PAPERS AND ORIGINALS

Management of maternal phenylketonuria: an emerging clinical problem

G M KOMROWER, I B SARDHARWALLA, J M J COUTTS, D INGHAM

British Medical Journal, 1979, 1, 1383-1387

Summary and conclusions

The children of untreated phenylketonuric women have a significantly higher mortality and morbidity than average. The success of neonatal screening for phenylketonuria (PKU) means that an increasing number of healthy intelligent women with PKU are reaching child-bearing age and will create a new therapeutic problem for physicians and obstetricians in the next decade. This unit managed six mothers with PKU and treated three of them with diets throughout four pregnancies. The treatment and outcome was assessed in relation to those in other reported cases. Although treatment was beneficial in the four pregnancies studied directly, in all the reported cases the outcome of treatment varied considerably and was not clearly related to any one factor such as onset of treatment or the type of PKU.

It is therefore not possible to give confident advice about the management of such cases. Since the number of women at risk will reach a peak in 10 years' time there is an immediate need for a well-planned prospective study of this problem.

Introduction

Although briefly mentioned by Dent in 1956,¹ maternal phenylketonuria (PKU) was not seriously considered by physicians and obstetricians until the mid-1960s, when Mabry *et al*² discussed six cases in detail. Since then several papers³⁻⁵ have described significant mortality and morbidity in the offspring of

untreated women with PKU, but there are few accounts of the outcome of pregnancies in which a low phenylalanine (Phe) diet was introduced.

If phenylketonuric mothers are untreated there is an increased abortion rate and a high incidence of severe congenital abnormalities, in addition to microcephaly and growth retardation and a lowering of intelligence in the group as a whole. Our recent but incomplete review of published reports showed 50 mothers with PKU who had given birth to 163 children as well as having 27 spontaneous abortions. Fourteen children died; eight had PKU; 21 had a normal intelligence quotient (IQ; above 80), although the maternal diagnosis was in doubt for three (two siblings) of these children; 119 had a low IQ. Although there was inadequate information in many cases, 72 congenital abnormalities were recorded, including microcephaly; growth retardation; serious lesions of the cardiovascular, skeletal, and gastrointestinal systems; and ocular defects. Observations on the effect of excess Phe and its transamination derivatives on cell transport and brain enzymes suggest that Phe excess is a more likely cause of teratogenic and brain developmental defects than the other possibility of tyrosine deficiency.

As well as a few fertile women with PKU who remain undiagnosed, healthy girls whose PKU was diagnosed and treated early after neonatal screening are now reaching adolescence and a marriageable age. The numbers of cases on the MRC's PKU register for 1964-73⁶ suggest that there will be about 500 fertile women of normal intelligence with PKU in Britain by the year 2000. Managing their pregnancies will thus present a problem. Accounts of treated cases have so far been usually about single cases. We therefore describe here the experience of our unit in diagnosing and handling these problems and compare our experience with that in other reported cases.

Patients and methods

Six mothers with PKU came under our care. Two were identified because their children were found to have PKU by the regional neonatal screening programme. One mother was identified by antenatal testing of the urine at 10 weeks using Phenistix. One was missed by Phenistix screening and was diagnosed postnatally by blood examination because her newborn baby had microcephaly (head circumference 29.7 cm). One mother was identified when investigated

Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA

G M KOMROWER, MB, FRCP, consultant paediatrician
I B SARDHARWALLA, FRCP, DCH, consultant paediatrician
J M J COUTTS, SRD, district dietitian
D INGHAM, RSCN, clinical liaison sister

to determine the reason for the gross mental retardation of her three children, and the last was referred by an obstetrician because she was known to have PKU and had been put on a low Phe diet during a previous pregnancy.⁷

These six women gave birth to 17 children including three babies with PKU; there were no miscarriages but two women had had a therapeutic abortion (table I). We treated three of these women during four pregnancies (table II); one mother (case 2) was treated through two pregnancies and another (case 3) was treated by us for a second time, since she had been put on a diet by Allan⁷ in an earlier pregnancy.

TABLE I—IQ of six mothers with PKU and the outcome of their pregnancies

Mothers	Children						
	Treated pregnancies				Untreated pregnancies		
IQ:	60-69	-79	>80	74	>80	41-60	61-80
No of subjects	4	0	2	1	4 (mean 88-127)	6 (mean 51)	6 (mean 65)

TABLE II—Birth measurements and developmental quotients in babies born after treated pregnancies

	Case 1	Case 2		Case 3
		1st Pregnancy	2nd Pregnancy	
Sex	Male	Female	Female	Male
Gestation (weeks)	39	40	40	38
Birth weight (g)	2720	3200	3000	2610
Length (cm)	46.4	50.3	48	49
Head circumference (cm)	32	33	33	31
Developmental quotient	74 at 6 years	127 at 2 years	122 at 1 year	88 at 2 years
Genotype	PKU baby	Heterozygote	Heterozygote	Heterozygote

AIMS OF TREATMENT

We wanted to treat the women at home, monitoring blood Phe concentrations by semi-quantitative methods at weekly intervals from postal specimens and at monthly intervals by column analysis during the visit to the clinic, when the mother was seen by the dietitian, clinician, and the clinical liaison sister. We hoped to achieve normal weight gain and good general health and nutrition throughout the pregnancy, maintain the mother's morale, and deal with any minor psychological problems. In three cases, ultrasonic measurement of the biparietal diameter of the baby's skull was carried out by the obstetrician, who also reported to us on the baby's growth and on his assessment of the mother's condition.

PROTEIN AND PHE INTAKES

The main source of protein was the amino-acid preparation PK Aid 1. The total protein intake varied from 1.0 to 1.5 g/kg/day, usually about 1.25 g/kg. We also gave the standard vitamin and metabolic mineral mixture in the form of Ketovite liquid 5 ml daily and Ketovite tablets three daily together with metabolic mineral mixture 8 g daily; this was increased to 16 g daily in the last trimester of pregnancy. To ensure an adequate intake of energy we stipulated the minimum quantity of low-protein bread and biscuits to be taken, and prescribed a definite quantity of Gastro-Caloreen (a glucose polymer) to be consumed each day. An arbitrary decision was made to keep plasma Phe concentrations below 0.6 mmol/l (10.0 mg/100 ml) and plasma tyrosine concentrations above 0.03 mmol/l (0.5 mg/100 ml).

With only the treatment given in previous cases by Allan and Brown,⁷ Arthur and Hulme,⁸ and Farquhar⁹ to guide us, we started treatment in case 1 with an intake of Phe of about 450 mg/day, expecting to increase this fairly promptly and being prepared to adjust it according to plasma Phe concentrations.

Results

CASE 1

This woman (IQ 69) already had one child with PKU born after an uneventful untreated first pregnancy. Although this child had been well controlled on a low Phe diet for the first four years of his

life, his head circumference (at birth 32.5 cm) remained below the third centile and his IQ was in the 10-50 range. A low Phe diet was started at nine weeks in the second pregnancy; the initial control was satisfactory, but the woman had little support from her family, and her new diet, together with the supervision of her child with PKU, proved too much for her and she was admitted to hospital at 32 weeks for further stabilisation, where she remained until delivery. We had no problem with her weight or general nutrition; the plasma tyrosine values were satisfactory but the Phe requirement increased in the last trimester, reaching a daily intake of 550 mg and a total protein of 52.0 g (fig 1). The baby was born at 38 weeks, weighing

FIG 1—Case 1. Phenylalanine intake and plasma phenylalanine (Phe) and tyrosine (Tyr) concentrations during pregnancy.

2750 g and with a head circumference of 34.5 cm. There were no important congenital abnormalities except in the left ear, where the pinna was not fully formed. Renal radiographs showed no abnormality. This child also had PKU, and low Phe treatment was started at seven days. At 6 years of age the child's IQ was 74, and he received little stimulation or encouragement at home. Nevertheless, his progress was better than that of his elder brother, and he attends a normal school.

CASE 2

First pregnancy

This woman (IQ 96) first came to our notice in 1971, when she was detected by antenatal urine screening with Phenistix. She elected to have a termination of the pregnancy, which was done at 19 weeks. She remarried soon after and in 1974 intentionally became pregnant.

Unfortunately we were not informed and could not start treatment until the eighth week of the pregnancy; we checked her husband to find that he was homozygous normal for PKU (the Phe: tyrosine ratio was 0.65). The patient was overweight (71.4 kg) and was given a reduced energy diet (1600 kcal (6.7 MJ)) and lost 4 kg in the first 14 weeks. This diet was maintained throughout her pregnancy. At 20 weeks her Phe intake was still around 400 mg daily, and PK Aid 1 dose was increased to 100 g daily, the total protein intake being 89 g. As the plasma tyrosine concentrations were low an extra 5 g of tyrosine was added to the diet by doubling the amount of this amino-acid in the PK Aid, and this augmented PK Aid preparation was used in the next two cases. This woman's subsequent progress was very satisfactory: she maintained a slow but steady weight gain, and after the 25th week the requirement for Phe increased steadily until she was receiving 650 mg daily at the end of the pregnancy with a total protein intake of 94 g daily (fig 2).

FIG 2—Case 2. Phenylalanine intake and plasma phenylalanine (Phe) and tyrosine (Tyr) concentrations during first pregnancy.

The baby was delivered by forceps in the 40th week, weighing 3200 g and with a head circumference of 33 cm. Immediate examination showed no abnormalities and the child's subsequent physical and mental progress was excellent: the most recent developmental quotient, at 2 years 2 months, gave a score of 127.

Second pregnancy

In this patient's second pregnancy the diagnosis of PKU was confirmed by the seventh week and treatment started. She had been placed on a reduced protein intake partly because there was an immediate need for her to lose an appreciable amount of weight. This was reflected in the plasma Phe concentration on her first attendance, which was 1.07 mmol/l (17.7 mg/100 ml). At that time she weighed 80.6 kg and during the next 12 weeks she lost 11 kg. Towards the end of that time we had difficulty persuading her to increase her energy intake. It was much harder to control the plasma Phe concentrations when she was losing weight rapidly, so we had to reduce the Phe intake to about 300 mg a day. By the 22nd week, however, she was under control, and from then on her plasma Phe concentrations remained within a satisfactory range but tended to be on the low side, and we increased the Phe intake to 1175 mg/day by the 38th week of pregnancy (total protein rose from 89 g to 104 g). From the start she had 100 g of PK Aid with the added tyrosine (fig 3). The second baby was born at term by normal forceps delivery: weight was 3000 g, length 48 cm, and head circumference 33 cm. Again the general examination and subsequent progress was satisfactory and when last seen in June 1978 at the age of 8 months her head circumference was on the 25th centile and the height and weight on the 50th centile. Her DQ at 1 year was 122.

This patient was well motivated and co-operative and supported by her husband.

FIG 3—Case 2. Phenylalanine intake and plasma phenylalanine (Phe) and tyrosine (Tyr) concentrations during second pregnancy.

CASE 3

This woman (IQ 68) lived some distance from the hospital and had three retarded children at home in addition to a "treated" boy.⁷ When first seen at 22 weeks she weighed 56 kg and her plasma Phe was 0.94 mmol/l. She was given a diet which included Phe 450 mg and protein 90 g daily. This was reasonably well tolerated until the 30th week of pregnancy, by which time her Phe intake had been increased to 1200 mg daily. She then abandoned the diet, and plasma Phe concentrations rose. At 34 weeks she was admitted to hospital for stabilisation and close supervision, and at 38 weeks she went into spontaneous labour, having been fit and well controlled during the last four weeks of her pregnancy (fig 4).

FIG 4—Case 3. Phenylalanine intake and plasma phenylalanine (Phe) and tyrosine (Tyr) concentrations during pregnancy.

Her baby boy weighed 2650 g and had a head circumference of 31 cm. There were no physical abnormalities, and developmental progress was satisfactory during the first year. By the child's second birthday, however, his head circumference had fallen below the third centile and DQ was 88. This poor score may have been due to the untreated maternal PKU in the earlier weeks of the pregnancy, but the family was of limited intelligence and could not give the baby much stimulation or training. The father was uncooperative and the family needed a great deal of support.

The birth measurements and subsequent development quotients are shown in table II. None of the three women suffered any nutritional deficiency, haemoglobin and serum protein concentrations being normal. Serial plasma amino-acid profiles throughout the pregnancies were also normal except for Phe and, on occasion, tyrosine.

OTHER CASES

Two of the three untreated mothers were sterilised, one (case 4) before PKU was diagnosed; none of her retarded children had

PKU. The second (case 5) already had a treated child without PKU as well as her child with PKU and was of low intelligence (IQ 67). She became pregnant for a third time and was sterilised after a therapeutic abortion at 16 weeks. After an interval of 24 months the third (case 6) (IQ 93) said that she wanted another child and was prepared to go on a diet before conception. She was given a diet which contained 70 g protein and 750 mg Phe and continued with it for four and a half months. As she was not pregnant, and finding her position stressful, she discontinued the diet and restarted contraception.

Comparison with other cases

We also compared our experience with that in other reported cases. Pueschel *et al*³ detailed eight cases including the three⁷⁻⁹ we have described earlier: of the remaining five cases, three were inadequately treated and one spontaneously aborted after one week on the diet. In the eighth¹⁰ case the diet was started at five weeks and was tolerated satisfactorily, the plasma Phe levels being within an acceptable range. The baby, born at term, weighed 2970 g but did not progress well, dying at 2 months because of a major congenital lesion. This case was similar to one described by Bush and Dukes¹¹ and another by Smith *et al*,¹² where the babies died within two weeks of birth, both with severe cardiac abnormalities. In each case treatment was started by the 10th week and maintained satisfactorily. In another case (M Fyfe, personal communication, 1978) the mother was treated from the 14th week of the pregnancy and plasma Phe concentrations were mostly below 0.35 mmol/l (5.8 mg/100 ml). The baby at birth had a small head (33 cm) and a Pierre-Robin malformation.

Information about treated cases is scarce and does not include any case where dietary treatment was started before conception (table III). The information is also conflicting. Four mothers who started treatment by the 10th week were satisfactorily controlled: three had babies with severe cardiac lesions who died (table III),

probably because of the growth of the uterine muscle, placenta, and the fetus and also because of the ability of the heterozygote fetus to metabolise Phe.

When we started treating case 1 we had only the results in three other reported pregnancies⁷⁻⁹ to guide us. In each case treatment had started at the 20th-22nd week and immediate and subsequent development of the children was good except in one case. The Phe intake had varied from a maximum of 10 mg/kg/day (620 mg) in Allan and Brown's case⁷ to 30 mg/kg/day (1800 mg) in Arthur and Hulme's case⁸ (this information was not recorded in the third case⁹). We started with a Phe intake of 450 mg/day. In retrospect we think that the first patient should have received more protein and more Phe during the last weeks of the pregnancy. The plasma concentrations of the amino-acid tended to be low and the baby's birth weight was less than that of the untreated first sibling.

The experience in the women we treated must, however, be balanced against that in other reported cases, in which the outcome has not been so consistent. This confusing information raises the question whether treatment for maternal PKU is necessary, what treatments are available, and whether dietary treatment is justifiable.

Treatment is clearly necessary since morbidity and mortality are so high among the offspring of mothers with PKU. The treatment available is either preventive—contraception or sterilisation—or dietary. The only clearly defined group is retarded women with PKU who already have retarded children and who get very little support from their families; with few exceptions sterilisation should be recommended.

The small number of good results of dietary treatment in both early and late pregnancy encourages us to believe that early treatment (before conception) in well-motivated intelligent

TABLE III—Information on reported cases of PKU in which treatment was started during pregnancy

	Mother			Child		
	Phe (mmol/l)	Untreated urine FeCl ₃	Treatment started (week)	IQ	Birth weight (g)	Present age
Arthur and Hulme ⁸	0.7-1.3	+	20	65	1990	8 yrs 3 mths
Farquhar ⁹	1.0-1.5	+	22	55	2380	5 " 1 "
Allan and Brown ⁷	1.65	+	21	68	3100	9 " 9 "
Bush and Dukes ¹¹	1.0	+	10	48-58	3216	Dead
Bovier-Lapierre <i>et al</i> ¹⁰	0.9-1.5	+	5	73	2970	Dead
Smith <i>et al</i> ¹²	1.8-2.4	+	7	76	2690	Dead
Fyfe*	1.2	+	14	92	2720	10 mths

*M Fyfe, personal communication, 1978

whereas the two siblings born to the fourth mother developed normally (case 2). The fifth mother (case 1), who started treatment early, was not so well controlled, but her child with PKU was much brighter than his elder sibling with PKU, who was born after an untreated pregnancy. In the five pregnancies where treatment was started after the 16th week (16-22 weeks) three children are developing well and have no congenital abnormalities. The two youngest babies do not seem to be progressing well, however, as head growth and developmental progress are delayed. After careful review of the plasma and urine findings of these cases we have not been able to establish any biochemical criteria to help us with the prognosis.

Discussion

The results in our cases suggest that a low-Phe diet can be introduced in cases of maternal PKU with satisfactory progress through the pregnancy so long as the energy, vitamin, and mineral requirements are attended to. In some cases we also thought it advisable to supplement the tyrosine intake.

Whenever possible weight reduction should be carried out before the low-Phe diet is introduced as it is harder to determine the Phe requirement during the period of weight loss owing to the availability of the amino-acid from tissue breakdown. The need for Phe increases from about the 26th week onwards,

women who had been on diets in childhood may allow the fetus to develop normally. Nevertheless, the alternative of contraception or sterilisation must be put clearly to any girl with PKU who is considering marriage or motherhood. If dietary treatment is to be carried out it should, whenever possible, start before conception and aim at keeping the plasma Phe level around 0.5 mmol/l (8.0 mg/100 ml). If this proves too difficult or seems unsuitable in a particular case a low-protein diet to prevent plasma Phe concentrations rising above 0.9 to 1.0 mmol/l should be introduced until the woman misses a period, when a stricter regimen should be started.

In cases where PKU had not been diagnosed before pregnancy we would treat women of reasonable intelligence (IQ 80) provided that the mother was anxious to have the baby and that we could be certain of sympathetic and practical help at home. Each case must receive unhurried and sympathetic consideration by the physician working in close accord with the obstetrician and dietitian, nurse, and biochemist.

With good motivation and adequate dietetic and nursing support it should be possible to handle the problem of maternal PKU on an outpatient basis in most cases. Most women who will require such supervision in future will have been treated from infancy and have a far better intelligence than patients cared for to date. They should receive far more help from their

husbands, who probably will be of similar intelligence and will have been told about the problem before pregnancy. In view of our very limited experience of this clinical condition a well-planned prospective study should be started to recommend a sensible therapeutic approach.

We thank the many people who have helped us in the writing of this paper: the staff of the Willink Laboratory, particularly Miss C Bridge and Dr B Fowler; our educational psychologist Mrs M A Riley; and Mr R Mitchell, of the Department of Medical Illustration, Salford Area Health Authority (Teaching), who prepared the figures for this paper. We also thank Dr Leonard Arthur and Mrs Hilary Gray (Derby), Professor J W Farquhar and Mrs Elsie Rivlin (Edinburgh), and Dr W M Fyfe and Dr J E Stevenson (Glasgow) for up-to-date information about their own cases.

References

- ¹ Dent, C E, *Report of 23rd Ross Conference*, Ross Laboratories, Columbus Ohio, 1956.
- ² Mabry, C C, *et al*, *New England Journal of Medicine*, 1963, **269**, 1404.
- ³ Pueschel, S M, Ham, C, and Andrews, M, *American Journal of Nutrition*, 1977, **30**, 1153.
- ⁴ Trouche, A M, *et al*, *Pédiatrie*, 1974, **29**, 33.
- ⁵ Pitt, D, and Gooch, J, *Australian Paediatric Journal*, 1974, **10**, 337.
- ⁶ MRC/DHSS, *Phenylketonuria Register News Letter*, No 2 May, 1974.
- ⁷ Allan, J D, and Brown, J K, *Some Recent Advances in Inborn Errors of Metabolism*, ed K S Holt and V P Coffey. Edinburgh, Livingstone, 1968.
- ⁸ Arthur, L J H, and Hulme, S R D, *Pediatrics*, 1970, **46**, 235.
- ⁹ Farquhar, J W, *Archives of Disease in Childhood*, 1974, **49**, 205.
- ¹⁰ Bovier-Lapierre, M, *et al*, *Pédiatrie*, 1974, **29**, 33.
- ¹¹ Bush, R T, and Dukes, P C, *New Zealand Medical Journal*, 1975, **82**, 226.
- ¹² Smith, I, *et al*, *Lancet*, 1979, **1**, 17.

(Accepted 3 May 1979)

Evaluation of one-visit endoscopic clinic for patients with dyspepsia

A K BEAVIS, S LA BROOY, J J MISIEWICZ

British Medical Journal, 1979, **1**, 1387-1389

Summary and conclusions

An evaluation was made of the feasibility of an instant upper-gastrointestinal endoscopy clinic for patients referred to hospital for the investigation of dyspepsia. A total of 200 patients underwent endoscopy using a small-diameter endoscope with only topical pharyngeal anaesthesia but no premedication or sedation. The procedure was successful in 187 of the patients. Its acceptability was high for both patients and doctors. The average duration of the hospital visit was 45 minutes.

Instant endoscopy with a small-diameter endoscope provides a convenient and fast primary diagnostic service for patients with dyspepsia.

Introduction

Dyspepsia is common, Doll and Avery Jones in 1950¹ estimating that some 30% of the adult population will experience dyspepsia during a five-year period. Barnes *et al*² calculated that in a population of 300 000 (about that served by a district general hospital) 4500 people are likely to have severe dyspeptic symptoms, of whom about 2700 will have a definite lesion of the upper gastrointestinal tract. These figures indicate the magnitude of the work load in departments of gastroenterology, which investigate and treat these patients.

Several studies have shown that endoscopy is more accurate than radiology in detecting lesions of the upper alimentary tract.³ Endoscopy is becoming generally accepted as the primary investigation of dyspepsia. Most patients referred to hospital for

investigation of dyspepsia are first seen in an outpatient clinic. Endoscopy is usually performed during a subsequent visit, usually entailing admission as a day case and sedation with intravenous diazepam. After endoscopy the patient is often followed up. This approach has several disadvantages: several hospital visits are necessary with consequent inconvenience to the patient, who also loses more than one working day; and drowsiness after intravenous sedation requires a period of recovery in a hospital bed after the test, and the patient should not drive or operate dangerous machinery for 24 hours. Many patients are unable to remember what the doctor told them after receiving intravenous diazepam. In addition, as each patient is seen several times, a backlog tends to develop.

If endoscopy without intravenous sedation using the small-diameter endoscopes such as the Olympus GIF P2 were acceptable to patients and if adequate examination of the oesophagus, stomach, and duodenum could be carried out under such circumstances, this procedure would considerably diminish the consumption of hospital resources. Thus patients referred with dyspepsia could be seen and examined and endoscopy carried out at only one visit, and treatment could be started immediately. Many patients would need only one visit to the hospital and could be immediately referred back to their own general practitioner. We have evaluated this approach to diagnostic endoscopic examination of the upper alimentary tract in patients with dyspepsia with respect to its feasibility, organisation, acceptability to the patient, and success rate.

Patients and methods

All the patients included in this study were consecutively referred by practitioners for investigation of dyspepsia. They were sent an appointment for a one-visit upper gastrointestinal investigation clinic. The letter contained the time of the appointment, a short explanation of the clinic arrangements, a simple description of endoscopy, and a request to attend fasting. Patients seen at morning clinics fasted from the previous evening, while those seen in the afternoon had only a light breakfast on the day of the appointment. The clinics were conducted by two doctors and an endoscopy nurse. Each patient was seen by one of the doctors, who took a full history and performed a physical examination. Blood for laboratory investigations was taken at this stage, and the doctor then decided whether endoscopy was indicated. The endoscopy was done by the same doctor, the patient

Department of Gastroenterology, Central Middlesex Hospital, London NW10 7NS

A K BEAVIS, MB, MRCP, research fellow and honorary senior registrar

S LA BROOY, MB, MRCP, research fellow and honorary registrar

J J MISIEWICZ, MB, FRCP, consultant physician and member of external scientific staff, Medical Research Council