Pregnancy in phenylketonuria: dietary treatment aimed at normalising maternal plasma phenylalanine concentration

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Abstract

The transport characteristics of the placenta, which favour higher phenylalanine concentrations in the fetus than in the mother, and regression data of head circumference at birth against phenylalanine concentration at conception in maternal phenylketonuria (PKU), suggest that treatment of maternal PKU should ideally aim to maintain plasma phenylalanine concentration within the normal range throughout pregnancy. A patient with classical PKU was treated from before conception by aiming to maintain plasma phenylalanine concentration within the range 50–150 $\mu\text{mol/l}$ and tyrosine within the range 60–90 $\mu\text{mol/l}$. The diet was supplemented with phenylalanine-free amino acids (100–180 g/day) and tyrosine (0–5 g/day). Plasma amino acid concentrations were monitored weekly by amino acid analyser. Dietary phenylalanine intake ranged from 6 mg/kg/day at conception to 30 mg/kg/day at delivery. Normal weight gain and fetal growth were maintained throughout the pregnancy. A normal baby was born at term with a head circumference of 35.5 cm; at 1 year of age no abnormality is detectable. These results show that with careful monitoring and compliance it is possible, and may be advisable, to maintain plasma phenylalanine concentration within the normal range in the management of PKU pregnancy.

The dietary management of phenylketonuria (PKU) both in infancy and in pregnancy has generally been monitored by measurement of phenylalanine concentrations using filter paper blood spot specimens. The limited reliability of these measurements at low phenylalanine concentration and the importance of avoiding phenylalanine deficiency have led to generally accepted therapeutic ideal ranges for plasma phenylalanine concentration of between 200–400 $\mu\text{mol/l}$ in children under 8 years¹ and between 120–360 $\mu\text{mol/l}$ during pregnancy.² Preconceptional and gestational control of phenylalanine concentrations within these limits in maternal PKU generally results in offspring having an intelligence quotient (IQ) and developmental quotient within the normal range.³ As yet there are insufficient data to conclude that mean IQ is the same as that of the general population.

The concentration gradient across the human placenta results in the fetus being exposed to phenylalanine concentrations approximately twice those in maternal plasma.^{4,5} The

developing fetal brain is likely to be at least as sensitive, if not more so, to damage by increased phenylalanine concentrations as that of the infant. These considerations would favour maintenance of maternal phenylalanine concentration at or below 50% of the recommended treatment range for infancy. This concept is taken further by regression data of phenylalanine concentration at conception in women with PKU against head circumference of offspring.⁶ These data have recently been extended to show that head circumference at birth falls by 0.46 cm for every 200 $\mu\text{mol/l}$ rise in phenylalanine concentration above normal.⁷ It has therefore been suggested that plasma phenylalanine concentration should be maintained in the normal range throughout pregnancy in a woman with PKU.⁷

We now report management and outcome of pregnancy in a woman with PKU using these principles. The limited sensitivity of the filter paper blood spot assay method⁸ led us to use the more precise method of automated amino acid analysis to monitor plasma amino acid concentrations, aiming for a therapeutic control range for phenylalanine of between 50–150 $\mu\text{mol/l}$ and for tyrosine of between 60–90 $\mu\text{mol/l}$ (that is, within the upper normal range). The rationale for control of tyrosine concentration was based on the remarkable inhibition of tyrosine transport into placental brush border membrane vesicles with increasing concentrations of phenylalanine.⁹

Case history

The patient was born in 1962 before the commencement of neonatal screening programmes for PKU in Australia. She first presented at the age of 2.5 years because of slow development and had a phenylalanine concentration of 1800 $\mu\text{mol/l}$. She was subsequently treated with a protein restricted, phenylalanine-free amino acid supplemented diet until the age of 9 years. Serial developmental assessments into teenage years placed her IQ in the low-normal range. Subsequent progress was uneventful until, at the age of 27 years, she planned pregnancy.

Dietary treatment was commenced 10 weeks before conception. The principles of the dietary regimen are summarised in the table. Phenylalanine-free amino acids, vitamins, and minerals were supplemented using a proprietary formulation (Maxamum XP, Scientific Hospital Supplies). An initial dose of 150 g/day was increased to 180 g/day at 24 weeks' gestation and subsequently decreased at 37 weeks to

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Principles of dietary management of maternal phenylketonuria aiming for normal plasma phenylalanine concentrations

	Before pregnancy	During pregnancy
Protein (as natural protein + amino acids)	<0.75 g/kg	<0.75 g/kg + 6 g
Phenylalanine	Initially 4–8 mg/kg,* adjust as indicated to maintain therapeutic range	Increase with advancing gestation to maintain therapeutic range
Tyrosine	Initially 160 mg/kg; adjust as indicated to maintain therapeutic range	Increase with advancing gestation to maintain therapeutic range
Calcium	800 mg	1100 mg first and second trimester, 1300 mg third trimester
Iron	12–16 mg	22–36 mg
Zinc	12–16 mg	16–21 mg
Folic acid (as total folate)	200 µg	400 µg
Macro and micro minerals and vitamins	Full range supplied from natural foods, protein substitutes, and supplements	
Essential fatty acids and cholesterol	From dietary fats and oils	
Energy	Individual assessment based on age, weight, appetite, activity	Add 850–1100 kJ to prepregnancy requirement
Weight gain		First 12 weeks: 1–2 kg Then 1–2 kg/month to term
Plasma phenylalanine	Monitor weekly, maintain 75–150 µmol/l for four weeks before ceasing contraception	Monitor weekly, maintain 75–150 µmol/l
Tyrosine	Monitor weekly, maintain 60–90 µmol/l for four weeks before ceasing contraception	Monitor weekly, maintain 60–90 µmol/l

*Depending on severity of PKU.
Intakes are given as daily requirements.^{10–12}

100 g/day as natural protein intake increased. The daily intake was divided into three equal portions and was taken with meals.

Changes in phenylalanine concentration in relation to dietary phenylalanine intake are shown in fig 1. Blood phenylalanine concentrations were monitored before conception and in the first four weeks after conception using filter paper blood spots and the bacterial inhibition assay; full amino acid chromatograms were obtained intermittently during this period. Subsequently, plasma phenylalanine and tyrosine

concentrations were monitored weekly by amino acid analyser (Biotronik LC 5000) because of concern over the precision of filter paper methods and the need to measure tyrosine concentration. All blood specimens were collected preprandially to simulate conditions under which the normal ranges were established. Blood was centrifuged and plasma separated immediately after collection. Plasma was then transported to reach our laboratory on the day of collection. After commencing treatment, the phenylalanine concentration rapidly fell to a little above the desired therapeutic range of 50–150 µmol/l. The patient's limited intelligence and her domicile in country Victoria, which restricted regular visits to the Royal Children's Hospital, made communication less than optimal on a number of occasions during the pregnancy. In mid-trimester plasma phenylalanine concentrations fell below the desired range several times, the lowest being 18 µmol/l at 15 weeks and 15 µmol/l at 22 weeks. These low concentrations may have been avoided through better communication. Plasma tyrosine concentrations (fig 2) were generally maintained close to or within the desired therapeutic range of 60–90 µmol/l. Tyrosine intake from natural protein, Maxamum XP, and additional tyrosine supplements is also shown in fig 2. The need for tyrosine supplementation additional to that provided by Maxamum XP and natural protein varied between 0 and 5 g/day; this was taken in three divided doses with Maxamum XP.

Maternal weight gain (fig 1) was satisfactory throughout the pregnancy, although there was some weight loss in the first trimester. Compliance with energy supplements in the form of

Figure 1 Dietary phenylalanine intake, plasma phenylalanine concentration, and maternal weight gain before and during pregnancy. Minimum phenylalanine concentration was 15 µmol/l at 22 weeks' gestation.

Figure 2 Tyrosine concentration in relation to intake before and during pregnancy.

low protein pastas and breads was poor at certain points during the pregnancy including the first trimester. Fetal growth was monitored by ultrasound examination at 18, 28, and 36 weeks of gestation. Despite suboptimal maternal energy intake and occasional sub-therapeutic phenylalanine concentrations, fetal growth was normal throughout the pregnancy. Ultrasound examinations revealed no evidence of malformation.

There were no obstetric complications throughout the pregnancy and the baby was born by normal delivery at 41 weeks' gestation. Birth weight was 3920 g (75th centile), length 51.0 cm (50–75th centile), and head circumference 35.5 cm (50–75th centile). The baby is quite normal to physical examination and now, at 12 months of age, has a Bayley developmental index (mental scale) of 106. Head circumference continues to lie on the 75th centile, weight on the 50th, and length on the 75th.

Discussion

The potentially disastrous effects of phenylalanine deprivation,¹³ the poor reliability of filter paper blood spot assay of low phenylalanine concentration,⁸ and the apparently good outcome of PKU treated by maintaining plasma phenylalanine concentration a little above normal,^{14, 15} have led to the great reluctance to maintain phenylalanine concentrations in children with PKU within the normal range. While mounting circumstantial evidence suggests that plasma phenylalanine concentrations should be better controlled during pregnancy than is necessary for treatment of childhood PKU,⁷ the exact optimal range is yet to be determined. We have demonstrated that the accuracy of amino acid analyser determinations of plasma phenylalanine and tyrosine concentration can result in very precise control of blood phenylalanine and tyrosine in PKU. The therapeutic range aimed for in this patient (phenylalanine 50–150 μmol/l, tyrosine 60–90 μmol/l) overlaps with that for normal pregnancy (phenylalanine 66–107 μmol/l, tyrosine 40–76 μmol/l, *n*=7, second trimester, personal communication, Dr E F Robertson).

No abnormality has been detected in the baby born to our patient. Head circumference measurements appear to be a sensitive indicator of outcome in maternal PKU^{6, 7} and on this measure the baby is normal. This conclusion is supported by a normal developmental assessment at 1 year of age. Nevertheless, complete evaluation of the strategy of maintaining normal phenylalanine concentration in maternal PKU will not be possible until a much larger number of cases similar to ours have been described and followed up long term.

At several points during the current pregnancy, compliance and communication difficulties resulted in phenylalanine concentrations falling outside the intended therapeutic range. Early in the pregnancy concentrations rose to 271 and 266 μmol/l at 9 and 10 weeks' gestation respectively. In a second pregnant PKU patient currently under treatment by the authors the phenylalanine concentration was well controlled before conception with a dietary phenylalanine intake of about 4 mg/kg/day, but the concentration rose to about 200 μmol/l in the middle of the first trimester. In both patients the first trimester increases most likely reflected difficulty in maintaining energy intake because of morning sickness of pregnancy. Our experience in conventional management of PKU pregnancy indicates that phenylalanine concentrations can be difficult to control in the first trimester. In the patient currently under treatment, control of the phenylalanine concentration within the desired range was obtained when an energy supplement in the form of glucose polymer (Polyjoule, Sharpe Laboratories, 100 g/day) was added to the regimen.

Very low phenylalanine concentrations were also documented on several occasions, despite which no symptoms of phenylalanine deficiency were noted in the mother and the baby continued to grow satisfactorily. The ability to concentrate phenylalanine across the placenta in favour of the fetus⁵ may protect the fetus from the effects of borderline maternal phenylalanine deficiency. Nevertheless, the potential risks of low phenylalanine concentration indicate the need for careful attention to increasing phenylalanine requirements, particularly during the second trimester. The narrow therapeutic range also requires accurate calculation of all dietary sources of phenylalanine including low phenylalanine bread, pasta, and biscuits and fruits and vegetables. Some of these foods are permitted without measurement in the diet of children with PKU on the basis that an average consumption provides a relatively constant intake of phenylalanine.

Tyrosine is a neurotransmitter precursor and low neurotransmitter concentrations have been suggested as one of the mechanisms by which damage may occur in PKU.¹⁶ An optimal range for plasma tyrosine concentration in pregnancy of a woman with PKU has not been established. The potential for even small rises in plasma phenylalanine concentration to inhibit placental tyrosine transport⁸ suggests that maintenance of tyrosine concentrations in the upper normal range may be ideal. Treatment with a tyrosine fortified formula such as Maxamum XP with

additional tyrosine supplements as required seems a satisfactory approach. The tyrosine concentration bore no consistent relationship to that of phenylalanine, presumably because the intake of each respective amino acid was adjusted independently in response to changes in blood concentrations. An unusually high tyrosine concentration (162 $\mu\text{mol/l}$) was recorded at 23 weeks. There was no clear explanation for this increase. However, it is likely that the concentration was even higher one to two hours postprandially on this occasion and the possibility that raised tyrosine concentrations may in themselves cause fetal damage should not be ignored.¹⁷ Excessive tyrosine supplementation should be avoided.

In summary, we have now documented for the first time implementation of a frequently discussed strategy of maintaining normal phenylalanine concentrations in maternal PKU. Early indications suggest a normal outcome, although long term follow up of this and subsequent cases will be needed to determine the advantages of this strategy as compared with those of more conventional treatment methods. Our experience coupled with solid theoretical background suggests that these further studies should be undertaken.

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