Short reports

Maternal phenylketonuria: abnormal baby despite low phenylalanine diet during pregnancy

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SUMMARY During a screening programme of 10 000 pregnant women by the Guthrie test, a previously unrecognised phenylketonuric woman was detected. A low phenylalanine diet introduced from the 16th week of gestation failed to prevent fetal abnormality and mental retardation. Maternal phenylketonuria requires earlier diagnosis than can be achieved at the initial antenatal clinic visit if its teratogenic effects are to be prevented.

Women with phenylketonuria (PKU) run a high risk of giving birth to infants with intrauterine growth retardation, mental retardation, microcephaly, or congenital heart disease.¹ The possibility that a low phenylalanine diet started in early pregnancy might protect the fetus from the harmful effects of maternal PKU during the rest of the pregnancy led to a pilot scheme by the PKU screening laboratory at Stobhill Hospital, and 10 000 pregnant women were screened for hyperphenylalaninaemia by the Guthrie test. Among those screened was a 27-year-old primigravida, who, when she booked for hospital confinement at 11 weeks' gestation, had a blood phenylalanine level above 20 mg/100 ml (>1.2 mmol/l). She was started on a low phenylalanine diet at 16 weeks' gestation (14 weeks from conception) and continued on this diet until she gave birth to a light-for-dates infant who was microcephalic and had the Pierre Robin syndrome.

Case report

A 27-year-old primigravida booked for hospital confinement at 11 weeks' gestation. She had fair hair and blue eyes, her height was 154 cm and her weight 57 kg. Her IQ (Weschler adult intelligence scale) was 92, with a verbal subscale of 99 and a performance subscale of 84. Blood phenylalanine by the Guthrie test was above 20 mg/100 ml. Serum phenylalanine concentration by chromatography was 22.3 mg/100

ml (1.35 mmol/l) and serum tyrosine 0.048 mmol/l. Her urine contained phenylpyruvic acid and o-hydroxyphenylacetic acid.

A low phenylalanine diet was started at 16 weeks and adhered to during the rest of her pregnancy. Blood phenylalanine levels were monitored by twice-weekly Guthrie tests and serum phenylalanine levels were determined by fluorimetry monthly, or when indicated by the Guthrie test. Between the 19th and 22nd weeks of gestation levels of <2 mg/100 ml (0.12 mmol/l) were detected by the Guthrie method. However, fluorimetric estimation of phenylalanine at 21 weeks was 1.9 mg/100 ml (0.11 mmol/l) and again at 22 weeks was 2.7 mg/100 ml (0.16 mmol/l). Thereafter, with three exceptions, Guthrie levels varied between 4 mg/100 ml (0.2 mmol/l) and 10 mg/100 ml (0.6 mmol/l) (Fig. 1).

Spontaneous onset of labour occurred at 40 weeks. Fetal distress was indicated by the drainage of

Conversion: SI to traditional units—1 mmol/l $\approx$ 16.5 mg/100 ml.

Fig. 1 Dietary control of phenylalanine levels and phenylalanine intake during the pregnancy.

meconium-stained liquor and a Kielland's rotation and delivery were performed when fetal tachycardia developed during the second stage.

The baby had a one-minute Apgar score of 5, and regular breathing was established by 3 minutes. He weighed 2.72 kg (< 10th centile on the Gairdner and Pearson chart²) (Fig. 2), occipitofrontal circumference was 33 cm (< 10th centile), and he was found to have a hypoplastic mandible (Fig. 3) with a posterior cleft palate. He began bottle feeding with Ostermilk Complete formula, but feeding difficulties due to respiratory difficulty were evident from birth, and each feed took between 60 and 90 minutes. Guthrie tests at 2 and 8 days gave phenylalanine levels of 2 mg/100 ml, while his mother, now taking an ordinary diet, had reverted to hyperphenylalaninaemia (1.6 mmol/l). At outpatient review, aged 17 days, his weight had fallen to 2.65 kg and he was admitted to hospital because of persistent failure to complete feeds. Nasogastric feeding did not produce a significant weight gain and was abandoned in favour of spoon feeding. On discharge aged 2 months, length, weight, and occipitofrontal circumference were each < 3rd centile with no evidence of catch-up growth at 18 months (Fig. 2). A Griffiths's developmental test when aged 47 weeks gave a General Quotient of 70 (locomotor subscale of 80, personal-social 73, hearing and speech 63, eye and hand co-ordination 70, performance 63). Chromosome analysis showed an apparently normal male karyotype.

Fig. 3 Appearance at birth.

Discussion

Allan and Brown³ recommended that women with blood phenylalanine levels > 10 mg/100 ml should be treated throughout pregnancy with a low phenylalanine diet, but no patient adequately treated in this way has been reported. Despite dietary control from as early as the 6th week of gestation, a woman gave birth to an infant with congenital heart disease.⁴ Other women with PKU, including our patient, treated with a low phenylalanine diet during a substantial period of their pregnancies have also given birth to infants with congenital abnormalities.⁵⁻⁶ However, normal infants have been born to mothers with PKU treated from the 16th week of pregnancy,³ and from the 20th week.⁷ The high incidence of congenital abnormalities, including congenital heart disease, in the offspring of such women suggests that PKU has a teratogenic effect in the early weeks of pregnancy and that prevention of these abnormalities will depend on treatment being started before conception. Nevertheless, when a low phenylalanine diet is not started until some time after conception, it might still be expected to halt progressive damage to the fetal nervous system in the same way as a low phenylalanine diet from early infancy successfully

Fig. 2 Growth record from birth to 18 months (Gairdner and Pearson chart).

prevents major neurological impairment in most PKU children.

Thus, on the basis of clinical experience to date, it is uncertain whether treating women who have PKU with a low phenylalanine diet during pregnancy lessens the harmful effects of phenylketonuria on the fetus. However, there are grounds for believing that such treatment may be beneficial, especially if started before conception.

The pilot study which led to the detection of this case was designed by Professor J Farquhar, Department of Child Life and Health, Edinburgh University, in collaboration with Dr J S Stevenson, Consultant Bacteriologist, Stobhill General Hospital. We thank Mr Robert Kennedy for doing the Guthrie tests, Dr M L McDonald for the Griffiths's test, Mr J De Courcy for the Weschler intelligence quotient, and Miss C M Fleming for advising on the diet.

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Commentary

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Successfully treated PKU girls are reaching child-bearing age. The number will grow even faster as those who were diagnosed by the Guthrie test reach maturity. Many have already stopped the diet. Most are eligible for marriage and some may believe that they will have normal children if they return to diet before or during pregnancy. Early experience of such

dietary manipulation must make us pause and consider. It ranges in Britain from some reassuring success to rather more disturbing failure without suggesting a clear reason for the difference. The above case falls into the unsuccessful group and even in the recent series from Manchester,¹ success, although impressive at an early stage in developmental testing, is not perfect. Buist *et al.* in Oregon² similarly have had mixed fortunes with a small group in whom the maternal serum phenylalanine was controlled from 8 to 30 weeks of gestation.

A worldwide review of phenylketonuric pregnancies was presented by Lenke and Levy³ at a meeting of the American Society of Human Genetics. In *untreated* pregnancies, in which the maternal serum phenylalanine level exceeded 1.2 mmol/l, microcephaly and mental retardation occurred in 90%. When the maternal level lay between 0.96 and 1.2 mmol/l they were found in 75% of children. Congenital heart disease was also present in many. It was concluded that treatment started after conception but before the 20th gestational week prevented microcephaly but not congenital heart disease. Recently Nielsen *et al.*⁴ reported the birth of an apparently normal baby to a relatively mild phenylketonuric woman whose blood phenylalanine level was held in an acceptable range (0.48 to 0.61 mmol/l) before conception and in the range 0.18 to 0.48 mmol/l from conception to delivery.

So far no absolutely consistent relationship has emerged between outcome and maternal serum phenylalanine level (or urinary phenylketones) at conception or later, the week of pregnancy at which control was achieved, age, or maternal intelligence. Future studies must ensure that there are no other fetal insults in each pregnancy. They will need to identify, if possible, the defect in maternal phenylalanine metabolism (including the rare bipterin deficiency). They will need to document phenylalanine levels during the prenatal weeks and throughout pregnancy and to record levels below 0.12 mmol/l as carefully as those above 0.6 mmol/l. Those with expertise in transplacental nutrition should examine the possibility that the low phenylalanine diet may impair fetal growth and development. Aborted fetuses should not be discarded without careful examination. It seems unlikely that poor PKU control in childhood and adolescence could by itself be mutagenic. Experience may now grow quickly and must be shared. The wiser PKU women may prefer to delay child bearing for a few more years until better informed advice can be given. The recent discovery⁵ that phenylalanine ammonia lyase (or PAL) may enable a PKU woman to eat a relatively normal diet while maintaining normal blood phenylalanine levels could greatly facilitate pre-pregnancy and pregnancy control.