Annotated Articles Guiding Preconception Care of Women with PKU

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Widaman KF, Azen C. 2003 Relation of Prenatal Phenylalanine Exposure to Infant and Childhood Cognitive Outcomes: Results From the International Maternal PKU Collaborative Study; <u>Pediatrics</u>*; 112: 1537-1543*

The primary objective of this study was to assess the relation between prenatal exposure to phenylalanine (phe) and measures of intellectual development in the children. 572 pregnancies were included in the International Maternal PKU Collaborative Study. 412 pregnancies resulted in 416 live births. The final offspring cohort included 413 offspring after the exclusion of two who had a diagnosis of PKU and one whose parents declined participation.

Demographic information such as maternal age, weight gain in pregnancy, and variables assessing socioeconomic status, maternal education and intelligence were analyzed. Offspring were analyzed as neonates and then at 1, 2, 4, and 7 years of age.

Pregnancy related variables included weight gain during pregnancy, percentage of recommended weight gain achieved at term, variability of Phe levels during pregnancy using the standard deviation of all Phe levels obtained over the course of gestation, the average Phe levels recorded during pregnancy, the week of gestation at which all remaining Phe levels were <600 micromolar, the week of gestation at which all subsequent Phe levels were <360 micromolar, the average daily protein intake during pregnancy, and the duration of pregnancy. Birth variables included offspring length, weight, and head circumference.

Measures included Bayley Scales of Infant Development including the Mental Development Index and the Psychomotor Development Index at ages 1 and 2 years. At age 4, the McCarthy Scales of Children's Abilities which included the General Cognitive Index and Composite Spoken Language Quotient was assessed. At age 7, the Wechsler Intelligence Scale for Children-Revised was used to assess intelligence with a Verbal and Performance IQ.

Complex mathematical modeling was utilized to assess the relationship between prenatal Phe exposure and infant and childhood cognitive outcomes. For prenatal Phe exposure, the point at which levels below

are assumed to have no teratogenic effect and levels above result in damage ranged between 234 and 486 micromolar with a best estimate of the critical threshold of 330 to 360 micromolar.

Of the maternal background variables, Phenylalanine Hydroxylase(PAH) mutation severity had the strongest influence. Of the pregnancy related variables, only the Phe level had notable effects on birth and cognitive outcome variables. Phe level had a large effect on birth head circumference and a moderate to large effect on the cognitive outcome variables.

The authors conclude that the influence of maternal PAH mutations on offspring cognitive outcome could be prevented in Phe levels are controlled at low levels during pregnancy with an average below the threshold of 330 to 360 micromol/L.

Reviewed and Posted April 27, 2009