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MATERNAL PKU

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Phenylketonuria (PKU) was first discovered in 1934 by a Norwegian biochemist and medical doctor called Dr Asbørg Følling (1). In 1957, Prof Charles Dent reported three children (without PKU) of mothers with PKU, all of whom had significant brain damage (2), but it was not until much later that the 'maternal PKU syndrome' was properly recognised, described and treated with a low phenylalanine diet for the mother with PKU in order to protect her developing foetus from the teratogenic effects of raised blood phenylalanine levels.

HISTORY OF MATERNAL PKU

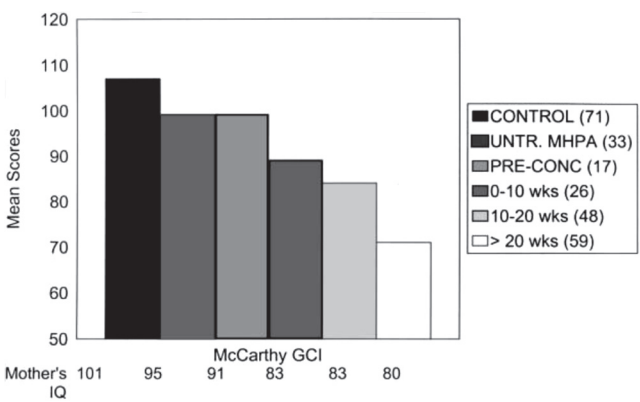
In 1980, Lenke and Levy (3) published an international survey that included data on 524 pregnancies in 155 women with PKU. They reported that in women with PKU untreated during their pregnancy, 92 percent of the babies had mental retardation, 73 percent had microcephaly, 12 percent had congenital heart disease and 40 percent had low birth weights (3).

The Lenke and Levy survey (3) paved the way for a prospective study of the treatment and its benefits, called the International Maternal PKU Collaborative Study (4). This study of 574 pregnancies in 382 women with PKU, demonstrated that intervention with a phenylalanine-restricted diet reduces microcephaly, intrauterine growth retardation, congenital heart disease and mental retardation in the offspring of PKU mothers (4).

These results are illustrated in the original graph below from the Koch et al paper (4). McCarthy general cognitive index (MGCI) scores are shown for offspring at four years of age, grouped by weeks of gestation after which maternal blood Phe was consistently below 600µmol/L.

Graph 1 illustrates the relationship between the timing of dietary inter vention and the outcome of the offspring. The earlier the Phe-restricted diet is started, the better the

Graph 1



outcome for the child. The ideal situation is to start the diet before conception, as children have the best outcome (MGCI = 99 at four years of age). Children of mothers with mild hyperphenylalaninaemia (MHPA) also have a similar outcome as Phe levels are controlled even without treatment. The offspring of women who started the Phe-restricted diet the latest (>20 weeks gestation) had the worst outcome with a MGCI of 70 at four years of age.

From this study, the US researchers recommended blood phenylalanine levels during pregnancy of 120-360µmol/L. In the UK, we tend to be slightly more conservative and use phenylalanine levels of 100-250µmol/L during pregnancy, possibly up to 300µmol/L in some UK metabolic centres.

KEY CHALLENGES DURING PREGNANCY

The first challenge during the preconception period is to understand the use of 50mg phenylalanine (phe) exchanges (1.0g protein), which must be accurately weighed and counted each day. Where the phe content of a food is not known, 1.0g protein exchanges are used and an understanding of food labelling will be needed to enable this to be calculated. For the many women who are not following a phe- restricted diet, this can prove difficult to understand at first as significant dietary changes will be needed and they may be unfamiliar with the concept of exchanges.

All women are encouraged to bring their partner or a relative to the education sessions for support, as this will be invaluable to help manage the diet at home. The format and number of education sessions is tailored to the individual and home visits may be required in addition to the monthly hospital visit. Cooking skills are essential when following a phe-restricted diet and this may need to be part of the education sessions. All the companies who manufacture low protein foods have excellent recipe books that give ideas and tips for the use of their products. The tolerance of the phe-free amino acid supplements, e.g. PKU Cooler, PKU Lophlex LQ, can prove problematic due to the unfamiliar taste and, in some cases, abdominal symptoms have been reported. These are essential to meet daily protein, vitamin and mineral requirements and dietary restriction cannot commence until these are established.

When phe control is sub-optimal in childhood, it can cause mild learning difficulties and the level of support required will be significantly increased. During preconception it is essential to control body weight as rapid weight loss can cause an unwanted rise in blood phe levels, which must be corrected as soon as possible, and further weight loss prevented. This is more likely in women who usually follow an unrestricted diet, as the low phe diet is less energy dense than their usual diet. Including a wide variety of low protein foods in the diet will help prevent this, although in some cases further energy supplementation may be required.

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NUTRICIA Metabolics

During the early stages of pregnancy, related nausea and vomiting can be problematic and can lead to reduced intake or absorption of the amino acid supplements.

Monitoring of blood phe levels is done by dried blood spot, which the women send from home directly to the laboratory twice weekly. These results are phoned or emailed to the patient as soon as they become available and advice is given if dietary changes are necessary. A minimum of four consecutive levels within the target range of 100-250μmol/l is required at Salford Royal Hospital before contraception can be discontinued. These phe levels need to be maintained throughout pregnancy for optimal outcome for mother and baby. Women need to be made aware that, although PKU does not obviously affect fertility, the length of time taken to conceive varies greatly and the low phe diet may be required for many weeks or months prior to pregnancy as well as during.

During the early stages of pregnancy, related nausea and vomiting can be problematic and can lead to reduced intake or absorption of the amino acid supplements. Accurate reporting of the quantity of supplement managed daily is essential and strategies, such as taking smaller more frequent amounts of supplement, often help. The Metabolic dietitian will carefully monitor phe levels to ensure these remain as optimal as possible. In some cases, medication can be used, or in severe cases, hospital admission may be required. At the start of pregnancy, the number of phe exchanges is usually low; in classical PKU this can be as few as two to five exchanges per day (2.0-5.0g natural protein). However, after approximately 20 weeks, these tend to increase as the demand for protein from the foetus increases and by the end of pregnancy some women can be on as many as 25 to 30 exchanges (25-30g natural protein). In women who usually follow a low phe diet, increasing the number of daily exchanges can prove challenging when only carbohydrate based foods are used for phe exchanges. The use of a high protein exchange list can help, using small quantities of High Biological Value protein e.g. one egg = six exchanges. The amino acid supplement intake is reviewed by the dietitian as natural protein intake increases and may be gradually reduced to maintain a steady total protein intake.

The Metabolic Team will liaise with the local obstetrician who may decide that additional growth scans would be beneficial. If phe control is good, these are not essential and not all maternity units carry these out. PKU does not carry any additional risks to the mother or baby during delivery. Post-partum, some women choose to remain on a phe-restricted diet, in which case the daily phe exchanges will need to be adjusted to control blood levels to approximately 700μmol/l. This is recommended if future pregnancies are desired and current advice in the UK recommends diet for life in all PKU patients. If returning to an unrestricted diet, the nutritional adequacy of this is essential and daily protein requirements must be met. If this is problematic, a small dose of amino acid supplement is recommended by the Metabolic dietitian at Salford Royal.

Case study

Nicola age 34 years old follows a relatively strict low phenylalanine diet (12 exchanges). She was initially worried about whether she could manage the diet and whether the baby would be OK. With reassurance and support from the dietitians, she commenced a preconception diet on only two exchanges. Weight loss in her first pregnancy resulted in the need to use extra artificial calories, as her diet was limited. Nicola found recording exchanges and the PKU Coolers helped; she also noted her phe levels and any changes in exchang-

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es. During her first pregnancy, Nicola struggled with being hungry, not eating enough and when to take the PKU Coolers. Good phe control was managed throughout the pregnancy and a healthy baby boy was born.

During her second pregnancy, Nicola included more low protein foods in her diet and did not require any artificial calories. Any nausea was overcome by snacking and Nicola found that taking the PKU Coolers at the same time as her meals helped with controlling her phe results. Good phe control was managed throughout the pregnancy and a healthy baby girl was born on her older brother's third birthday.

"For the time you are on the diet, it does take over your life and it is a struggle, but you can do it because you want to. It's all about planning your diet, using the low protein foods, getting family involved, be it support or making food for you just take it seriously and stick at it ...it's all very worthwhile."

WHAT ABOUT THE BABY AND PKU?

The baby of a mother with PKU will inherit one copy of the mother's PKU gene, but this does not mean that the baby will have PKU. The father of the child needs to be a carrier of the PKU gene in order to 'pass on' another copy of the PKU gene, as two copies are required to result in a child with PKU.

There is approximately a one in 100 chance of this happening, as the carrier rate for PKU in the UK is one in 50 and there is a one in two chance of the baby inheriting the father's copy of the PKU gene.

In summary, approximately one percent of babies born to PKU mothers have PKU themselves.

When the baby is born, he/she will be screened for PKU in the same way that all newborn babies in the UK are screened, with the heel prick test taken on day five to eight of life. The heel prick test is not only to detect PKU but other inherited conditions too.

CONCLUSION

Managing a PKU pregnancy is both challenging and rewarding for the Metabolic team and the patient involved. It requires focused education and intense support from the Metabolic dietitian as well as motivation and determination from the woman with PKU and her family. With the right support in place, both mother and baby can achieve a healthy outcome.

About the authors

Paula Hallam is the Dietitian Advisor for the NSPKU (www.nspku.org), working with families, adults with PKU and healthcare professionals who care for people with PKU to improve care and treatment for all. Paula also works as a Clinical Dietitian in the Metabolic team at Great Ormond Street Hospital, London.

Sarah Ripley began working at Salford Royal in 2009 and was solely responsible for establishing a dietetic service for adult metabolic patients. Sarah has over 20 years' clinical experience and has worked at both paediatric and adult hospitals in a variety of specialist areas.

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Questions relating to: *Maternal PKU*
Type your answers below and then **print for your records** or print and complete answers by hand.

Q.1	What is maternal PKU syndrome and what are the risks to a developing foetus?
A	
Q.2	Describe the key findings of the 1980 Lenke and Levy survey into maternal PKU.
A	
Q.3	What did the 1998 International Maternal PKU Collaborative Study demonstrate regarding the phenylalanine-restricted diet?
A	
Q.4	What are the recommended blood phenylalanine levels in the UK compared to those in the US?
A	
Q.5	Outline the first main challenge faced by a pregnant woman with PKU.
A	
Q.6	Describe other factors that need to be addressed in education sessions during the preconception period.
A	
Q.7	Why is it essential for body weight to be controlled during preconception?
A	
Q.8	What effect can sickness and nausea have on the dietary management of maternal PKU?
A	
Q.9	Describe the main challenges that need to be managed after 20 weeks of pregnancy.
A	
Q.10	Explain what the likelihood is of PKU passing from mother to baby.
A	

Please type additional notes here . . .