12 Nutrition Management of Maternal Metabolic Disorders

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Core Messages

- Children born to mothers with phenylketonuria (PKU) who have high blood phenylalanine during pregnancy are at risk of developing intellectual disability, microcephaly, congenital heart defects, low birth weight and facial dysmorphism.
- Women with PKU should maintain blood phenylalanine below 360 µmol/L before and during pregnancy for optimal pregnancy outcomes.
- In inherited metabolic disorders other than PKU, the fetus does not appear to be at risk; however, the mother is at risk of metabolic crises associated with catabolism during pregnancy or in the post-partum period unless energy intake is sufficient.
- The maternal diet for amino- and organic acidopathies typically includes a disease-specific medical food as the main source of protein, a limited amount of intact protein, and sufficient energy, fat, vitamins and minerals to support fetal growth.

12.1 Background

The nutrition management of inherited metabolic disorders during pregnancy runs the spectrum from maternal phenylketonuria (PKU) that has been studied for decades to case reports for rarer metabolic diseases. More women with urea cycle disorders, maple syrup urine disease and organic acidemias have been well-treated from birth and are now of childbearing age. The impact of metabolic disease on pregnancies differs according to the specific disorder. In PKU, it is well understood that high maternal blood phenylalanine concentrations can affect the developing fetus, whereas in other inherited metabolic disorders it is the mother who is at greater risk, especially during the post-partum period when protein catabolism is greatest. Unlike in PKU, it appears that in these disorders, the infant is not at increased risk of adverse outcomes. Regardless of the metabolic disorder, proper nutrition management and monitoring is important to assure positive pregnancy outcomes.

12.2 Maternal Phenylketonuria

Maternal PKU (MPKU) refers to pregnancy and childbearing in a woman with PKU. Phenylalanine is teratogenic to the developing fetus and there-

fore, in MPKU, the infant is at risk because of the metabolic disorder of the mother. Children born to mothers with PKU whose blood phenylalanine is not controlled before and during pregnancy may be born with intellectual disability, microcephaly, congenital heart defects (CHD), low birth weight and facial dysmorphism [1, 2]. The incidence of adverse outcomes in MPKU is related to maternal blood phenylalanine concentration, and is highest in children born to mothers who did not have blood phenylalanine in the recommended treatment range during their pregnancies. The recommended maternal blood phenylalanine concentration throughout pregnancy is 120–360 μmol/L. [3–6] This recommendation is based on the MPKU Collaborative Study, a 12-year study of 413 pregnancies which showed lower intelligence in offspring of mothers whose average blood phenylalanine concentration exceeded 360 μmol/L. [7]

The British Registry of 228 live births found a negative correlation between intellectual outcomes of the offspring and maternal blood phenylalanine concentrations exceeding 300 μmol/L; therefore, in the United Kingdom, it is recommended that blood phenylalanine be maintained between 100 and 250 μmol/L for optimal outcomes [8]. In Australia, even lower blood phenylalanine concentrations of 60–120 μmol/L are recommended during pregnancy [9]. Many centers in the United States also counsel women to maintain blood phenylalanine under 240 μmol/L [5]. However, there is some evidence that low (<120 μmol/L) blood phenylalanine concentrations may be associated with poor fetal growth [10] and suggests that low blood phenylalanine should be avoided. With the advent of medical management for PKU, the potential for a woman to have a sustained low blood phenylalanine during pregnancy is greater than with diet management alone. Care must be taken to ensure that adequate amounts of phenylalanine are available to support normal fetal growth.

Stability of blood phenylalanine throughout pregnancy was associated with better development in the offspring of MPKU in one study [11], which showed that the variability in maternal blood phenylalanine concentration had an impact on intellectual outcome at 1, 8 and 14 years, even in women who had good metabolic control. Variability of blood phenylalanine may be a marker for the severity of PKU; women who have severe PKU are less able to tolerate day-to-day changes in dietary phenylalanine intake and, therefore, have greater variation in blood phenylalanine concentrations. In the MPKU Collaborative Study, women were given a severity score (based on genotype, untreated blood phenylalanine concentration and dietary phenylalanine tolerance) and the score was the strongest predictor of both maternal blood phenylalanine during pregnancy and of variability in maternal blood phenylalanine concentrations [12].

In addition to phenylalanine, other nutrients are of importance in MPKU outcomes, including protein, fat, energy and vitamin B_{12}. Maternal protein, fat and energy intake are negatively correlated with blood phenylalanine concentration [13]. Inadequate energy intake was associated with poor maternal weight gain and lower birth measurements. A higher incidence of congenital heart defects was seen in children born to women with lower total protein intakes (intact and medical food), especially when both low vitamin B_{12} and folate intake were also observed [14].

12.3 Nutrition Management of MPKU

The principles of nutrition management in MPKU are to maintain blood phenylalanine concentrations in the target range, support normal weight gain for pregnancy (Table 12.1) and provide adequate nutrients for pregnancy. Other than phenylalanine, protein and tyrosine, the nutrient needs of a pregnant woman with PKU do not differ from the Dietary Reference Intakes (Table 12.2) [15]; however, obtaining adequate nutrition for pregnancy while on a phenylalanine-restricted diet can be a challenge.

Table 12.1 Recommendations for total and rate of weight gain during pregnancy by prepregnancy BMI [22]

Prepregnancy BMI	BMI[a] (kg/m^2)	Total weight gain (pounds)	Rates of weight gain in second and third trimesters[b] (pounds/week)
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25.0–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	>30.0	11–20	0.5 (0.4–0.6)

[a] To calculate BMI go to www.nhlbisupport.com/bmi/
[b] Calculations assume a 0.5–2 kg (1.1–4.4 lbs) weight gain in the first trimester [74–76]

Table 12.2 Recommended daily intake of phenylalanine, tyrosine and protein in pregnancy and lactation for women with MPKU [13]

	Phenylalanine (mg)	Tyrosine (mg)	Protein (g)
Trimester 1	265–770	6000–7600	≥70
Trimester 2	400–1650	6000–7600	≥70
Trimester 3	700–2275	6000–7600	≥70
Lactation	700–2275	6000–7600	≥70

12.3.1 Phenylalanine and Tyrosine

Phenylalanine should be provided in the amount needed to maintain blood phenylalanine in the target range. For a woman with PKU who comes to the attention of the clinic during pregnancy, it is important to reduce phenylalanine intake as soon as possible. Some centers suggest a "washout" period where only medical food, fruits, low phenylalanine vegetables, and low protein foods are included in the diet until the blood phenylalanine concentration decreases to within the desired range. In severe PKU, the average phenylalanine intake is 250–300 mg/day; if a patient's phenylalanine tolerance is not known, this is a reasonable goal, to begin with. Phenylalanine intake in the first trimester ranges from 265 to 770 mg/day [5].

With frequent monitoring of blood phenylalanine and food intake records, dietary phenylalanine can be adjusted until the target range is reached. If blood phenylalanine concentrations are not in good control within a few days, consider whether the woman is getting enough protein (medical food) and/or energy (Box 12.1). Morning sickness or hyperemesis gravida can also be a cause of high blood phenylalanine. Prolonged morning sickness can be treated with antiemetics. In cases where metabolic control is compromised due to hyperemesis gravida, hospitalization may be necessary in order to reverse catabolism and reduce blood phenylalanine concentrations. Hospitalization may also be necessary for intensive diet education.

Box 12.1: Points to Consider if Blood Phenylalanine Is Too High

- Is medical food intake sufficient?
- Is phenylalanine intake excessive?
- Is energy intake sufficient?
- Has there been adequate weight gain?
- Has there been an illness?

If the blood phenylalanine concentration becomes too low, 10–25% more phenylalanine is added to the diet. As pregnancy progresses and the woman gains weight, phenylalanine tolerance will increase. This is especially true in the second and third trimesters when the fetus is growing rapidly and phenylalanine intake doubles or triples over prepregnancy intake [5].

Tyrosine is a conditionally essential amino acid in the MPKU diet. Medical food is the major source of dietary tyrosine; therefore, if a woman has low blood tyrosine, check to make sure that she is consuming all of her medical food. Blood tyrosine fluctuates diurnally and is lowest after an overnight fast. Before adding a tyrosine supplement, monitor non-fasting blood tyrosine concentrations to assess whether supplementation is necessary [16].

12.3.2 Protein

The Dietary Recommended Intake (DRI) for protein in pregnancy is 71 g/day [15]. This is an additional 21 grams over non-pregnancy protein

recommendations in order to support the growth of the placenta and fetal tissue. Medical food is the major source of protein for individuals with PKU treated with diet alone. When protein is supplied as medical food containing L-amino acids, it is oxidized more rapidly than intact protein and, therefore, the amount of protein needed is greater than normal (1.2 times the DRI or 85 g/day). In severe PKU, medical food provides about 80% of the protein or about 68 g protein/day. A simple way to assure that adequate protein is being provided during pregnancy is to meet the DRI for protein from amino acid-based medical food alone.

The nutrient content of medical foods varies widely. If high-protein, lower-calorie medical foods are used, the volume of medical food required is lower, but fat and energy content are also lower and sufficient energy must be supplied elsewhere in the diet. Conversely, when lower-protein, higher-fat medical foods are used, a higher volume of medical food is necessary to meet protein requirements. The choice of medical food is made on an individual basis depending on the needs and preferences of the pregnant woman, and sometimes a combination of medical foods is best. Additional medical food or intact protein is often needed as the pregnancy progresses and should be added if plasma prealbumin or plasma amino acid concentrations are low for pregnancy (Table 12.3).

Medical foods containing glycomacropeptide (GMP) (Chap. 10) have been used successfully in MPKU pregnancies. While GMP-medical foods contain a small amount of phenylalanine (less than 2 mg per gram of protein equivalent) [17], the amount provided is usually well tolerated, especially during periods of anabolism such as pregnancy. In case reports, reduction in phenylalanine from food has not been needed to account for the phenylalanine provided in the medical food [18]. However, for women with very low prepregnancy phenylalanine tolerance, the additional phenylalanine from GMP may need to be counted in the dietary prescription. Ideally, the effect of the additional phenylalanine in medical food on blood phenylalanine concentrations would be determined during the prepregnancy period.

Large neutral amino acids (LNAA) are contraindicated as a sole source of protein in women with MPKU because LNAA do not sufficiently lower blood phenylalanine to within the desired treatment range of 120–360 μmol/L. [19] The proposed mechanism of action of LNAA is to block uptake of phenylalanine into the brain by supplementing other amino acids that share the LAT-1 transport system across the blood-brain barrier. Some reduction in blood phenylalanine has been seen with LNAA use, but not to the degree necessary to protect the fetus [20].

Table 12.3 Amino acid concentrations during pregnancy (in women without PKU; [Mean +/– SD (μmol/L) [77]

	<20 weeks	20–30 weeks	>30 weeks
Isoleucine	53 ± 23	53 ± 15	46 ± 15
Leucine	114 ± 38	107 ± 30	91 ± 23
Methionine	34 ± 54	20 ± 7	27 ± 7
Phenylalanine	67 ± 30	60 ± 18	54 ± 12
Threonine	118 ± 34	168 ± 42	193 ± 50
Tyrosine	55 ± 22	50 ± 11	50 ± 17
Valine	196 ± 60	179 ± 43	162 ± 43

12.3.3 Energy

Energy requirements in pregnancy are the same for women with PKU as other individuals [21]. Sufficient energy is especially important in MPKU to prevent protein from being used as an energy source, thereby increasing blood phenylalanine concentrations. Energy intake is sufficient if the woman with PKU is gaining weight appropriately (Table 12.1) [22].

12.3.4 Fat and Essential Fatty Acids

Fat is needed in pregnancy to supply sufficient energy as well as the precursors for essential fatty acids that are needed for fetal brain development. In pregnancy, about 30–35% of calories should come from fat [15]. For a 2400-calorie diet, this translates to 93 grams of fat, the equivalent to approximately 6 tablespoons of fat. For expectant mothers on a fat-free or low-fat medical food,

Box 12.2: Facts About Fat in the MPKU Diet

- Provide 30–35% of energy as fat.
- DRI for essential fatty acids [15]:
  - Linoleic acid (omega-6) – 13 g/day
  - α-linolenic acid (omega-3) – 1.4 g/day
- Soybean and canola oils are readily available essential fatty acid sources.
- DHA intake of 300 mg/day is recommended.

special attention must be paid to providing other sources of dietary fat.

The type of fat is also important in order to ensure that the requirements for the essential fatty acids, linoleic and α-linolenic acid are met (Box 12.2). Essential fatty acids compete for the same desaturase enzymes and omega-6 and omega-3 fatty acids must be provided in the proper ratio of approximately 5:1, or synthesis of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from the omega-3 fatty acids may be inadequate. In order to ensure that sufficient DHA is provided, 650 mg of omega-3 fatty acids, of which 300 mg is DHA, is recommended [2].

12.3.5 Vitamins and Minerals

The DRI for pregnancy should be met for all vitamins and minerals. Medical food is the source of many vitamins and minerals in the MPKU diet; however, if not taken as prescribed or if the medical food does not contain a full complement of vitamins and minerals, intakes may be low. Vitamins and minerals that are of particular concern in MPKU are vitamin B_{12} and folate [14] as low maternal intakes have been correlated with increased risk of congenital heart defects in the offspring. Women with PKU are also at risk for deficiencies in zinc, iron and vitamin B6 as these nutrients are most often found in high protein foods that individuals with PKU do not usually consume. Prenatal supplements or specific vitamins and mineral supplementation may be necessary if monitoring of intake and/or if nutritional biomarkers indicate a problem.

Excessive intake of vitamin A intake leads to hypervitaminosis A that has been associated with birth defects, including malformations of the eye, skull, lungs, and heart [23]. High intakes are possible in the diet for MPKU if a medical food containing vitamin A is taken along with a prenatal supplement or fish oil. The upper safe limit for vitamin A intake during pregnancy is 2800–3000 μg/day, or approximately 10,000 IU (1 μg Retinol Activity Equivalent is equal to 3.3 IU) [24]. Vitamin A from animal sources (fish oil, or vitamin A palmitate, retinol and acetate) is of concern, but vitamin A supplied as carotenoids does not cause hypervitaminosis A because the conversion of beta-carotene to the active form of vitamin A is highly regulated by the body. Prenatal vitamin supplements often specify the source of Vitamin A.

12.4 Nutrition Management in Lactation and the Postpartum Period

Women with PKU are counseled to be on diet for life including in the postpartum period. It is possible for the woman with PKU to breastfeed her infant. If the woman chooses not to be on diet after pregnancy yet is breastfeeding, there will be a slightly higher phenylalanine content in her breast milk, but this has no effect on the infant's blood phenylalanine concentration, as long as the infant does not have PKU. Even then, limited amounts of breast milk would be allowed in combination with a phenylalanine-free infant formula. While staying on the phenylalanine-restricted diet is not necessary for breastfeeding, it is encouraged in order to maintain optimal neuropsychological functioning, which is important for coping with the demands of caring for an infant [25].

The nutrient requirements for breastfeeding are the same as in the third trimester of pregnancy due to the high protein, phenylalanine and energy demands of producing breast milk. Monitoring of blood phenylalanine and continued support of the woman with PKU is needed but this is often difficult to accomplish once the mother's attention turns from her diet and pregnancy to caring for an infant.

12.5 Medical Management in Maternal PKU

12.5.1 Sapropterin Dihydrocloride

Medical management for PKU includes sapropterin dihydrochloride (Kuvan®) and pegvaliase-pqpz (Palynziq®). Gene therapy trials are underway (Chap. 8). Because of the well-known adverse effects of high blood phenylalanine on the developing fetus, the imperative is great for health care providers to consider all treatment options for women who are not able to keep blood phenylalanine within treatment range on diet alone. Yet, information on the use of medical therapies in pregnant women is gained gradually with commercial use over time.

Evidence about sapropterin dihydrochloride from a registry of women who have been on sapropterin during pregnancy shows that they tolerated the drug well, maintained blood phenylalanine in good control during pregnancy, and had normal birth outcomes [25]. The typical sapropterin dose was 20 mg/kg at the start of pregnancy and was not adjusted for weight gain during pregnancy. Likewise, a European study of pregnant women treated with sapropterin concluded that its use was safe and effective [26]. Consensus is that sapropterin should be used in women with PKU who are planning pregnancy if they are known responders, or if they are unable to attain good metabolic control. If a woman with PKU presents during pregnancy, sapropterin can be tried as long as it does not delay the onset of other therapies [27]. There is no evidence regarding the safety of sapropterin dihydrochloride use during lactation [3].

12.5.2 Pegvaliase

Per the pegvaliase label in the US, pegvaliase is not contraindicated during pregnancy and lactation; therefore, the decision about its use is left to the medical provider's clinical judgement. Consideration should be given on a case-by-case basis to the benefits–risks of continuing pegvaliase therapy versus the teratogenic effects of hyperphenylalaninemia [28]. There is very limited evidence about the use of pegvaliase during pregnancy. In one case study, a pregnant woman who continued pegvaliase during pregnancy had a positive outcome [29]. Close monitoring and diet adjustment are needed to prevent low maternal phenylalanine concentrations in order to support normal fetal growth.

Should the decision be made to discontinue pegvaliase for a planned pregnancy, women should be advised to stop pegvaliase at least 4 weeks prior to pregnancy as pharmacological data shows that this is sufficient time to washout the drug [28]. Resuming a low phenylalanine diet for a planned pregnancy after being on a normal diet is possible, but difficult [30]. Pegvaliase treatment can be reintroduced successfully in the post-partum period [30].

Information on the presence of pegvaliase in breast milk is limited; one case study reported that pegvaliase was not present in a single breast milk sample. Therefore, the decision to allow breastfeeding while on pegvaliase should include the benefit to the mother (lower blood phe) and the infant (optimal nutrition) as well as psychological factors. Although no study data are available, there is no evidence to suggest that pegvaliase is contraindicated in men anticipating fatherhood.

12.6 Monitoring

Box 12.3: Nutrition Monitoring of a Patient with Maternal PKU[a]

- Routine assessments including anthropometrics, dietary intake, physical findings
- Laboratory Monitoring
  - Diagnosis-Specific
    Plasma amino acids
    - Phenylalanine
    - Tyrosine
  - Nutrition laboratory monitoring of patients on phenylalanine-restricted diets may include markers of:
    Protein sufficiency (plasma amino acids, prealbumin, albumin)
    Nutritional anemia (hemoglobin, hematocrit, MCV, serum vitamin B_{12} and/or methylmalonic acid, total homocysteine, ferritin, iron, folate, total iron binding capacity)
    Vitamin and mineral status: 25-hydroxy vitamin D, zinc, trace minerals, folic acid
    Essential fatty acid sufficiency: plasma or erythrocyte fatty acids.
    Others as clinically indicated

[a] For suggested frequency of monitoring: www.southeastgenetics.org/ngp

Careful metabolic and nutritional monitoring of a pregnant woman with PKU is important to ensure that the fetus is not exposed to high blood phenylalanine and sufficient nutrition is provided for proper fetal development. Frequent (once or twice weekly) monitoring of blood phenylalanine is especially important, as is routine monitoring of protein status including plasma amino acids and prealbumin levels (Box 12.3). The reference ranges for many laboratory tests, including amino acids, differ for pregnancy. The laboratory monitoring can be completed by the metabolic clinic or by the obstetrician if the woman lives far from the clinic or if traveling becomes difficult later in pregnancy, as long as communication between providers occurs. Weight gain should be monitored regularly, and ultrasounds performed twice during pregnancy, once early in pregnancy to establish that the fetus is viable, and once at 18 weeks' gestation to rule out cardiac and other anomalies [22].

12.7 Pregnancy in Maple Syrup Urine Disease

Pregnancies in women with classical maple syrup urine disease (MSUD) require close monitoring throughout pregnancy, delivery and the postpartum period. There are eight publications that describe maternal MSUD cases [31–38], and other successful pregnancies are known to the MSUD Family Support Group as well [39]. Significantly increased tolerance of leucine is reported (2–3 times prepregnancy leucine needs), especially during the second and third trimesters as additional leucine is required for maternal and fetal growth. In all cases, additional caloric support (oral and/or IV) was provided during delivery. Elevated leucine concentrations were noted in the postpartum period as protein catabolism increases after delivery with the rapid involution of the uterus [40]. Plasma leucine concentrations >1000 μmol/L were reported in three women on day 9 or 10 postpartum [31, 32, 35]; one of these women did not adhere to postpregnancy recommendations and died 51 days after delivery [33], emphasizing the importance of continued monitoring and treatment after delivery in these women. In all cases, normal infant outcomes were reported, even for an infant born to a woman with poor leucine control throughout pregnancy [33]. Successful breastfeeding while maintaining maternal metabolic control is possible [34, 38].

12.8 Pregnancy in Propionic Acidemia

There are four published reports of successful pregnancy in women with propionic acidemia [31, 41–43] and additional pregnancies in women with mild propionic acidemia (7% and 9% residual propionyl-CoA carboxylase activity) are

known to the author. Frequent monitoring to adjust both diet treatment and carnitine supplementation was necessary throughout the pregnancies and additional caloric support (oral and/or IV dextrose) was provided during delivery and the immediate postpartum period. Complications included placenta previa [41], preeclampsia (Case Report 2), hypothyroidism and gestational diabetes [44]. One woman developed heart failure symptoms two days after delivery but responded to aggressive treatment that included IV dextrose and insulin [44]. None of the infants showed congenital anomalies and normal developmental outcomes in infancy were reported.

12.9 Pregnancy in Methylmalonic Acidemia

There have been several reports in the literature of pregnancies in women with various forms of methylmalonic acidemia (MMA), including mutase, cobalamin A and mild cobalamin C defects; both cobalamin responsive and unresponsive phenotypes are included in these reports [41, 45–51]. A summary of ten pregnancies in women with MMA found a wide range of treatment regimens including diet, L-carnitine supplementation and/or intramuscular (IM) hydroxocobalamin injection [50]. Half of the completed pregnancies resulted in preterm deliveries (32 to 36 weeks' gestation) with 7 of 10 pregnancies requiring Cesarean section delivery, often because of fetal distress [50]. At delivery, all women were treated with IV dextrose (+/-IV carnitine) for up to 8 days postpartum. No adverse outcomes for the infants were reported, despite elevated serum methylmalonic acid concentrations throughout pregnancy.

12.10 Pregnancy in Urea Cycle Disorders

Numerous cases in the literature describe pregnancy and fetal outcome in women with various urea cycle disorders (UCD) [52–60]. Similar to pregnancies in MSUD and organic acidemias, women with UCD are especially at risk for metabolic decompensation during the first trimester when poor energy intake is common, during any intercurrent illness, with prolonged delivery, and in the postpartum period. Women are especially vulnerable to hyperammonemia during the postpartum period when severe mental status changes, coma and death have been reported after delivery in UCD, even in women with mild forms of the disorder [52, 53, 60]. In some reports, the patient was not diagnosed with a UCD until she developed symptoms during the postpartum period [53, 54, 60].

During pregnancies in women with UCD, frequent monitoring is needed to prevent essential amino acid (EAA) deficiency and reintroduction of an EAA-based medical food may be necessary [56]. During delivery, initiating IV dextrose with or without oral supplements (i.e. glucose polymer solutions) is typical. To prevent increasing ammonia concentrations following delivery, additional energy support, increased nitrogen scavenger medications and L-arginine with gradual reintroduction of protein sources may be necessary [56, 60]. Initiation of IV nitrogen scavenger medications and L-arginine throughout delivery in two women who were carriers of ornithine transcarbamylase deficiency (OTC) prevented initial hyperammonemia for their male neonates who were prenatally diagnosed with severe OTC deficiency [61].

12.11 Overview of Recommendations for the Nutrition Management for Pregnancies in Women with Disorders of Protein Metabolism

Based on published cases and the author's experience, there are some general recommendations that apply to all pregnancies in women with disorders of protein metabolism:

12.11.1 Maintain Normal Maternal Weight Gain During Pregnancy

Generally, weight gain goals are the same for pregnancies in women with inherited metabolic disease as for the general population (Table 12.1).

Weight loss should be avoided to prevent protein catabolism and elevations in amino acids, ammonia and other associated metabolites. Energy needs increase as pregnancy progresses, especially in late pregnancy when fetal growth is the greatest [24].

12.11.2 Maintain Adequate Energy and Protein Nutriture Throughout Pregnancy

Both energy and protein needs increase as pregnancy progresses to allow for increased maternal requirements and adequate fetal growth [24] (Fig. 12.1). To prevent protein deficiency, any woman requiring a medical food prior to pregnancy will need to continue this throughout pregnancy. Even if a woman has a milder form of a disorder and has not required medical food as an adult, reintroduction of a medical food may be necessary during pregnancy [43]. Protein needs are also higher when consuming an amino acid-based medical food compared with a diet exclusively of intact protein sources (Chap. 6).

12.11.3 Maintain Plasma Amino acid Concentrations Within the Reference Range and Anticipate a Higher Intact Protein Tolerance as Pregnancy Progresses

Blood concentrations of many amino acids decrease as pregnancy progresses with the increases in maternal plasma volume, urinary protein excretion and fetal utilization during pregnancy [62]. This needs to be considered in the interpretation of plasma amino acid profiles (Table 12.3).

As with total protein, the needs for individual amino acids increase as pregnancy progresses, especially in the late second and third trimesters when fetal growth is the greatest [22, 31]. Even for patients with classical phenotypes, higher protein foods may be needed towards the end of pregnancy to maintain normal plasma amino acid concentrations. Adding milk to the medical food, if tolerated, is an easy option.

Over restriction of amino acids may have contributed to the poor fetal growth detected in the second and third trimester in MSUD and MMA pregnancies [31, 50]. If a single amino acid is supplemented as part of treatment, additional supplementation may be required to prevent low plasma concentrations, even with the increase in intact protein intake as pregnancy progresses.

In the author's experience with MSUD pregnancies, supplementation of valine and isoleucine may be needed, even for women who did not require supplementation to maintain normal plasma concentrations before pregnancy. If the plasma leucine concentration is in the goal range, but elevated valine and/or isoleucine are noted, the amount of the supplements should be decreased rather than reducing intake of intact protein. Although the teratogenicity of the branched-chain amino acids (BCAA) remains uncertain, limited experience suggests that moderate elevations in valine and isoleucine may not pose harm to the mother or fetus.

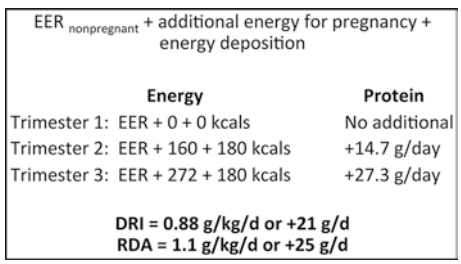

Fig. 12.1 Estimated energy and protein requirements for each trimester of pregnancy [24]

12.11.4 Plan Ahead for Intercurrent Illness and Complications Affecting Dietary Intake

As with any pregnancy, persistent nausea and vomiting and intercurrent illness can occur. For women with intoxication disorders, these catabolic events need to be aggressively addressed to prevent increasing concentrations of amino acids and associated toxic metabolites. Antiemetics can be prescribed. For women who have a difficult time consuming medical food, a gastrostomy tube

may need to be considered [63]. A plan for any needed admissions should be established ahead of time and emergency protocols updated [64].

12.11.5 Refer to an Obstetric Clinic Specializing in High-Risk Pregnancy

Given the risk of metabolic decompensation during pregnancy and the postpartum period, women with amino acidopathies, organic acidemias or urea cycle defects should be followed by an obstetric clinic specializing in high-risk pregnancies [31]. Frequent assessment of fetal growth is often needed. For successful maternal and fetal outcomes, a multidisciplinary approach is required with input from both the obstetric and metabolic teams [34, 56, 59].

Box 12.4: Nutrition Interventions for Pregnancy in Women with Disorders of Protein Metabolism

- Promote normal maternal weight gain during pregnancy.
- Provide adequate energy and protein nutriture throughout pregnancy.
- Maintain plasma amino acid concentrations within the reference range.
- Anticipate a higher intact protein tolerance as pregnancy progresses.
- Plan ahead for intercurrent illness and complications affecting dietary intake.
- Refer to an obstetric clinic specializing in high-risk pregnancy.
- Anticipate postpartum catabolism and plan to provide adequate nutrition.

12.11.6 Anticipate Postpartum Catabolism

Delivery and the postpartum period are catabolic processes and women with amino acidopathies, organic acidemias or UCD are at high risk for metabolic decompensation during these times. The risk may be greatest for women with classical forms of these disorders, although severe decompensation has been reported in women considered to have milder phenotypes [52, 57]. The risk for decompensation increases if delivery is prolonged and/or a sufficient source of energy and protein equivalents is not provided during delivery and the postpartum period.

Postpartum catabolism is caused by rapid protein turnover associated with hormonal changes and the involution of the uterus. Uterine mass decreases approximately 50% during the first 10 days after delivery [40]. In the author's experience with MSUD pregnancies, the greatest risk for decompensation occurred between 3 and 14 days after delivery. Many of the cases reported in the literature note an increase in concentrations of amino acids or associated metabolites during this time frame. Even after discharge, frequent monitoring and contact with the mother are needed to assure adequate energy intake and to assess for signs of decompensation. Catabolism gradually slows, but it may take 6–8 weeks after delivery for protein metabolism to return to a prepregnancy state [40, 64] (Box 12.4).

12.12 Pregnancy in Fatty Acid Oxidation Disorders

The metabolic changes and energy demands of pregnancy, delivery, and the postpartum period present challenges for a woman with a disorder in long-chain fatty acid oxidation (LC-FAOD) and can be influenced by the severity of the disorder. The course of pregnancy and the postpartum period has been reported for 12 pregnancies among 8 women with very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD) [65–68] and one woman with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) [69] although a few other women with LCHAD and trifunctional protein deficiency (TFP) who experienced successful pregnancy are known [70]. Pregnancy-related nausea and vomiting leading to catabolism is a concern. Elevated creatine kinase (CK) concentrations with myalgia and rhabdomyolysis are commonly reported compli-

cations [65, 67, 68] that resolve with IV dextrose support and bed rest [68]. Nutrition management guidance during pregnancy includes minimizing fasting, adhering to restrictions of dietary long-chain fat intake and supplementation with medium-chain triglycerides (MCT), use of L-carnitine, and providing additional energy from carbohydrate and protein sources in the second and third trimesters of pregnancy [65, 67–69, 71]. Additionally, supplementation with omega-3-fatty acids and use of nocturnal cornstarch was included in LCHAD pregnancy management [69, 71]. Laboratory monitoring during pregnancy can include CK, plasma carnitine, and plasma acylcarnitine profile [65–69] Reports documented reductions of CK and acylcarnitine concentrations in the second and third trimester attributed to fatty acid oxidation by the placenta [65, 67, 68]. Higher concentrations of these metabolites returned following delivery [67, 68]. Both vaginal and Cesarean deliveries with successful infant outcomes are reported [65–67, 69]. Planning for labor and delivery included the use of continuous IV dextrose along with oral energy sources to meet metabolic demands and prevent catabolism, rhabdomyolysis, and renal insufficiency [67, 68].

Women with LC-FAOD are also at risk for rhabdomyolysis and abnormal laboratory findings in the postpartum period due to inadequate energy intake and catabolism associated with tissue breakdown during the puerperium period, the period of about 6 weeks after childbirth when the mother's reproductive organs return to their original nonpregnant condition [67, 68]. Acute heart failure due to cardiomyopathy was reported after delivery in a woman with VLCAD who had hyperemesis gravidarum with severe metabolic decompensation at gestation week 14 [66] and unresolved tachycardia requiring Cesarean section delivery at 34 weeks' gestation in a woman with LCHAD [69].

Breastfeeding is not contraindicated; however, it can contribute to catabolism if maternal energy needs are not met [68]. Close monitoring of the woman's nutritional intake and laboratory markers should continue through at least 8 weeks postpartum and as long as the woman is breastfeeding [68].

12.13 Pregnancy in Disorders of Carbohydrate Metabolism

Successful pregnancy and infant outcomes have been documented in women with GSD type Ia, type 1b and type III [72, 73]. Carbohydrate requirements increase during pregnancy, especially during the first trimester. An increase in frequency and severity of hypoglycemia has been noted during pregnancy in some women. Close glucose monitoring, increased cornstarch doses and/or overnight enteral feedings have been utilized during pregnancy to maintain euglycemia. A goal of preventing maternal hypoglycemia is paramount as intrauterine growth retardation and low birth weight has been reported in inadequately controlled pregnancies [73]. Close monitoring of preexisting maternal complications (such as hepatic adenomas, cardiac dysfunction) is necessary as these can be exacerbated during pregnancy [72, 73]. Intravenous dextrose has been administered during delivery and the postpartum period to reduce the risk of hypoglycemia during these times. With optimal metabolic control during gestation, infant outcomes have been positive [72].

Another disorder in carbohydrate metabolism requiring medical nutrition therapy is galactosemia due to deficiency of galactose-1-phosphate uridyltransferase. Primary ovarian insufficiency affects >90% of women with classical forms of this disorder resulting in infertility for the majority [71]. However, as more treated women are reaching child-bearing age, an increase in viable pregnancies has been reported [71]. This needs to be considered in the treatment and counseling for women with this disorder.

12.14 Summary

Maternal PKU Women with PKU must maintain blood phenylalanine below 360 μmol/L before and during pregnancy to prevent the MPKU Syndrome. Because of the teratogenic effect of phenylalanine on the fetus, all treatment options to control blood phenylalanine including a phenylalanine-restricted diet, sapropterin and pegvaliase should be considered. The

phenylalanine-restricted diet must provide sufficient protein, energy, fat and micronutrients to support a developing fetus. Medical food for PKU provides protein equivalents with limited or no phenylalanine and, depending on the nutrient profile of the medical food, supplemental energy, fat, essential fatty acids, vitamins and minerals may be needed. Insufficient protein and vitamin B_{12} in the diets of women with PKU are associated with fetal congenital heart defects. Close monitoring of blood phenylalanine and other laboratory values, as well as assessment of weight gain and nutrient intake is recommended. Women with PKU are encouraged to breastfeed their infants and to stay on the diet in the postpartum period. More data on medical therapy in pregnancy is needed.

Other IMD Although experience is still limited, it appears that women with inherited metabolic disorders that pose a risk for metabolic decompensation are at greater risk for adverse outcomes than are their infants. The postpartum period is of particular concern for metabolic decompensation in these women. Infant outcomes are often reported as normal, although in most cases reports, the children were not followed beyond toddler years and formal developmental testing was not completed. However, despite overall poor control in some of the reported pregnancies, the infants do not have the dysmorphology, microcephaly, cardiac defects or developmental delays that have been described in infants born to women with poorly controlled PKU. Systematic collection of data from additional pregnancies is needed before definitive conclusions and standardized recommendations can be provided.

Additional information about pregnancy in other inherited metabolic diseases includes classical homocystinuria (Chap. 14) and hereditary tyrosinemia (Chap. 13).

12.15 Case Reports

To illustrate the recommendations described in this chapter, the following case reports of pregnancy in a woman with classical MSUD and a woman with mild propionic acidemia are discussed.

Case Report 1: Pregnancy in Maple Syrup Urine Disease

A 22-year-old woman homozygous for the classical variant Y393N found in the Mennonite population presented to the metabolic clinic at approximately 4 weeks gestation in good metabolic control. Her history included a severe neonatal presentation at 4 days of age with numerous admissions for illness as a child. However, as an adolescent and adult, she was able to manage the majority of illnesses at home. She maintained excellent metabolic control throughout her life and had no evidence of cognitive delay or other complications associated with poorly treated MSUD.

Plasma amino acid concentrations were monitored one to two times per week. Goals for the pregnancy included maintaining leucine and isoleucine concentrations between 100 and 300 μmol/L and valine concentrations between 200 and 400 μmol/L. Prealbumin, albumin and other nutrition markers were monitored monthly. She was referred to a high-risk obstetrics clinic and a fetal ultrasound was completed monthly after the first trimester. Maternal weight gain and fetal growth were normal throughout pregnancy.

During the first trimester, the patient struggled with morning sickness and required antiemetic medication. Her leucine tolerance remained essentially unchanged during the first trimester but increased rapidly during the second and third trimesters (Fig. 12.2b). Her initial leucine tolerance was 550 mg/day and increased to 3400 mg/day prior to delivery. Weekly increases of >100 mg leucine/day were required to prevent low leucine concentrations after 25 weeks' gestation (Fig. 12.2a, b).

A vaginal delivery was planned, but the fetus was in a breech position and a Cesarean section was performed at 39 weeks' gestation. Since delivery and the postpartum period are catabolic processes, a central PICC line was placed prior to delivery to administer BCAA-free parenteral solution with dextrose and lipid for energy. Isoleucine and valine supplements were given orally. To reduce postpartum catabolism, her treatment plan included maintaining the same

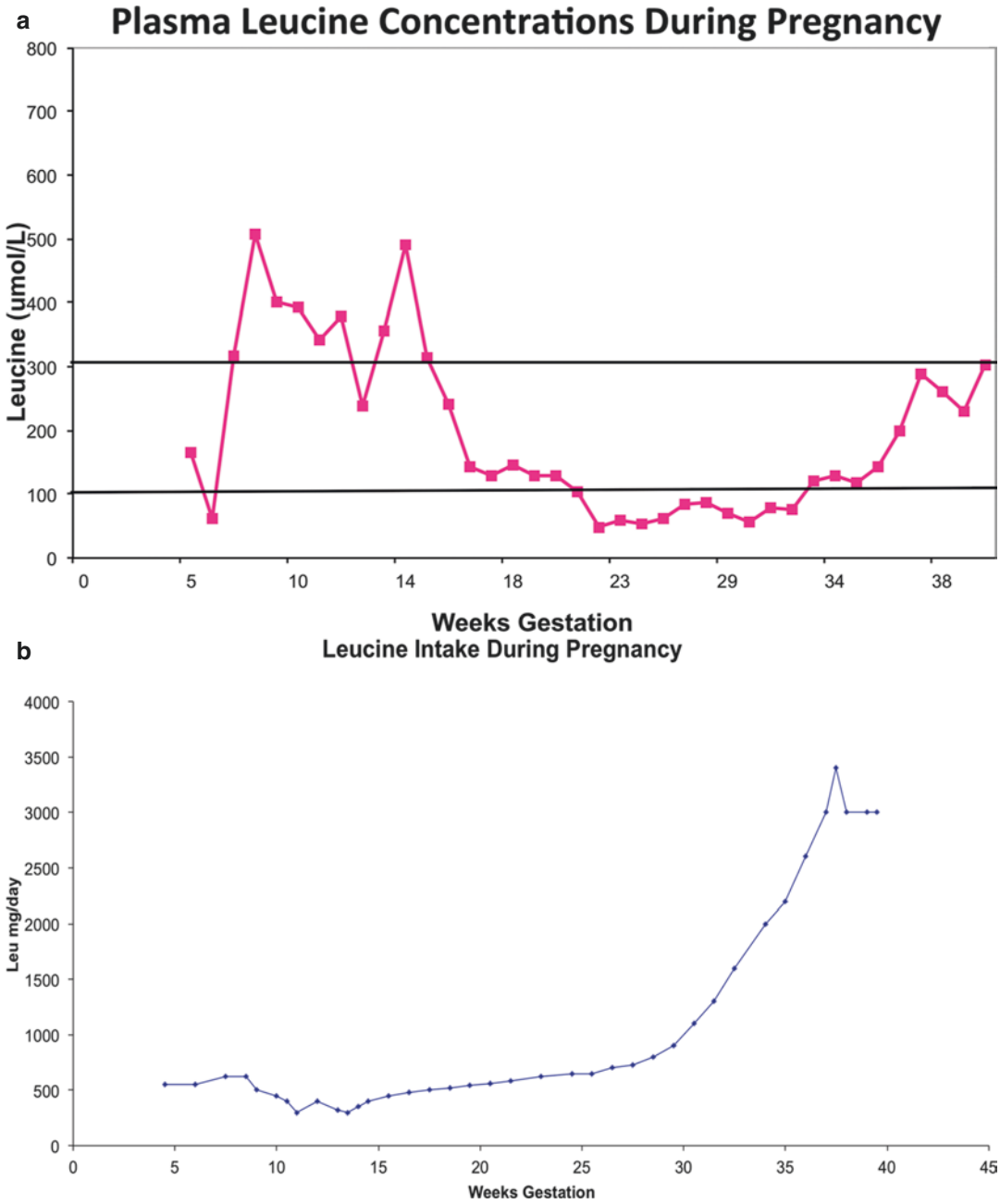

Fig. 12.2 (**a**, **b**) A marked increase in dietary leucine prescription was required to maintain plasma leucine concentrations between 100 and 300 μmol/L after 25 weeks' gestation in a woman with classical MSUD

energy and protein intake that she tolerated at the end of pregnancy. Plasma amino acids were measured daily, and reintroduction of dietary leucine was based on the plasma leucine concentration.

The patient was able to restart medical food by 12 hours after delivery and by postpartum day 2, she was consuming as much medical food as she consumed at the end of pregnancy. Leucine concentrations remained within the normal range.

Thus, she was weaned off of parenteral solutions over a two-day period, and her oral leucine prescription was incrementally increased to her prepregnancy leucine requirement of 550 mg/day. However, her leucine concentration began to increase on Day 5 after delivery so intact protein sources were removed from the diet and additional energy was provided by reintroduction of IV glucose and lipid solutions. However, the plasma leucine continued to increase, and it was only after reintroduction of protein equivalents from the BCAA-free parenteral amino acid solution that the plasma leucine concentration decreased. On Day 6, she was consuming 3.0 g/kg protein equivalents (50% formula, 50% IV) and 4500 kcals from both oral and IV sources. The leucine concentration decreased rapidly on this regimen.

To prevent another spike in plasma leucine, IV energy and amino acid sources were reduced gradually over a four-day period. She was discharged on Day 11 after delivery. After discharge, plasma amino acids were checked two times/week for 2 weeks and then weekly. Her dietary leucine tolerance increased slowly, and it was not until 30 days after delivery that she tolerated her prepregnancy leucine intake of 550 mg/day.

The infant had normal APGAR scores at birth with weight at 25%ile and length at 50%ile. The mother attempted to breastfeed, but her milk production remained poor even with pumping. It is unclear if MSUD contributed to this; however, a subsequent report describes a woman with MSUD who was able to breastfeed successfully [34]. At the age of 3 years, the child was developing and growing without concern.

This woman's second pregnancy progressed similarly to her first with a dramatic increase in BCAA tolerance as the pregnancy progressed. To avoid the increase in leucine concentrations during the postpartum period as seen in her first pregnancy, the reduction in energy and protein from parenteral sources was reduced gradually over 7 days and leucine from oral sources was introduced more gradually. At her discharge 10 days after delivery, her leucine prescription was only 60% of her prepregnancy prescription. Her leucine tolerance did not reach her prepregnancy tolerance until 6 weeks after delivery.

Case Report 2: Pregnancy in Propionic Acidemia

This is the second pregnancy for a 28-year-old woman with variants in the β-subunit of the gene for propionyl-CoA carboxylase. She was diagnosed at 4 years of age in a metabolic coma. She had a history of seizures and a cardiac complication of long-QT syndrome. As an adult, she did not consume a medical food, but self-restricted her protein intake to 0.6–0.8 g/kg prior to pregnancy. Her first pregnancy was complicated by preeclampsia requiring a Cesarean delivery at 31 weeks' gestation with slowed fetal growth by ultrasound. Despite complications of prematurity, the child showed no cognitive or growth delays at 10 years of age.

Unlike her first pregnancy when a medical food was not started until 14 weeks gestation, a medical food was started prior to pregnancy to assure better protein nutriture during her second pregnancy. Maternal weight gain was normal. To maintain normal plasma concentrations of valine, isoleucine, methionine and threonine, her intake of intact protein increased as pregnancy progressed. Even with the increased intake of intact protein, valine and isoleucine supplements were added later in pregnancy to achieve normal concentrations of these two amino acids. She continued biotin (10 mg/day) and L-carnitine supplementation throughout pregnancy. Plasma carnitine concentrations were frequently monitored, and her L-carnitine dose was gradually increased from 50 to 150 mg/kg prepregnancy weight to maintain low normal free carnitine concentrations for pregnancy.

Ultrasounds showed improved fetal growth during her second pregnancy. Despite more aggressive treatment, she again developed preeclampsia and delivered at 32 weeks' gestation by Cesarean section. A 10% dextrose solution was provided by peripheral line during delivery and for 3 days postpartum. Despite prematurity complications, the child showed no cognitive or growth delays at 7 years of age. Improved energy and protein nutriture may have played a role in better fetal growth during the second pregnancy. Figure 12.3

	1st Pregnancy (◆)	2nd Pregnancy (■)
Pre-Pregnancy Total Protein intake	0.7 g/kg	1.0 g/kg
Total Protein intake @ 20 weeks	1.1 g/kg	1.3 g/kg
Total Protein intake at Delivery	1.4 g/kg	1.6 g/kg
Initiation of medical food	14 weeks	Pre-Pregnancy
Total maternal weight gain	15 kg (33 lbs)	13 kg (28 lbs)
Carnitine dose at Delivery	150 mg/kg	100 mg/kg
Gestational age at delivery	31 1/7 weeks	32 0/7 weeks
Birth Weight	1170 g	1826 g

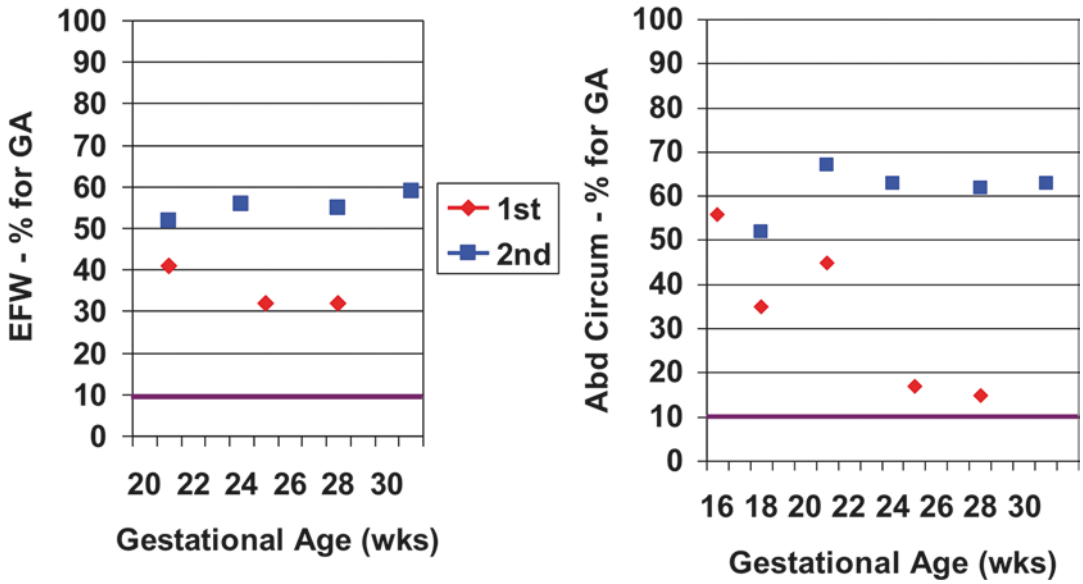

Fig. 12.3 Comparison of energy and protein intake and estimated fetal weight (EFW) and abdominal circumference (Abd Circum) measured by ultrasound in two pregnancies in a woman with mild propionic acidemia. Ultrasound measurements are reported as percentiles based on gestational age

shows total protein intake, maternal weight gain and fetal growth measurements during both pregnancies.

It is unknown if propionic acidemia played a role in the development of preeclampsia for this woman. The other 3 pregnancies to women with propionic acidemia known to the author delivered at term. In all 5 pregnancies, there were no cognitive delays or other complications reported in the children.

12.16 Diet Example for a Pregnant Woman with PKU

Patient Information	The following are the intake goals for this woman
29-year-old woman with severe PKU 4 weeks gestation Blood phenylalanine concentration: 960 μmol/L (16 mg/dL)	Protein from medical food: at least 70 g/day Phenylalanine (protein) from intact sources: washout; as low as possible Energy: at least 2200 kcal/day Fat: 73 g/day (30% of total energy) Supplements: prenatal supplement with 300 mg DHA, per day

Initially, counsel the pregnant woman to avoid all "counted foods" until her blood phenylalanine is in treatment range. During the washout, she should consume low protein foods and uncounted foods (Appendix G).

Table 12.4 is an example of a diet that contains 2300 kcal and 80 g of protein. Amounts are shown for the dietitian's use; the patient is counseled to include unlimited "Uncounted Foods" from the Simplified Diet (Appendix G). According to the diet analysis (MetabolicPro®), this diet contains 220 mg of phenylalanine.

Table 12.4 Example diet for pregnant woman with PKU

Diet plan	Amount
Lophlex LQ, tropical	4 pouches
Uncounted foods	
Breakfast	
Low protein bread	2 slices
Butter	2 pats
Jelly	2 Tbsp
Coffee, decaf	1cup
Nondairy coffee creamer	1 oz
Grapes	10
Lunch	
Low protein cheese	1 slice
Low protein bread	2 slices
Butter for grilling	2 tsp
Baby carrots	10
French dressing	1 Tbsp
Dinner	
Tomatoes, cherry	10
Lettuce	1 cup
Celery	1 stalk
Salad dressing, Italian	2 Tbsp
Low protein pasta	2 cups
Olive oil	2 tbsp
Garlic	2 cloves
Snacks	
Low protein cookies	2
Sorbet	1 cup

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