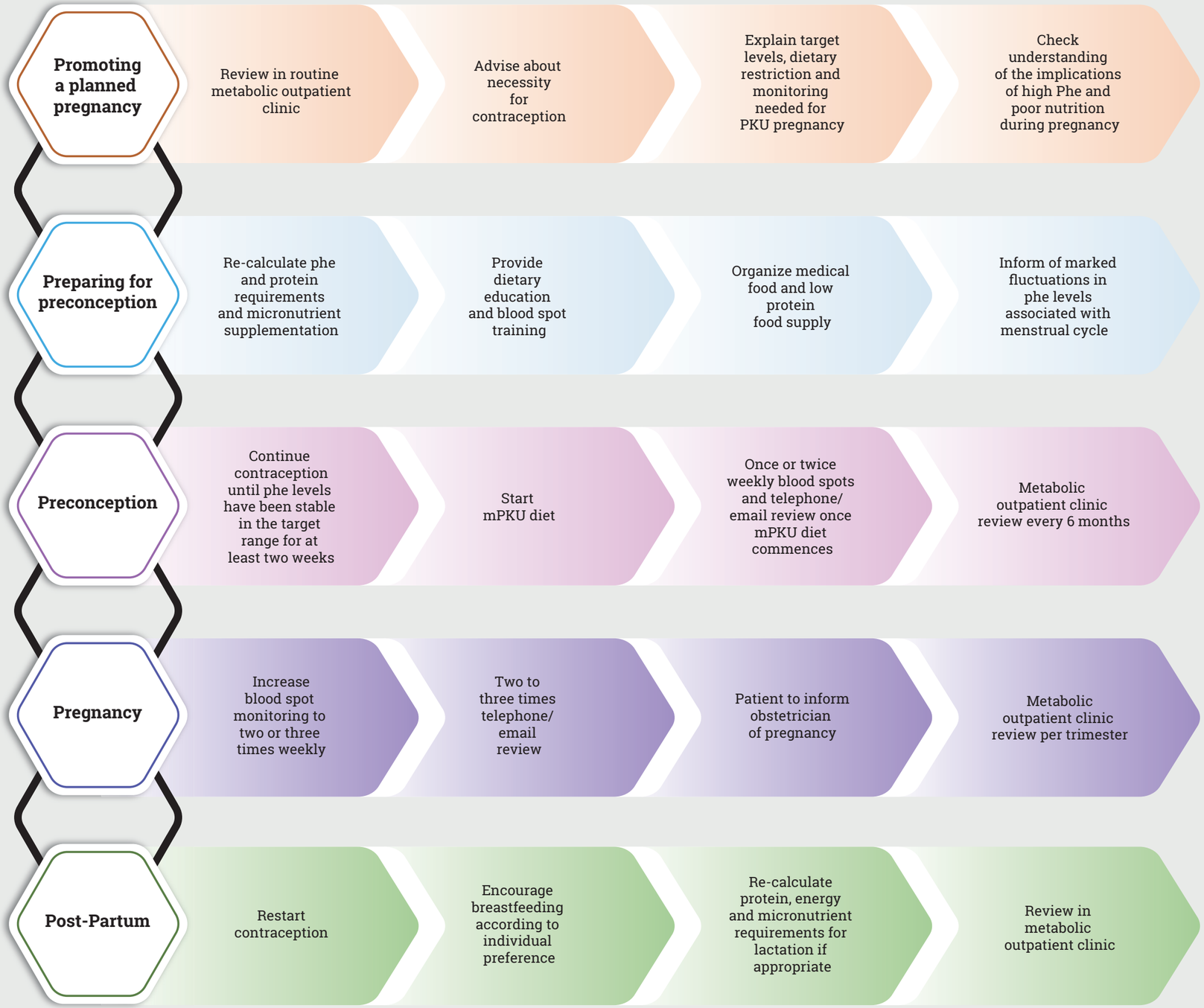
6 g per day[7]

In PKU, tyrosine (tyr) becomes an essential amino acid. At least 6 g of tyr is adequate to meet requirements for pregnancy[7]. Sufficient tyr should, therefore, be provided by medical foods.

Some centers may supplement with additional tyr. Vitaflo's Tyrosine 1000 single dose amino acid packets are available. These are presented in single dose packets, making it convenient to add into the diet, if required.

Additional Tyrosine supplementation (to that present in medical foods) should be undertaken with caution. Van Spronsen et al recommended not giving extra free tyrosine without knowing the diurnal variations in the blood tyrosine concentration and having biochemical evidence of a tyrosine deficiency[68].

Summary of maternal PKU management



8.0 Vitaflo's product range supporting the dietary management of mPKU

8.0

8.0 Vitaflo's product range supporting the dietary management of mPKU

Vitaflo's range of medical foods

Designed with features intended to aid adherence, which include a designed consumer friendly packaging, lower* volume, lower* energy, lower* sugar and specific flavor blends, which in combination, may help adherence and facilitate metabolic control.

Product	Presentation	Pack	Flavors	Micronutrients	LCPs	Suitability for mPKU management
PKU cooler 	Ready-to-drink resealable pouches	20 g PE 15 g PE 10 g PE	Red White Orange Purple	Yes	Yes (DHA)	**A familiar product** and so may be a first choice for the mPKU diet for some. Available in a **range of pack sizes allowing dose adjustment** in 5 g PE intervals as nutritional needs change. Smaller pack sizes **can facilitate a 'little and often' approach** to taking medical food. Could be useful during nausea as consumed directly from the resealable pouch, limiting exposure to the smell of the product. **It is the only ready-to-drink medical food available in a neutral (white) flavor which might be less intense.**
PKU Air 	Ready-to-drink resealable pouches	20 g PE	Green (Citrus Twist) Yellow (Mango Breeze) Gold (Coffee fusion)	Yes	Yes (DHA)	Specifically designed with the needs of adults in mind with **flavor blends designed for a mature palate**. This will offer **novel flavor options** to individuals returning to medical food for the mPKU diet. **The lowest calorie ready-to-drink medical food for PKU****. Could be useful during nausea as consumed directly from the resealable pouch, limiting exposure to the smell of the product.
PKU Express 	Pre-measured, single use packet	20 g PE 15 gPE	Unflavored Orange Lemon Tropical	Yes	No	Flexible preparation options. **Suitable to be taken as a paste, low volume mini drink or diluted to be a less concentrated drink, adapting to changing preference throughout pregnancy.** **Pre-measured, accurate** dose of powdered medical food which **can be personalized** by reconstituting with water, or other permitted drinks to make shakes and smoothies. Provides a **lightweight option that is easily transportable** for individuals traveling for work or leisure during pregnancy.
PKU sphere 	Pre-measured, single use packet	20 g PE 15 gPE	Red Berry Vanilla	Yes	Yes (DHA)	GMP-based medical foods provide an alternative taste to traditional amino acid medical foods which may **optimize adherence**. Similar to the appearance and smell of standard protein shakes. Using the PKU sphere shaker, PKU sphere can be **reconstituted on the go without appearing to be a medical food product.** **Due to the phe content (36 mg phe per 20 g PE), the phe-restricted diet could need adjustment in those individuals with low phe tolerance.** Changes should be made gradually and closely monitored

Vitaflo's additional supplementary products

	Presentation	Description	Suitability for mPKU management
Tyrosine1000 	4 g packet = 1000 mg of L-Tyrosine	A powdered tyrosine amino acid on a carbohydrate base.	Flavorless powder which can be mixed with water, permitted drinks or added to powdered medical foods such as PKU express or PKU sphere before reconstituting.

* Lower compared to traditional medical foods
** Per gram of protein equivalent

9.0 References

9.0

9.0 References

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10.0 Appendix

10.1 Example Letter of Medical Necessity

The following has been drafted for healthcare professionals (i.e. dietitian or physician) to complete in support of medical food reimbursement coverage. This template can be customized to fit the patient's individual needs and it is the health care professional's responsibility to ensure the content is appropriate. Please note that this resource does not guarantee insurance coverage or reimbursement of medical foods.

Hospital contact information and logo

LETTER OF MEDICAL NECESSITY TEMPLATE

DATE:
TO:
FROM:
PATIENT NAME:
DOB:
ICD DIAGNOSIS CODE:

Ht: Wt:
MEDICAL FOOD ORDER:
INSURANCE ID:
SUBSCRIBER:
GROUP NO:

To Whom It May Concern:

The purpose of this letter is to explain the medical necessity of Vitaflo [product prescribed] and request insurance coverage for this medical food.

[NAME] is a **[AGE]** year old patient diagnosed with phenylketonuria (PKU), an inborn error of metabolism. This patient's metabolic disease was diagnosed **through newborn screening which is mandated by law in the USA** on **[DATE DIAGNOSED]**. PKU is a life-long inherited metabolic disease, characterized by the body's inability to utilize the essential amino acid, phenylalanine (Phe). PKU is caused by a deficiency of the enzyme phenylalanine hydroxylase. Due to this enzyme deficiency, the affected individual is unable to metabolize Phe, leading to an accumulation of Phe in the blood. This accumulation is toxic to the central nervous system leading to severe problems, including **[severe neurological complications, IQ loss, memory loss, concentration problems, mood disorders, and potentially mental retardation].** The standard of care is to severely restrict protein containing foods, and prescribe a medical food designed to provide the amino acids (excluding Phe), vitamins, minerals and trace elements in a precise mix to meet the patient's nutrient needs. The patient requires this phe-free medical food as their primary source of dietary protein.

Additionally, this patient is planning to become pregnant. Women with PKU must optimize metabolic control when planning, and during pregnancy. High blood Phe is teratogenic and can result in **[maternal PKU syndrome: microcephaly, mental retardation, cardiac defects, and low birth weight (<2500g) in the offspring.]** Tight control isnecessary due to the positive amino acid gradient a cross the placenta, thereby exposing the fetus to higher Phe concentrations than the mother. Maternal PKU syndrome can be avoided with diligent dietary management prior to conception and during pregnancy. The American College of Medical Genetics and Genomics management guidelines recommend maintaining Phe levels between 120-360µmol/L prior to conception and throughout pregnancy.

The patient is currently prescribed **[PRODUCT]**, a medical food formulated to meet the specialized nutrient needs of patients with PKU fed orally or enterally. The prescribed medical food is imperative in the dietary management of this patient's condition and to support a normal healthy pregnancy. When dietary management recommendations are adhered to, the chances of a good pregnancy outcome are comparable to the general population**. [PRODUCT]** is medically necessary to ensure that metabolic control is maintained.

[PRODUCT] is a medical food, manufactured in the UK for Vitaflo USA, LLC (1-888-848-2356.) HCPCS is B4162 (Pediatric) & B4157 (Adult). Reimbursement codes for **[PRODCUT]: [10-DIGIT CODE] (FLAVOR)**;
[If applicable include: [PRODUCT] is on the State of **[_____ Medicaid, BCMH, and/or Metabolic formulary.]**

I appreciate your consideration of this request. Your authorization of this prescribed order will provide this patient the medical food needed to support adherence to dietary management recommendations and support a good pregnancy outcome.

Please feel free to contact me if you have additional questions.

Sincerely,
Name of Physician
Institution
Contact Information
Attachments: Prescription

Clinic Notes

10.2 Example Monthly Summary Letter

This is a an example monthly summary letter which is used at CDMU. This letter is sent to the patient, their primary care physician, and obstetrician. It aims to provide regular communication on the individual's metabolic control during their pregnancy and provide an opportunity to highlight issues (if any) to all healthcare professionals involved.

Hospital contact information and logo

DATE:
PATIENT NAME:
PATIENT ADDRESS:

Dear (PATIENT NAME)

Here is a summary of your results over the past month:

DATE	BLOOD PHENYLALANINE (UNITS)
DD-MM-YY	XX
DD-MM-YY	XX
DD-MM-YY	XX
DD-MM-YY	XX
DD-MM-YY	XX

COMMENT:

Your Phenylalanine levels have been excellent over the past month. The ideal targe range for preconception and pregnancy is (INSERT TAGRET RANGE AND UNITS). Well done and keep up the good work!

DIETARY ADVICE:

Please continue with:

- (INSERT MG OF PHE OR GRAMS OF PROTEIN) per day
- 4 x 25g packets of PKU express /day

NEXT BLOOD TEST:

(INSERT DAY/DAYS)

Please do not hesitate to contact us if you have any queries.

With best wishes,

Metabolic Dietitians

Copy to: Primary Care Physician
Obstetric