Maternal Phenylketonuria: Experiences From the United Kingdom

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ABSTRACT. Charles Dent was one of the first physicians to recognize the teratogenic effects of maternal phenylalanine (Phe) on the fetus in 1956. This article describes the clinical experiences of women with phenylketonuria (PKU) within the unit that was established by Dent in the United Kingdom. Between 1977 and 2002, 79 infants were born to women with PKU. Of the 79, 18 (23%) were conceived while the women were on a normal diet with high blood Phe levels. The mean birth weight was 2.89 kg, and head circumference was 32.8 cm. At 1 year, the mean developmental quotient was 105.5 and at 4 years was 82.3. Four of these infants had congenital heart disease (2 of whom died as a result). In the remaining 61 infants, Phe-restricted diet started before conception. None of them had congenital heart disease. The mean birth weight was 3.23 kg, and head circumference was 34.0 cm. At 1 year, mean developmental quotient was 108.0 and at 4 years was 90.9. They continue to be followed up with additional neuropsychometric assessments at 8 and 14 years of age.

This cohort is a proportion of infants who were born to mothers with PKU in the United Kingdom. Between 1978 and 1997, 255 live births were reported. Of these, 56% were conceived on unrestricted diet with subsequently poor outcome. This relatively high rate of conception off PKU diet is likely to reflect the scarcity of medical services for adults with metabolic disorders.

We conclude that many features of the maternal PKU syndrome can be prevented but still occur because of the lack of appropriate resources to care for at-risk women. The precise targets for blood Phe and other nutrients during pregnancy are not entirely clear, neither are the reasons that some offspring are spared the harmful effects of Phe. The impact of the postnatal environment in which these infants find themselves requires additional assessment, too. Pediatrics 2003;112:1553–1556; maternal phenylketonuria, outcome, pregnancy, fetal.

ABBREVIATIONS. PKU, phenylketonuria; Phe, phenylalanine; UCL, University College London; DQ, Development Quotient.

However, it was the survey of Lenke and Levy2 that brought this disorder to the fore of the medical community. In their survey, only 34 (6.4%) of 524 pregnancies reported a Phe-restricted diet at any stage during the pregnancy, with only 3 starting before conception. Since then, data from the prospective International Collaborative Study3 and others have shown that a reduction in Phe before or perhaps soon after conception has a significant impact on fetal outcome with improvements in brain growth, as well as neurologic and psychometric dysfunction. Congenital heart disease is virtually abolished. One of the main challenges therefore is the timely reintroduction of an appropriate diet to protect the fetus.

This article describes experiences of caring for women with PKU through their pregnancies over the last 25 years in a single center within the United Kingdom. These are placed in the context of those from the United Kingdom as a whole, where health care has been free at the point of delivery since 1948, when the National Health Service was founded.

THE METABOLIC SERVICE AT UNIVERSITY COLLEGE LONDON HOSPITALS

The Charles Dent Metabolic Unit was established by Charles Dent after the second World War and so is one of the longest established and largest serving adolescents and adults with inborn errors of metabolism in the world. Previously trained as a chemist, Dent was one of the early physician-scientists who brought the amino acid analyzer into the clinical scenario for the first time. The unit was based at University College Hospital and was taken over by David Brenton, one of Dent’s research fellows, in the mid-1970s. Much of the data presented in this article were derived from his work with his dietitian, Margaret Lilburn. In the early 1990s, he moved the metabolic work to the Middlesex Hospital after the 2 hospitals merged. He retired in 1998, and the unit was subsequently moved to its present site at the National Hospital for Neurology and Neurosurgery which by then had joined the University College London (UCL) Hospitals Trust. Its position near Great Ormond Street Hospital for Children allows for smooth transition of patients from the pediatric services. Facilities available to the patients include a metabolic diet kitchen, invaluable for practical education, and a 5-day adult hospital ward for admission.

MANAGEMENT OF MATERNAL PKU

The aim of the UCL Hospitals service is to begin Phe-restricted diet before conception with a target...
Assessment of tone according to Amiel-Tison. In-trologic examination with particular emphasis on cardiovascular system. The infants are seen in the metabolic clinic with a particular emphasis on the car-tritional status. After delivery in the patient hospital, the infants are examined routinely by the trition team. They are followed in the metabolic clinic for 12 weeks. The mothers are taught how to draw their own capillary blood onto Guthrie cards to measure Phe concentrations twice a week before pregnancy and 3 times per week after conception. The women are encouraged to continue with contraceptive methods until the target Phe range has been achieved for 4 weeks. Referral to the Reproductive Medicine Unit is offered to the couple, if they wish, after 6 months without successful conception. If a woman with PKU presents already pregnant but off Phe-restricted diet, then she is admitted as an emergency to lower the blood Phe rapidly, counsel the woman and her partner about the risks to the fetus, and obtain a detailed fetal ultrasound scan. The choice to proceed or terminate the pregnancy is made by the couple with the support of the metabolic team.

If the woman has conceived on Phe-restricted diet, then routine obstetric care (dating scan at ~12 weeks and anomalies scan at ~20 weeks' gestation) is advised. They are followed in the metabolic clinic at 6 weekly intervals to check weight gain and nutritional status. After delivery in the patient’s local hospital, the infants are examined routinely by the neonatal staff with a particular emphasis on the cardiovascular system. The infants are seen in the metabolic center by 6 weeks of age for a thorough neurolologic examination with particular emphasis on assessment of tone according to Amiel-Tison.5 Infants who are conceived off diet are referred to a pediatric cardiologist for echocardiogram. Subsequently, the offspring are seen at 1 year, 4 years, and 8 years of age for formal neuropsychometric evaluation with Griffiths,6 McCarthy,7 and Wechsler Intelligence Scale for Children8 tests, respectively. Fourteen-year assessments are also being attempted.

THE MATERNAL PKU COHORT AT UCL HOSPITALS

Between 1977 and April 2002, 79 infants were born to women with PKU. Figure 1 shows how the workload has increased over time. Sixty-one (77%) were conceived on diet (preconception group) and 18 (23%) off diet (postconception group); only 1 of the latter was entirely untreated. Mean blood Phe concentrations were not surprisingly lower in the preconception group during the first trimester (mean ± standard deviation: 273 ± 88.5 vs 536 ± 316 μmol/L). There remained a tendency for them to be higher during the second (191 ± 51.4 vs 249 ± 89.2 μmol/L) and third (224 ± 62.6 vs 267 ± 70.3 μmol/L) trimesters. Of the 61 infants in the preconception group, 1 had mild hyperphenylalaninemia not requiring dietary restriction and 1 has an unrecognized neurodevelopmental dysmorphic syndrome. None had congenital heart disease. In the postconception group, 4 (21%) infants had congenital heart disease, 2 of whom died as a result.

The infants’ head circumferences at birth (32.9 ± 1.48 vs 34.1 ± 1.54 cm) and birth weight (2.89 ± 0.53 vs 3.20 ± 0.54 kg) were smaller when diet started after conception. In the postconception and preconception groups, respectively, 1-year Griffiths Development Quotient (DQ; 106 ± 7.6 vs 110 ± 14.9), 4-year McCarthy IQ (83 ± 23.9 vs 90 ± 17.7), and 8-year Wechsler Intelligence Scale for Children scores (82.5 ± 105) did not differ significantly (Fig 2). Preconception Phe levels correlated well with average Phe levels during the first, second, and third trimesters but did not correlate with 1-year DQ (r = −0.03) or 4-year IQ (r = −0.11). Those children from nonmanual families had significantly higher 1-year DQ (113 ± 12.7 vs 105 ± 13.9) and 4-year IQ (100 ± 7.9 vs 79 ± 19.6) than those from manual or armed forces families. Unfortunately, maternal and/or offspring genotypes were not examined.

Figure 3 shows the neurologic outcome assessed neonatally, at 1 year, and at 4 years. It demonstrates that increased tone was more likely to be present in the postconception group than in the preconception group, although not universally. In addition, it shows that there were high levels of neurologic abnormality in the preconception group neonatally, which disappeared with time.

UK PKU REGISTRY

From 1978 to 1997, the UK PKU Registry funded by the Medical Research Council and Department of
Health collected information on 255 live births of PKU women, some of which has already been reported. Of these, 59 children (25 girls) were born to 38 mothers who had PKU and were cared for at UCL Hospitals. Forty-four percent of the entire UK cohort were conceived with Phe-restricted diet already commenced; this was the case in 46 (78%) of 59 of the UCL Hospital pregnancies. Excluding the UCL Hospitals’ pregnancies, 66 of 196 infants (34%) were born to mothers who had commenced Phe-restricted diet before conception. Fifty-four children were born to mothers who had PKU and had never been on a restricted diet during pregnancy. The outcome data for this UK cohort are currently under analysis for subsequent reporting.

**DISCUSSION**

These data, derived from a single center dedicated to the care of adults with inborn errors of metabolism, do not allow clear conclusions about neurodevelopmental outcome to be drawn, especially as in the majority of pregnancies, Phe-restricted diet began before conception. However, it is clear that women with PKU need to start Phe-restricted diet before conception to improve brain growth and neurologic outcome. The data by Koch et al (see this supplement) suggest that commencing diet before 8 weeks’ gestation can protect against congenital heart disease. However, we believe that to start a necessarily restrictive diet at a time of heightened anxiety during the early stages of pregnancy cannot be recommended. High rates of diet started before conception can be achieved despite the experiences in the rest of the United Kingdom and the findings of the International Maternal PKU Collaborative Study, which had only 26% of pregnancies conceived after diet was started. Variations in the structure of health care provision may lie behind these differences, but facilities and personnel appropriate for adults with metabolic disease may be important, too. We believe that it is important to strive to start Phe restriction before conception because our data show that women who become pregnant while on an unrestricted diet find it hard to obtain good metabolic control for the rest of the pregnancy. This may be because of their heightened stress, making dietary education difficult or for the same reasons why their pregnancy was unplanned. Despite this, we have had a few offspring who have had good outcomes despite poor metabolic PKU control, and we have also had poor outcomes despite possibly too strict metabolic control. It is likely that there are important, as-yet-undetermined, factors that affect outcome other than maternal blood Phe concentration. However, once high preconception diet rates are achieved, the postnatal environment may become an important determinant of neuropsychometric outcome and is an area that requires more input than it currently receives. It is interesting that a number of the offspring are actually brighter than their mothers, which can make family dynamics difficult. The postnatal environment for these children is as important as the prenatal period.

In conclusion, the maternal PKU syndrome is preventable but still occurs because of the lack of appropriate resources to care for at-risk women with PKU. Improved programs for the transition of female individuals with PKU from pediatric to adult services, more staff and facilities dedicated to the care of adults with inherited metabolic disease, and more secure funding processes all are necessary. How often blood Phe should be measured and the precise targets for blood Phe, as well as other nutrients during pregnancy, are not entirely clear; neither are the reasons that some offspring are spared the harmful effects of Phe. A home Phe monitor may enable more subtle and accurate adjustment of diet on a day-to-day basis to improve outcome. Whether aggressive dietary management can protect the fetus despite conception off diet also needs to be evaluated—intuitively exposing the embryo to high Phe levels does not seem safe. The impact of the postnatal environment in which these infants find themselves requires additional assessment, too.

Furthermore, the pathogenic basis for maternal PKU with regard to Phe toxicity and tyrosine deficiency requires disentangling, and the influence of maternal and fetal genotype on outcome needs evaluating. One way to achieve this would be the use of better statistic descriptors of metabolic control than those currently used. Our understanding of the maternal PKU syndrome has certainly improved considerably since Dent’s original description. However, we still have a long way to go to optimize care for these mothers.

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**REFERENCES**

1. Dent CE. Discussion of Armstrong MD. The relation of biochemical abnormality to the development of mental defect in phenylketonuria.


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