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Psychosocial issues and outcomes in maternal PKU ☆

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ABSTRACT

Elevated phenylalanine (Phe) levels in pregnant women with PKU are teratogenic. Fetal damage due to elevated maternal Phe levels during pregnancy is known as maternal phenylketonuria (MPKU). The risk of birth defects in MPKU, including global developmental delays, microcephaly, congenital heart disease, and low birth weight, can be dramatically reduced by controlling Phe levels during pregnancy (metabolic control). Phe levels should be maintained in the range of 120–360 μmol/L, ideally starting before pregnancy begins (i.e., when planning a pregnancy). If control is not achieved before pregnancy (e.g., if the pregnancy was unplanned), good outcomes are still possible if metabolic control is established by 8 weeks of pregnancy. Unfortunately, metabolic control before and during pregnancy can be poor. As well, many mothers stop treatment after pregnancy, which can decrease the mother's ability to focus on her child and increase her risk of behavioral and psychological problems. This can have a negative effect on the home environment. Many factors affect adherence to the strict diet used to control Phe levels, including poor access to medical care, lack of reimbursement for medical foods (in some regions, such as parts of the United States), practical difficulties with implementing the diet, financial constraints, demographics, and psychosocial issues. A comprehensive treatment approach that begins prior to pregnancy and continues after the infant is born may help to improve the management of MPKU. This approach should include education of girls about MPKU at an early age, interventions to prevent unplanned pregnancies, psychosocial support, improved treatment access and reimbursement for medical foods, and treatment guidelines. Treatments such as sapropterin may also have a role in improving metabolic control during pregnancy.

Introduction

Phenylketonuria (PKU[1]; OMIM 261600 and 261630) is an inherited metabolic disorder associated with a deficiency in phenylalanine hydroxylase (PAH; EC 1.14.16.1), the enzyme that metabolizes phenylalanine (Phe) to tyrosine. PKU causes elevated Phe levels which, if left uncontrolled, can lead to intellectual disability, seizures, microcephaly, autistic-like behaviors, musty body odor, and eczema-like skin problems. Phe levels can be controlled with a Phe-restricted (low natural protein) diet supplemented with a special formula containing all the amino acids in natural protein, except for Phe.

Phe is actively transported across the placenta, reaching fetal concentrations that are 1.25–2.5 times greater than maternal concentrations [1]. Elevated Phe levels in a pregnant woman with PKU are teratogenic [2]. Fetal damage due to elevated maternal Phe levels during pregnancy is known as maternal phenylketonuria (MPKU) [3]. The problem of MPKU was originally described by Charles Dent [4] in the 1957 report of the 23rd Ross Conference. An international survey by Lenke and Levy [5] in 1980 reported that children of women with PKU had a high rate of birth defects, including global developmental delay (92%), microcephaly (73%), congenital heart disease (CHD, 12%), and low birth weight (40%). Other features of MPKU include postnatal growth retardation, mild craniofacial dysmorphism, and neurological abnormalities [2]. Prenatal Phe exposure, as with MPKU, is also associated with

☆ *References to electronic databases:* Phenylketonuria, OMIM 261600 and 261630. Phenylalanine hydroxylase, EC 1.14.16.1.
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[1] *Abbreviations used:* PKU, phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; MPKU, maternal PKU; CHD, congenital heart disease; ADHD, attention deficit hyperactivity disorder; ADD, attention deficit disorder inattentive-type; HOME, Home Observation for Measurement of the Environment; MPKUCS, Maternal PKU Collaborative Study; WAMPKUP, Western Australian Maternal PKU Program; IQ, intelligence quotient; CBCL, Child Behavior Checklist; DQ, developmental quotient; WISC-R, Wechsler Intelligence Scale for Children – Revised; MHP, mild hyperphenylalaninemia; FAS, fetal alcohol syndrome; BH_4, tetrahydrobiopterin; PAL, Phe ammonia lyase.

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hyperactive or impulsive-type symptoms of attention deficit hyperactivity disorder (ADHD) while postnatal exposure, as with PKU, is more likely to cause attention deficit disorder inattentive-type (ADD). This suggests that the timing of Phe exposure affects outcomes, which may be explained by the fact that different brain areas develop at different times [6,7].

The study by Lenke and Levy [5] stimulated the publication of studies in the United Kingdom by the Charles Dent Metabolic unit review of the PKU Registry [8] and the report of the United Kingdom Registry [9] as well as the efforts by the National Institutes of Health in the United States (US) [10] and by the Heidelberg group [11] headed by Horst Bickel in Germany. Recommendations of these three studies varied, but all highlighted improved outcome of maternal PKU pregnancies as an important public health issue.

The Maternal PKU Collaborative Study (MPKUCS) found that achieving early control of blood Phe levels dramatically reduced the risk of cognitive problems, microcephaly, and low birth weight. CHDs occurred in 2% of pregnancies among women who achieved metabolic control by 10 weeks of gestation compared to an overall study rate of 7%. One percent of pregnancies in non-PKU women result in CHD [12].

Ideally, to achieve optimal pregnancy outcome, women with PKU need to plan their pregnancies, attain metabolic control prior to pregnancy, and maintain their blood Phe levels within the recommended range of 120–360 μmol/L (2–6 mg/dL) throughout pregnancy [12].

While there is some difference of opinion as to what the exact range of blood Phe should be in the early weeks of pregnancy, there is no disagreement among professionals that maternal blood Phe levels greater than 360 μmol/L increase the risk of CHD and/or microcephaly in the offspring.

Delays in achieving metabolic control: relationship to worsening outcomes

The Western Australian Maternal PKU Program (WAMPKUP) studied 30 pregnancies and 16 live births. There were seven spontaneous abortions and seven elective terminations. In all 16 live births, mothers did not achieve metabolic control (Phe < 360 μmol/L) prior to pregnancy or even by 10 weeks of gestation. Only three women achieved control by 13 weeks, and four women by 26 weeks. The authors do not state when the others achieved metabolic control, only that they did not achieve control by 26 weeks of pregnancy. Therefore, they either did not achieve control at all or achieved control later than 26 weeks of pregnancy. There was a linear relationship between time to metabolic control and lower intelligence quotient (IQ) in the offspring, with a significant correlation between lower IQ scores and delayed metabolic control. Pregnancies with delayed control were also significantly more likely to result in offspring with behavioral problems (clinically significant behavior issues as rated by the Achenbach Child Behavior Checklist [CBCL]) [13].

Maillot et al. [14] conducted a retrospective review of outcomes in 105 children born to mothers with PKU in the United Kingdom (UK). They found that IQ and developmental quotient (DQ) at age 1 and age 8 were higher in children whose mothers started a Phe-restricted diet before pregnancy compared with those whose mothers started the diet after pregnancy began, at a mean gestational age of 10 weeks. Starting the diet before the beginning of pregnancy also reduced the risk of CHD (0% for the prior-to-pregnancy diet group vs. 12.5% for the group initiating diet 10 weeks after pregnancy began). Interestingly, they also found that variations in Phe level control (measured by the standard deviation of Phe values) had a strong negative correlation with IQ at 4, 8, and 14 years of age. This suggests that Phe levels should not only be controlled early, but also be controlled consistently throughout the pregnancy, avoiding fluctuations [14]. In the 572 pregnancies studied by the MPKUCS (an international study with a large number of American centers) [15], outcomes in terms of IQ, birth length, birth weight, and head circumference were similar between infants born to mothers who attained control prior to pregnancy and those who achieved metabolic control by 10 weeks of pregnancy. The mean offspring IQ was 105 for women who attained control before pregnancy began. For women who attained Phe levels of 120–360 μmol/L in the first 10 weeks of pregnancy, the mean offspring IQ was 104. For those who reached Phe levels of 360–600 μmol/L by 10 weeks of pregnancy, the mean offspring IQ was 100. In women who attained control (Phe 120–600 μmol/L) by 10–20 weeks of pregnancy, the mean offspring IQ was 93. This score was better than expected. These data may be useful to consider during genetic counseling for women who have had an unplanned pregnancy. However, there was a linear relationship between each of these parameters (IQ, birth length, birth weight, and head circumference) in the offspring and the number of weeks to metabolic control in the mother [12]. In a subset of 251 MPKUCS patients with diet analyses available, there were 85 infants born with microcephaly. Seventy-eight (92%) of these infants were born to women with blood Phe greater than 600 μmol/L at 8 weeks of gestation, while 7 (8%) of them were born to women with blood Phe levels less than 600 μmol/L at 8 weeks of pregnancy [16].

Tests of cognitive outcomes and behavior in children from the MPKUCS at 7 years of age showed that a variety of cognitive outcomes were negatively affected by delays in achieving metabolic control. These included memory, language, behavior, visual motor skills, and achievement. Children born to mothers with delayed control (after the first 10 weeks of pregnancy) had behavioral problems such as aggression, hyperactivity, and poor impulse control. Significantly more women in the group who attained control after 10 weeks of pregnancy compared to women who attained metabolic control earlier scored in the lowest quartile of the Home Observation for Measurement of the Environment (HOME) scale, measuring level of support and stimulation in the child's home [17,18]. The child's developmental outcome as measured by the WISC-R (Wechsler Intelligence Scale for Children – Revised) was correlated with weeks to maternal metabolic control ($r = -0.61$, $P < 0.0001$) [17].

Adequacy of a Phe-restricted diet for optimal fetal development – effects of Phe "spikes in early pregnancy

Temporarily high Phe levels ("spikes") and nutrition both play a role in MPKU [12]. In the MPKUCS, all infants with CHD were born to mothers with Phe levels >600 μmol/L in the first 8 weeks of pregnancy [19]. In these infants, CHD risk was significantly higher when the mother had an inadequate protein intake (less than 50% of the recommended daily allowance), compared to cases where the mother had an adequate protein intake [19]. Low protein intake was mainly due to a low intake of medical food [19,20]. Inadequate intakes of vitamin B_{12} and fat were also associated with a significantly increased CHD risk [19]. Compared to women who achieved metabolic control later than 10 weeks of pregnancy, women who achieved metabolic control (Phe < 360 μmol/L) in the first 10 weeks of pregnancy tended to have higher intakes of protein, fat, and energy. Increasing protein, fat, and energy intake may help to control Phe levels in cases where control is difficult to attain [21].

A substudy of the MPKUCS was conducted to evaluate the effect of the quality of dietary treatment and to investigate whether Phe spikes could pose a risk to the fetus during the first 20 weeks of