



Case Report

Dietary management of maternal phenylketonuria with glycomacropeptide and amino acids supplements: A case report



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ABSTRACT

Background: In maternal PKU, protein substitute (PS) is provided by phenylalanine (PHE)-free L-amino acids (AA), but glycomacropeptide-based protein substitute (GMP) is an alternative consideration.

Objective: To describe the first Portuguese Maternal Phenylketonuria (MPKU) partially managed with GMP.

Case report: A 31 year old MPKU female with classical PKU (mutations P281L/P281L), diagnosed by newborn screening, had a lifelong history of poor metabolic control. She has a history of partial bicornuate uterus and had a previous miscarriage in the first trimester. Pre-conception, her median blood PHE was 462 $\mu\text{mol/L}$ but throughout pregnancy the median reduced to 258 $\mu\text{mol/L}$. GMP provided 30 g/day protein equivalent (46 mg/day PHE). Total protein equivalent from PS increased from 58 to 86 g/day during pregnancy but AA provided all additional protein equivalent intake. Both GMP and AA were well tolerated with no morning sickness. Normal morphologic evaluation and adequate fetal growth with cephalic biometry near the 5th percentile was determined. The infant was born at 39.3 weeks: weight 2570 g (3rd percentile), length 47.5 cm (10th percentile) and head circumference (HC) of 31.5 cm (1st percentile). In the neonatal period, the infant had craniofacial dimorphism with metopic suture prominence. Father also had bitemporal narrowing. By 12 months of age, the infant's weight (15th percentile), length (50th percentile) and HC (10th–50th percentile) were normal although bitemporal narrowing persisted.

Conclusions: This is the first case reporting the use of GMP in MPKU. Its PHE content did not adversely affect metabolic control although it only provided part of the PS intake. Some intrauterine development delay occurred in the last trimester, although we consider that this is unlikely to be associated with MPKU syndrome or the use of GMP. More published data is essential to examine the impact of using GMP in MPKU on morning sickness severity and aversion, maternal weight gain, blood amino acid concentrations and variability of blood PHE concentrations.

1. Introduction

Maternal phenylketonuria PKU (MPKU) syndrome [1–3] was first described over 60 years ago [4]. There is a convincing correlation between high maternal blood phenylalanine (PHE) concentrations, particularly during critical periods of embryogenesis in early pregnancy and fetal abnormalities including fetal growth retardation, microcephaly, and structural heart defects [1–3]. There is also a relationship between poor maternal nutritional status and infant microcephaly,

decreased fetal growth and congenital heart defects [5,6]. Therefore, in MPKU it is crucial to achieve satisfactory maternal nutritional status together with optimal blood PHE control pre-conception and sustain this throughout pregnancy [7,8].

MPKU is managed by a strict low PHE diet (commonly ≤ 6 g/day natural protein is tolerated in the early stages of pregnancy but PHE amount is dependent on PKU severity), together with a PHE-free L-amino acid supplement (AA) (supplemented with tyrosine, vitamins, minerals and commonly EPA/DHA), and sufficient energy intake to

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ensure adequate maternal weight gain during pregnancy [9,10]. The protein equivalent from AA and natural protein should supply ≥ 70 g/day protein equivalent [8]. Additional tyrosine supplements may be necessary if intake is < 6 g/day from AA [8]. Dietary management is challenging [11] because some women may have relaxed or stopped their low PHE diet therapy prior to pregnancy and therefore find it particularly demanding to adhere to the prescribed amounts of AA [6,12,13]. Nausea and vomiting during the early phases of pregnancy is common and may lead to inadequate intake of AA and energy [10,14] and unsatisfactory blood PHE control [14].

In 2003, it was described that glycomacropeptide could be extracted from sweet whey [15]. Unmodified glycomacropeptide is without the amino acids histidine, tyrosine, tryptophan, cysteine, arginine, and contains low amounts of leucine and methionine. The large neutral amino acids, threonine and isoleucine, are two to three times higher than the amounts added to conventional AA. Commercial glycomacropeptide based protein substitutes (GMP) are now available for PKU. They are supplemented with leucine, histidine, methionine, tryptophan and tyrosine but also contain some residual PHE (PHE = 1.8 mg/g of protein equivalent) due to contamination during the glycomacropeptide extraction process. Thereby, 20 g protein equivalent provided by a GMP supplement will provide an additional 36 mg/day PHE. GMP is associated with improved patient taste, adherence and smell [16] and may be beneficial for MPKU when women are unable to accept or tolerate traditional AA, particularly with hyperemesis.

There is no peer reviewed evidence reporting the use of GMP in the management of MPKU. It is unknown if it is safe or well tolerated and the impact of its PHE content is not described in MPKU. The objective of this paper is to present a female PKU patient from Centro Hospitalar do Porto, Portugal, taking GMP as part of her protein requirements during pregnancy. Written informed patient consent was given prior to the publication of this case report.

2. Case report

A 31 year old MPKU female was diagnosed by newborn screening, with a neonatal blood [PHE] level of 1260 $\mu\text{mol/L}$, categorized as classical PKU when blood [PHE] > 1200 $\mu\text{mol/L}$ according to the Portuguese Nutritional Consensus [17]. Genotype analysis indicated the P281L mutation in both alleles.

A low PHE diet was commenced at 18 days of age. Unfortunately, since 1 y of age, she was unable to fully adhere with dietary restrictions and almost all her blood [PHE] levels were above the Portuguese Nutritional Consensus [17] upper target range (aged < 12 y: 120 to 360 $\mu\text{mol/L}$ and aged > 12 y: 120 to 480 $\mu\text{mol/L}$ (Fig. 1). During her first year of life, the annual median blood PHE was 300 $\mu\text{mol/L}$ but by the age of 2 y, this had increased to a median blood PHE of 720 $\mu\text{mol/L}$. Since the age of 3 y, median values were consistently > 1200 $\mu\text{mol/L}$ until pre-conception and pregnancy (Fig. 1).

At the age of 8 y, her IQ was 77 assessed with “The Stanford–Binet Intelligence Scales” [18]. When repeated at age 28 y, using the Wechsler Adult Intelligence Scale (WAIS-III) [19], her global IQ was 68. She had learning difficulties at school, received a special education program and did not progress beyond elementary school level. Psychological assessments consistently identified high anxiety levels and low self-control. She received little maternal support throughout life. She attempted several jobs but failed to maintain any of them. She had a history of partial bicornuate uterus and miscarriage.

At 24 y, she commenced pre-conception dietary treatment with the aim of maintaining blood PHE within the Portuguese Nutritional Consensus [17] target range of 120–360 $\mu\text{mol/L}$ but preferably 120–240 $\mu\text{mol/L}$, for at least 2 weeks prior to conception. Blood PHE levels were measured with fasting blood spots twice weekly during pre-conception and pregnancy.

A diet restricting natural protein (PHE intake 658 mg/day), and supplemented with special low protein foods and a combination of GMP

(Bettermilk®) and AA (PKU3 Advanta®) was implemented. Folic acid, and general vitamin and mineral supplementation was given before and during pregnancy. Throughout dietary treatment, she was supported by her partner and mother in law who helped with meal preparation and overall dietary management.

The case study had a sapropterin® loading test two months prior to pregnancy, with a blood PHE reduction of 35%. The multidisciplinary team chose not to treat her with BH4 during pregnancy when she had not received prior treatment with this drug.

She only consistently achieved blood PHE within target range when she reported her pregnancy at 4 weeks' gestational age. Metabolic control during pregnancy is presented in Fig. 2. Median blood PHE during pregnancy was 258 $\mu\text{mol/L}$ (Fig. 2) compared with 486 $\mu\text{mol/L}$ pre-conception diet (Fig. 1).

Nutritional intake during pregnancy is described in Table 1. GMP was started 18 months prior to pregnancy. She took 30 g/day of protein equivalent from Bettermilk® (2 \times 15 protein equivalent sachets/day providing 45 mg of PHE/day), with the remaining protein substitute (PS) supplied by AA (PKU3 Advanta®), providing 28 g/day of protein equivalent. She remained on the same amounts of GMP throughout pregnancy. The AA was increased to 42 g/day of protein equivalent at 16 weeks and to 56 g at 18 weeks' gestation (Table 1). The percentage of protein equivalent provided by GMP decreased throughout pregnancy (52% at 4 weeks, 42% at 16 weeks and 35% at 18 weeks, respectively).

At pregnancy notification (gestational age 5 weeks), PHE intake from natural protein sources was reduced to 458 mg/day to improve metabolic control (Table 1). By 7 weeks of pregnancy, PHE tolerance had increased to 643 mg/day (Table 1). PHE intake was not reduced to compensate for the PHE content of GMP (Fig. 2 for blood PHE control during pre-conception and throughout pregnancy). Median blood tyrosine levels measured by fasting blood spots were 43 $\mu\text{mol/L}$ ($n = 29$ samples) until 16 weeks of pregnancy and 51 $\mu\text{mol/L}$ ($n = 46$ samples) after 16 weeks.

The case study did not report any nausea or vomiting during pregnancy, which assisted good adherence with both GMP and AA supplements. Adherence was better with both PS compared to her pre-pregnancy history. Increasing intake of AA supplements was well tolerated.

Biochemical analyses are reported prior, during and post-pregnancy (Table 2). An oral glucose tolerance test at 21 weeks was not abnormal (blood glucose of 84, 94 and 86 mg/dL at 0, 60 and 120 min respectively, with ingestion of 75 g of glucose). Selenium and zinc concentrations were below normal ranges during pregnancy (0.44 and 7.48 mmol/L, respectively).

Maternal weight gain during pregnancy was 15 kg (for a pre-pregnancy BMI of 23, recommended weight gain is between 11.5 and 16 kg [20]).

2.1. Intrauterine development and anthropometric development

A combined risk assessment positive for trisomy 18 and 13 was detected by low β human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 10 weeks. Maternal weight gain (15 kg) was normal during pregnancy. There was normal morphologic evaluation and adequate fetal growth with cephalic biometry (an indicator of fetal head shape) near the 5th percentile.

2.2. Delivery

An elective cesarean delivery, for breech presentation was scheduled at 39.3 weeks gestational age. The infant birth weight was 2570 g (3rd percentile), with a length of 47.5 cm (10th percentile) and head circumference of 31.5 cm (1st percentile). In the neonatal period, the infant had craniofacial dimorphism with metopic suture prominence.

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