PKU sphere™

PKU sphere™ case study series.

Experiences of introducing **PKU sphere** in children and adults with PKU.

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Supporting education in the dietary management of rare diseases

Contents

Introducing PKU sphere™ in an 8 year old with a low Phenylalanine (Phe) tolerance and managing Phe control.

Anne Daly MSc, RD (Senior metabolic dietitian, Birmingham Children's Hospital, UK).

Patient Details & Medical History

Age: 8

Gender:

Weight: 24kg (25th percentile)

Height: 125cm (25th percentile)

Protein Equivalent (PE) from Amino Acid (AA) - based protein substitute: 60g/day (3 x 20g PE)

Natural protein intake: 4g/day **Total protein intake:** 2.7g/kg/day **Target phenylalanine (Phe) range:** 120-360µmol/L

Background

An 8-year-old girl taking conventional AA based protein substitute three times a day expressed an interest in taking a new Glycomacropeptide (GMP) - based protein substitute after tasting it in the PKU clinic. The median blood Phe concentration for her previous 12 months was 245 µmol/L with 76% of her blood spot Phe levels within the recommended target range for age. This was considered good control. Her growth, both weight and height were on the 25th centile, with an appropriate body mass index. She ate a limited variety of foods (low protein bread, potato products, salad and low protein biscuits only) despite many attempts to try to expand the variety of foods eaten in her diet. She was taking 60g/day PE from 3 x 20g PE AA based protein substitutes (2.5g protein/kg) and 4g/day of natural protein (200 mg/day Phe).

Introduction of (GMP - based protein substitute) PKU sphere20

The guidelines for the introduction of PKU sphere in section 2.5 of the 'Practical guide for PKU sphere' were followed. No adjustment or reduction of Phe exchanges was required.

Stage 1

1. One sachet of PKU sphere20 replaces one AA based protein substitute
2. Continue taking 2 x AA based protein substitutes
3. Weekly fasting capillary blood spots
4. Growth monitored frequently

Table 1. Introduction of 1 x PKU sphere20 (20g PE) in addition to 2 x AA based protein substitutes (40g PE)

Week	Phe µmol/L	Tyr µmol/L	Comments
1	240	40	No difficulties were observed and the new product was taken well. Weight stable.
2	190	50	
3	120	40	
4	280	50	

After 4 weeks of introducing one sachet of PKU sphere20, blood Phe concentration remained within target reference range.

Therefore, PKU sphere20 increased to 2 sachets per day with 1 x AA based protein substitute.

Stage 2

1. Two sachets of PKU sphere20 replace 2 x AA based protein substitutes
2. Continue taking 1 x 20g PE of AA based protein substitute
3. Weekly fasting capillary blood spots
4. Growth monitored frequently
5. Review after 4 weeks and change to all PKU sphere20 providing Phe levels are consistently below the target reference range

Table 2. Introduction of 2 x PKU sphere20 (40g PE) in addition to 1 x AA based protein substitute (20g PE)

Week	Phe µmol/L	Tyr µmol/L	Comments
5	260	30	No illness. Reported taking all protein substitute. Weight stable.
6	400	50	
7	120	40	
8	580	50	

Comments

There appeared to be no obvious reason for the increase in the blood Phe concentration. The patient had no illness and appeared to be adherent with her diet. However, her parents noticed she was reluctant to finish all her AA based protein substitute making total protein substitute intake less consistent than usual. A home visit established a few potential causes:

a) It was holiday time and the familiar daily routine of taking protein substitute was changed. Each morning she had a 'lie in' in bed therefore took the protein substitute later in the mornings.

b) Intake of food was less regular and Phe exchanges had not been measured accurately when eating outside the home.

c) She had attended a 'sleep-over' on two occasions and delayed taking her protein substitute till later in the morning.

Plan

As it appeared the fluctuating Phe control may have been either due to inadequate protein substitute intake or extra natural protein intake when eating out, it was agreed to repeat stage 2 and review after 4 weeks.

Table 3. Continuation of 2 x PKU sphere20 (40g PE) in addition to 1 x L-AA supplement (20g PE)

Week	Phe µmol/L	Tyr µmol/L	Comments
9	270	40	Routine established. Weight stable.
10	130	50	
11	190	40	
12	260	50	

Once her usual routine returned and she was back in school, the Phe concentrations returned to the patient's usual high standards. She was able to change to 3 sachets daily of PKU sphere20 after 8 weeks of following 2 sachets of PKU sphere20 and 1 pouch of AA PS.

Stage 3

1. Increase to three sachets of PKU sphere20
2. Stop AA protein substitute
3. Weekly fasting capillary blood spots
4. Growth monitored frequently

Table 4. Increase to 3 x PKU sphere20 (60g PE)

Week	Phe µmol/L	Tyr µmol/L	Comments
13	180	40	No illness. Reported taking all protein substitute. Weight stable.
14	220	50	
15	190	40	
16	240	40	

This young girl continued to have regular assessment of blood concentrations and she demonstrated good control of both Phe and Tyrosine concentrations (see Table 4.). Her growth continued to follow the 25th percentile for both height and weight and she continued to do well with her GMP-based protein substitute; PKU sphere20.

Summary

- Transitioning to any new protein substitute needs regular monitoring.
- If Phe control deteriorates it is important to consider changes to daily routine, in addition to other common causes of poor Phe control.
- Using a methodical method of introducing a new dietary change provides confidence to the family and allows identification of the cause and the solution if any problems arise.

A case study outlining the transition from an amino acid based protein substitute to PKU sphere in a thirteen year old.

Justin Ward, Specialist Paediatric Metabolic Dietitian, Bradford Teaching Hospitals.

Patient Details & Medical History

Age:
13

Gender:

Anthropometry at time of commencing PKU sphere:
Weight (kg): 52.6 (< 91st centile) Height (cm): 151.3 (>50th centile)

Biochemistry prior to commencing PKU sphere:
Average Phenylalanine (Phe) 360-600µmol/l. Recent blood spot sampling, provided once monthly, had shown results at the upper end of the permitted range or above it. The patient associated this rise in Phe levels with a growing dislike of his Phe-free amino acid-based protein substitute (PFAA).

Diet:
Aiming for 1.5g/kg of total protein per day.
Dietary assessment revealed a variable daily protein intake of ≈ 60g protein equivalent (PE) (3 x 20g PE) from PFAA plus an estimated 20g of natural protein, from diet.
It is noteworthy that the patient does not strictly count 1g protein exchanges, but rather opts to avoid high protein foods such as meats, fish and dairy.

Aim and Plan of Management

To transition from the PFAA to PKU sphere, a glycomacropeptide (GMP)-based protein substitute, in an attempt to reverse the gradual deterioration in metabolic control.

- To gradually introduce PKU sphere into the diet, 1 x 20g PE sachet at a time, with a corresponding decrease in PE from the PFAA.
- To increase Phe monitoring to once weekly and maintain a Phe level <600µmol/l during the transition phase.
- To investigate any Phe results >600µmol/l and assess whether the Phe inherent in PKU sphere (36mg/20gPE) was responsible.
- To ensure overall nutritional adequacy of the diet.
- To continue to monitor growth and development.

Transition

Despite discussing the benefits of a staged transition from one product to the other, to allow monitoring of the impact of PKU sphere's Phe content, the patient opted to immediately switch all his PFAA to PKU sphere following PKU clinic. Furthermore, the patient continued to conduct blood spot sampling on a monthly basis as opposed to weekly which was recommended. Given these issues, the transition was instantaneous and difficult to monitor; nevertheless, a notable improvement in plasma Phe has been observed in the three results received since commencing PKU sphere (ranging between 113-364µmol/l).

Outcome

A correlation was observed between the introduction of PKU sphere and an improvement in the patient's Phe control. Inevitably, there are limitations when drawing conclusions from this case report. Arguably, the most significant limitation is the lack of adherence to a fixed number of 1g protein exchanges during the pre and post transition period. The increased flexibility of self-selecting a low protein diet as opposed to following a formal regimen creates another variable that could influence overall Phe control. Nevertheless, the patient reported eating a diet similar diet pre and post transition, highlighting that a reduction in plasma Phe was achieved despite no quantifiable reduction in natural protein intake. In effect the patient has acted as his own control in a case-control study.

The relatively short time frame (3 months) between commencing PKU sphere and the production of this case study, in addition to the long distance between the patient's home and the clinic, hampered the retrieval of anthropometric data. As a consequence of this, any impact of PKU sphere on growth cannot be commented upon.

As mentioned previously, the patient did highlight that he struggled to consume the required amount of his previous PFAA due to the dislike of its taste, an issue which the GMP formula has remedied.

The patient has not reported any adverse effects whilst taking PKU sphere.

Summary

- This case does not represent the ideal transition from a PFAA to a GMP-based protein substitute. Future cases would ideally utilise patients who adhere to a strict and measured natural protein intake and who followed the approved protocol whilst integrating PKU sphere into the diet.
- Moreover, regular blood testing throughout the transition would highlight any deviation in plasma Phe levels in a timely manner and allow potential modification of the diet to ensure safety is maintained throughout the process.
- The outcome of this case study is overwhelmingly positive as our patient now has an enjoyable protein substitute that he takes in the prescribed amounts and is benefiting with much improved Phe control.

References:

1. Burgard P Lachmann, RH Walter J (2016) Inborn Metabolic Diseases: Diagnosis and Treatment. Edited by Jean-Marie Saudubray, Matthias R. Baumgartner and John H. Walter. Berlin: Springer
2. van Spronsen FJ, van Wegberg AM, Ahring K, et al (2017) Key European guidelines for the diagnosis and management of patients with phenylketonuria. The Lancet Diabetes & Endocrinology. DOI: http://dx.doi.org/10.1016/S2213-8587(16)30320-5.

Use of PKU sphere as a protein substitute during preconception for a patient with Hyperphenylalaninemia.

Melanie Hill, Specialist Dietitian for Adults with Inherited Metabolic Diseases,
Sheffield Teaching Hospitals NHS Foundation Trust

Hyperphenylalaninemia is a disorder of Phenylalanine (Phe) metabolism. It is an autosomal recessive inherited condition and its presentation can range from mild to severe. It is caused by a deficiency in the enzyme Phenylalanine Hydroxylase (PAH). This limits Phe conversion to Tyrosine (Tyr) in the body. The accumulation leads to high Phe concentrations which are neurotoxic especially to the brain. Usually people with mild hyperphenylalaninemia on a normal diet have a blood Phe concentration of 120-600µmol/l, therefore there is a low risk of neurological impairment.

Some milder patients can continue with a normal diet, however if they wish to have children they need to adopt a low protein diet to prevent maternal PKU syndrome. The recommended Phe range for maternal PKU is 120-360µmol/l[1].
Therefore, reducing dietary protein and introducing additional protein substitutes free of Phe is required in these patients.

Phe and Tyr levels are closely monitored and the diet adjusted accordingly. This will ensure that the foetus doesn't suffer from the teratogenic effects of high Phe levels such as developmental delay, microcephaly, cardiac defects and low birth weight[1].

Patient Details & Medical History

Age:
28

Gender:

Diagnosis
Variant hyperphenylalaninemia diagnosed via newborn screening, Phe 450µmol/l at 5 days old.

Relevant Medical history

Usual blood Phe between 200 – 700µmol/l.
Previous conception 5 years ago but this sadly ended in miscarriage.
Keen to start a family and referred to our metabolic service via her GP.

Dietietic assessment

Adhered to a low protein diet from age 4-14 years, Phe levels were between 370-680µmol/l.

5 years ago she followed a preconception diet which involved removing High Biological Value (HBV) protein and starting protein substitutes, this provided an additional 40g of protein equivalent (PE). Since stopping her low protein diet Phe levels have been 370-680µmol/l.

Height: 1.73m Weight: 84.6kg BMI: 28.3kg/m^2

Current intake: Normal diet with no protein substitutes. Protein intake estimated at 80g per day including HBV sources.

Aim and Plan of Management

To achieve consistent phe levels between 120-360µmol/l.

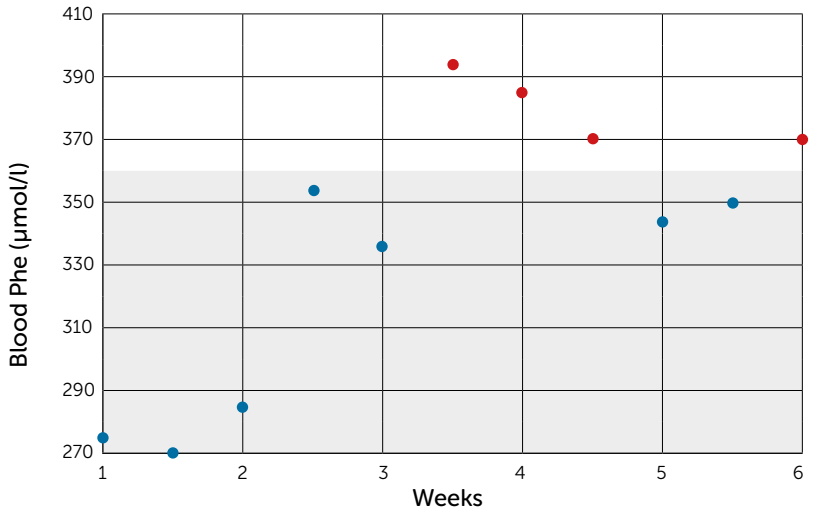
Tried samples of amino acid (AA) and glycomacropeptide (GMP) based protein substitutes and chose to take PKU sphere20 (GMP-based) o.d and PKU air20 (AA-based) o.d to provide 40g PE per day.

PKU sphere20 and PKU air20 were introduced immediately. The Vitaflo guidelines for introducing GMP for patients in a relaxed non-adherent diet were consulted[2]. She was also advised to reduce intake of HBV protein to 30g per day; which involved reducing her portions of dairy foods and removing meat/fish and poultry from her diet. Phe levels and tolerance were closely monitored. Twice weekly blood spots for Phe levels were taken while on the preconception diet.

She also commenced on a pre-pregnancy multivitamin and mineral which contained 5mcg Vitamin D, 400µg folic acid and 14mg Iron.

Phenylalanine levels:

Baseline Phe levels prior to starting preconception diet were 496umol/l. Despite PKU sphere20 containing 36mg of Phe, within 1 week of commencing the preconception diet alongside both protein substitutes, Phe levels improved to be consistently within the recommended range up until the period shown on the graph below.



The graph shows twice weekly Phe levels 6 weeks prior to conception, when on several occasions Phe was high due to eating HBV foods at Christmas parties and takeaways. She had also started a new job with a long commute, reducing time to prepare suitable low protein meals. Both GMP and AA based protein substitutes were tolerated with no problems.

Key:
- ● - out of recommended blood Phe range
- ● - within recommended blood Phe range

Summary

- PKU sphere20 was well tolerated on the preconception diet. She liked the taste and found it easy to prepare. PKU sphere20 was introduced quickly and Phe levels remained within recommended range, despite PKU sphere20 containing 36mg of Phe per sachet.
- No gastrointestinal side effects were reported. She became pregnant 4 months after commencing the preconception diet and continues PKU sphere20 o.d and PKU air20 o.d, with regular reviews planned for throughout the pregnancy.
- PKU sphere is suitable to use as part of the preconception diet in patients with hyperphenylalaninemia.

References
1. Van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. The Lancet Diabetes & Endocrinology. 2017.
2. Vitaflo dietitians in collaboration with Macdonald A and Daly A The introduction and use of PKU Sphere, a glycomacropeptide (GMP) based product in children and adults with PKU 2017.

Use of PKU sphere as a protein substitute during pregnancy.

Claire Nicol, Specialist Metabolic Dietitian, Great Northern Children's Hospital (Royal Victoria Infirmary), Newcastle Upon Tyne

Patient Details & Medical History

Age:	Gender:	Diagnosis:	Relevant history:
30		Phenylketonuria (PKU) via new born screening	One previous pregnancy; a 2 year old daughter (non PKU) who is growing and developing well. Both the current and previous pregnancy were unplanned.

Relevant medical history:

Presented November 2016 with a positive pregnancy test, estimating she was around 6 weeks pregnant. Prior to presentation, the patient was following a relaxed PKU diet (self-restricting natural protein but no protein substitute); blood Phenylalanine (Phe) varied between 900-1000 µmol/L. (Pre-conception and pregnancy target phe = 120-360 µmol/L)[1]

Dietary Plan

Recommended usual protein substitute (amino acid (AA) based, ready to drink) - 60g PE/ day. Protein exchanges reduced to 0 to rapidly reduce blood Phe to desired levels of 120-360 µmol/L.

At week 20, and on 17 protein exchanges per day, it was apparent that the patient was struggling to take her full prescribed dose of protein substitute (60g PE/day). Patient was complaining of nausea, sickness and stomach pain.

Patient was asked by dietitian to try PKU sphere, a new glycomacropeptide (GMP)-based protein substitute. Patient preferred taste of GMP-based product, resulting in improved tolerance of protein substitute. Prescription and home delivery of PKU sphere organised.

The product guidelines for PKU sphere recommend that it is introduced cautiously and under careful supervision during pregnancy, due to its Phe content (36mg/20g PE).[2]

Introduction of PKU sphere20

Start

20g PE + 20g PE + 20g PE

Prescribed 3 x AA-based protein substitutes per day (60g PE)

Baseline Phe levels- 100-143 µmol/L

Step 1 – Week 21 gestation

20g PE + 20g PE + 20g PE

1 x PKU sphere20 (20g PE, 36mg Phe)
2 x AA based protein substitutes per day (40g PE)

Blood Phe levels checked twice weekly:
Blood sample 1: 153 µmol/L - no further changes made
Blood sample 2: 96 µmol/L - protein exchanges increased by 1 (Total: 18 exchanges/day)

Step 2 – Week 22 gestation

20g PE | 20g PE | 20g PE

L-AA + sphere + sphere

To increase PKU sphere20 to b.d (40g PE, 72mg Phe)
Reduce AA based protein substitute to o.d. (20g PE)

Blood sample 1: 159 µmol/L - no further changes made
Blood sample 2: 150 µmol/L - no further changes made

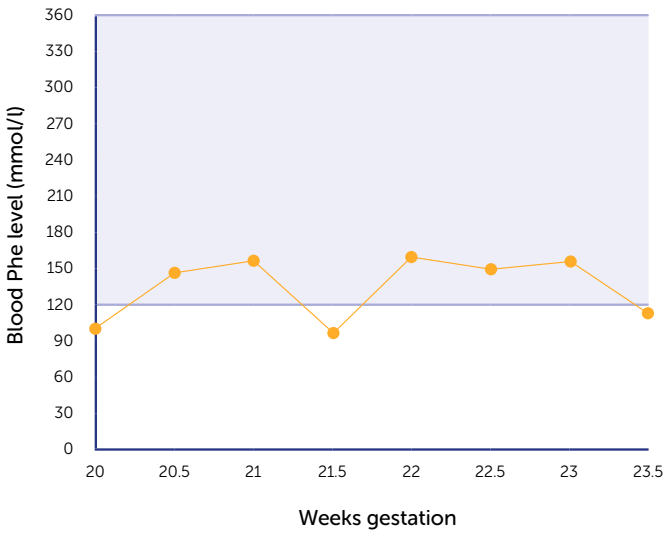
Step 3 – Week 23 gestation

20g PE | 20g PE | 20g PE

sphere + sphere + sphere

PKU sphere20 increased to t.d.s. (60g PE, 108mg Phe)

Blood sample 1: 156 µmol/L - no changes made
Blood sample 2: 112 µmol/L - protein exchanges increased by 2 (Total: 20 exchanges/day)



Due to the poor tolerance of her AA-based protein substitute the patient requested an immediate switch to PKU sphere. A compromise was made to increase by one PKU sphere20 per week, whilst still closely monitoring tolerance and Phe levels, with twice weekly blood samples.

Fortunately, this worked well with the patient being very compliant with both her blood sampling and dietary regimens. High Phe levels were not observed - see graph on left.

The patient continued with PKU sphere for the rest of her pregnancy and gave birth to a healthy baby boy. As she tolerated it so well, compared to her previous AA-based protein substitute, she plans to carry on using PKU sphere as her protein substitute post pregnancy, ensuring her protein requirements are met.

Summary

- PKU sphere may be well tolerated during pregnancy and in this case it reduced feelings of nausea and sickness allowing the full dose of protein substitute to be taken.
- Improved tolerance, compared to the previous protein substitute, a huge relief for this individual. Not being able to take her full dose of protein substitute caused anxiety during pregnancy and finding a substitute she liked helped her relax about her diet and enjoy her pregnancy.
- PKU sphere can be introduced relatively quickly without affecting phe levels. During the 3-week introduction, despite the additional dietary Phe supplied by PKU Sphere and an increase in natural protein intake, metabolic control was not compromised. This helped make the diet more achievable and varied, enabling full compliance.

References

1. van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. The Lancet Diabetes & Endocrinology. 2017.
2. Vitaflo dietitians in collaboration with MacDonald. A and Daly A. The introduction and use of PKU sphere, a Glycomacropeptide (GMP) based protein substitute, in children and adults with PKU. 2017.

Use of PKU sphere during an unplanned* pregnancy with complications of severe morning sickness.

Kath Singleton, Lead Metabolic Dietitian, University Hospital of Wales, Cardiff

Patient Details

Age:	Gender:	Diagnosis:	Relevant history:
19 years		Diagnosed with Phenylketonuria (PKU) via new born screening.	Lives with parents.

Relevant medical history:

PKU diet was followed as a child. Phenylalanine (Phe) levels ranged from 250-600 µmol/l. On transfer to adult clinic, patient stopped following PKU diet. Dietary intake remained limited and there were risks of nutritional deficiencies being addressed. Patient agreed to return to a full PKU diet following a recent miscarriage as she wished to try for another baby. PKU amino acid protein substitutes were started, alongside a low protein diet. Patient announced second pregnancy 6 weeks later.

Dietetic Assessment

Anthropometry: 55Kg; 158cm; BMI; 22kg/m^2

Dietetic Plan

Aim:

To achieve Phe levels of 120 – 360µmol/l as per European guidelines[1], but aim for nearer 250umol/l to allow for possible raised levels associated with nausea and vomiting.

Target plan:

1.1 g/Kg/d Protein equivalent (PE) from amino acid protein substitutes, 10 protein exchanges daily as natural protein. PKU Express 20 x 3 per day (60g PE) + low protein foods

Main concern:

PKU amino acid substitutes were not tolerated due to nausea and vomiting.
A range of other amino acid based protein substitutes were trialled with no success. Several anti-emetic medications were introduced but nausea and vomiting continued. At approximately 10 weeks into the pregnancy Phe levels were 500- 700µmmol/l.

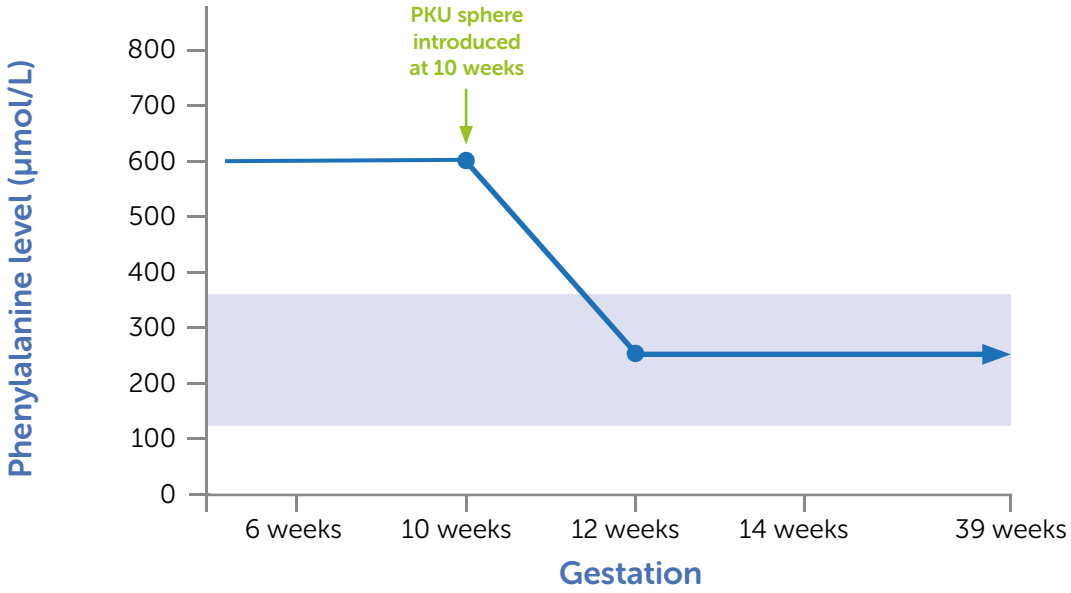
Transition:

The Multidisciplinary team (MDT) discussed a trial of glycomacropeptide (GMP) based protein substitute as Phe levels were too high.

PKU sphere was commenced at ~10 weeks of pregnancy with good tolerance. Patient took red berry flavour mixed with a low protein milk substitute. The full requirement of protein substitute was introduced rapidly to minimise risk of adverse effects of high Phe levels to the unborn baby.

At 12 weeks of pregnancy 2- 3 sachets of PKU sphere 20 were being taken per day. At 16 weeks patient was taking 3 x PKU sphere 20 (60g PE + 108mg Phe) per day. They were not divided equally throughout the day and despite advice this was never achieved. Blood Phe levels reduced to target ranges (120-360umol/l) very quickly and remained within range for the rest of pregnancy.

By 34 weeks, exchanges of natural protein increased to 16 and patient remained on the 3 sachets of PKU sphere daily.



Outcome

A healthy baby girl was delivered by caesarean section at 39 weeks due to a breach presentation. The patient decided to stop her PKU diet at this point, despite medical advice to continue with the protein substitutes to aid wound healing and nutritional quality of diet.

She is now completely off PKU diet, refusing all protein substitutes and attempting to eat a more nutritionally balanced diet.

Summary

- Once PKU sphere was introduced, blood Phe levels dropped to within acceptable limits for pregnancy and as with many maternal PKU patients, natural protein intake increased in the second and third trimesters.
- PKU sphere was better tolerated by this patient during pregnancy. Anti-emetics were required well into the second trimester. Following our experience with this patient and despite PKU sphere containing 36mg Phe per 30g PE, it would be considered for other maternal PKU patients experiencing problems with morning sickness or protein substitute tolerance.
- PKU sphere was started at the full protein requirement for this patient. The MDT would have preferred a more graduated introduction to test response to the Phe in GMP as per product guidelines.
- PKU sphere guidelines recommend that it is introduced cautiously and under careful supervision due to its Phe content (36mg/20gPE)[2]. As blood Phe levels were not being obtained frequently, the MDT decided it was in the patient and unborn baby's best interest to trial the full dose of GMP immediately. Metabolic control then improved quickly.
- PKU sphere was successfully used in this unplanned pregnancy (Phe levels out of range, not following PKU diet) when other amino acid protein substitutes were not tolerated. The GMP did not adversely affect natural protein intake and exchanges were increased during the pregnancy while Phe control remained within the European guidelines for pregnancy[1].

*Unplanned pregnancy in PKU relates to when mothers Phe levels are out of range and/or mother is not on PKU diet before conception.

References:

1. van Wegberg, A.M.J., et al., The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet Journal of Rare Diseases, 2017.
2. Vitaflo dietitians in collaboration with MacDonald. A and Daly A. The introduction and use of PKU sphere, Glycomacropeptide (GMP) based protein substitute, in children and adults with PKU. 2017

Notes

Notes

PKU sphere is a Food for Special Medical Purposes

All information correct at the time of print

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