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Maternal phenylketonuria

A study from the United Kingdom

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Abstract By November 1994, 39 pregnancies had been completed in phenylketonuric mothers. Dietary control was post-conception in 6 and 2 of these offspring died of congenital heart disease and 1 other needed surgery for coarctation. There were no heart defects in the 34 offspring of the 33 pregnancies following preconception diet controlled by Guthrie assays of maternal phenylalanine three (Phe) weekly. These Phe results were analysed by trimester for the means, the number of days over 300 μmol/l or below 60 μmol/l. Generally good control was achieved suggesting the UK guidelines drawn up by the MRC Working Party are broadly achievable but excessively high and low values occur intermittently in many pregnancies both of which may adversely affect the fetus. Though developmental assessment scores at 1 year were over 100 in all but five, early outcome results suggest that intellectual development may still be impaired at 4 years. Until much more information is available caution is still needed in discussing outcome with phenylketonuria patients who wish to conceive.

Key words Phenylketonuria · Pregnancy outcome · Maternal phenylketonuria · Griffiths Developmental Quotient · McCarthy General Cognitive Index

Abbreviations *Phe* phenylalanine · *PKU* phenylketonuria

Introduction

The adverse effects of high maternal phenylalanine (Phe) on the fetus reported by a number of authors was brought sharply into focus by Lenke and Levy [2]. It was confirmed from the considerable experience of phenylketonuria (PKU) in Ireland [3]. There is universal agreement that the mother's Phe needs to be controlled in pregnancy and if the risks of congenital heart disease are to be avoided (about 15% of offspring when the mother's Phe level > 1000 μmol/l) dietary control must start before conception. Dietary control started within the first 8 weeks of pregnancy may provide a more favourable outcome for the CNS than no control at any stage of the pregnancy but individual case reports still suggest that microcephaly may be attributable in some cases to poor first trimester control. The first 23 pregnancies in the series reported here from one centre in South East England has already been reported [1] in some detail. The number of completed pregnancies on preconception diet has now risen from 23 to 33 and this report is an interim analysis, which is not yet completed, of 32 of them.

Aims and experience of the clinic

The broad aims of the clinic for maternal PKU are to provide good control of the maternal Phe concentration while sustaining good nutrition in order to prevent abnormalities in the offspring and to report the outcome. Contraceptive and preconception advice is provided followed by tuition by a dedicated dietician when conception is planned. Patients are taught how to collect their own blood samples

Table 1 Maternal PKU 39 Pregnancies 40 Offspring

Preconception diet			Post-conception diet
33			6
Number of offspring			Number of offspring
34			6
Number of mothers			Number of mothers
22			5
11	–	Single offspring	– 4
1	–	Twins	– 0
9	–	Two offspring	– 1
1	–	Three offspring	– 0

for three Guthrie tests weekly. All results come back to the dietician who contacts the patients 2–3 times weekly. Conception has been encouraged as soon as plasma Phe values fall to 300 μmol/l. Up until the present time we have been able to retain a small diet kitchen where out-patients or in-patients can be taught the practicalities of dietary treatment. It also provides the means for preparing PKU meals when pregnant women have to be admitted urgently to deal with rapidly rising Phe values most often caused by pregnancy vomiting. The experience of the clinic for maternal PKU is shown in Table 1. Of the six offspring born when diet began postconception, two died of severe congenital heart disease and a third needed an operation for co-arctation of the aorta but survived. These six are not considered further but illustrate the very real risk of very serious congenital heart disease.

Diets and Phe measurements

Pre-conception diets have almost invariably been based on "XP Maxamum" as the sole dietary product for providing nutritional supplementation in a standard dose of 150 g/day. From week 18 an additional 2 g/day of tyrosine was added, although there was no clear justification for this practice which was maintained in the interests of uniformity. No attempt was made to keep plasma tyrosine values in any particular range. The dose of "XP Maxamum" was usually reduced in later pregnancy to 120 g/day if dietary protein intake rises sufficiently.

In all cases the mother's Phe concentration has been measured using the Guthrie technique three times weekly once pregnancy begins and approximately once monthly by full amino acid analysis. The Guthrie technique was deliberately chosen for speed of analysis and because multiple measurements at short time intervals were preferred even though accuracy was less good compared to other techniques. This proved a problem at lower blood Phe concentrations (see below) and now high performance liquid chromatography is used to measure Phe and tyrosine in blood spots. The target blood Phe concentrations were generally those recommended by the MRC Working Party [4] after the first few pregnancies, i.e. to keep the maternal Phe between 60 and 250 μmol/l. Initially rather higher blood Phe values were accepted with the aim of keeping the blood Phe below 500 μmol/l.

Management of the pregnancy

Once diet has been introduced pre-conception and the Phe has been reduced to below 300 μmol/l, which generally takes 7–14 days, contraception is stopped. Apart from dietary care the pregnancies are managed in the normal way by the obstetricians. In the early cases monitoring of the fetal head size was carried out by ultrasound in the belief that termination could be contemplated before 18 weeks if growth was poor. This was discontinued when it became apparent that head size falls away slowly from the mean during the pregnancy and was not useful in practice. Ultrasound examinations are used now as in all pregnancies when clinically indicated and routinely around 20 weeks for major fetal anomalies.

The control of blood Phe concentrations

The results by trimester are shown in Table 2. The figures for the mean Phe values are not accurate in that the Guthrie assay only measures Phe concentrations in steps of 60 μmol/l and moreover, any value recorded below 60 μmol/l has been given a value of 60 μmol/l for the purpose of working out the means. Nevertheless, the figures given in Table 2 give a fairly clear idea of the results which were achieved. However, the figures hide two variables which may be crucial to outcome. The means may look good but disguise the fact that a good mean value may be produced by a mixture of very high and very low results. For this reason the analysis in Table 3 is included. Arbitrarily Phe control is categorised as good, intermediate or poor depending upon not only the mean Phe concentration but the number of days the Phe was over 300 μmol/l. The latter is a reasonably accurate estimate from graphs when blood Phe values are measured three times weekly. If it is necessary (and it may not be) to maintain blood Phe values fairly consistently below 300 μmol/l in

Table 2 Mean Phe concentrations by trimester

Mean Phe	Number of pregnancies		
	First trimester	Second trimester	Third trimester
< 300 μmol/l	23 (139–281)	29 (87–241)	30 (97–238)
⩾ 300 μmol/l	9 (300–496)	3 (313–330)	2 (326–342)
Total pregnancies	32	32	32

Range of mean Phe concentrations in parenthesis

Table 3 Summary of maternal Phe control

	Control		
	Good	Intermediate	Poor
Mean maternal Phe	< 300	< 300	> 300
Days ≫ 300 μmol/l	≪ 15	16–30	> 30
First trimester	14 (44%)	9 (28%)	9 (28%)
Second trimester	27 (84%)	2 (6%)	3 (10%)
Third trimester	29 (91%)	1 (3%)	2 (6%)

Number of pregnancies in first and second and third trimester categorised as good, intermediate or poor control according to mean maternal Phe and the number of days over 300 μmol/l.

order to achieve a good pregnancy outcome we succeeded in under half the patients in the first trimester. Moreover, if Phe values recorded as less than 60 μmol/l in the mother are harmful to the fetus, then the second trimester is the time of greatest danger (Table 2).

The practical difficulties of patient management

High Phe values are most common in the first trimester. Dietary tolerance is at its lowest and nausea and vomiting at their most frequent. Admission of patients during this trimester was common and usually this in itself was sufficient for symptoms to diminish and Phe concentrations to fall. Sometimes the rise in Phe was rapid over a few days. The low Phe values of the second trimester were often due to the rapidly rising dietary tolerance from 16–18 weeks of pregnancy and raising the dietary intake of protein exchanges too slowly.

Although most patients are intensely dedicated to doing the diet well a small number do not ever seem to conform and continue to manage things in their own way. Pregnancy in the PKU woman is a stressful experience and it is possible that it is more than some women can cope with.

Outcome measures

These include birth weight, head circumference at birth and 1 year, neurological assessment, Griffiths Development Quotient at 1 year, General Cognitive Index at 4 years (McCarthy) and the Revised Wechsler Intelligence Score for Children at 8 years. Comments on the specialised neurological assessments are not included here. The data on head size and body weight have been published for the first cases [1]. The data have not been reanalysed since there are not many additional cases included here. The original findings were that head circumference at birth and 1 year correlated negatively with mean Phe values in the first trimester. That was surprising

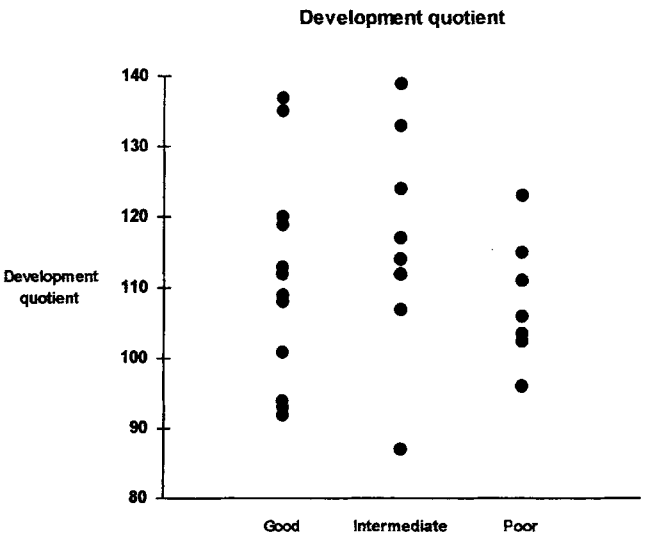

Fig. 1 Developmental quotients at age 1 related to first trimester control of maternal blood Phe levels

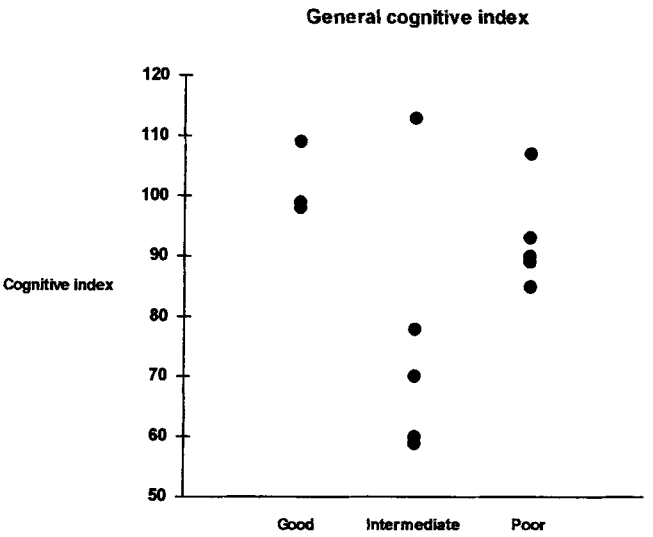

Fig. 2 General cognitive index (McCarthy) at age 4 related to first trimester control of maternal blood Phe levels

since the range of mean Phe values was small. It remains to be seen whether this correlation is still significant when there are larger patient numbers. No significant correlation was found with birth weight.

The 1 year Griffiths Developmental Quotient is largely a measure of motor development and the results are shown in Fig. 1. They are generally very normal but values of 90 or less may be questionable. There was no clear relationship to the degree of control. The McCarthy General Cognitive Index at 4 years has given some disappointing results (Fig. 2) but they may be biased for two

reasons. The oldest children are from earlier pregnancies when control of Phe was less good and some of the early mothers had a degree of intellectual impairment which probably affected choice of spouse and upbringing of the children. Nevertheless, the results are less good in some cases than hoped for.

In a series of 32 pregnancies the success and difficulties in controlling blood Phe are described. The MRC recommendations have been more or less achieved for most of the patients but attempts at very strict control may lead to more frequent low Phe values which have been a problem in the second trimester. Whether that matters to the well-being of the fetus is not clear but it would be prudent to avoid them. With the current pregnancies not included in this series, using high performance liquid chromatography for the measurement of Phe and tyrosine in blood spots the aim is to keep the mother's Phe between 100 and 300 μmol/l. The emotional stress on the mother of striving to get good Phe results is considerable which needs more appreciation.

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