

## ***Before, Between & Beyond Pregnancy***

### **The National Preconception Curriculum and Resources Guide for Clinicians**

## **Annotated Articles Guiding Preconception Care of Women with PKU**

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*Levy HL, Guldborg P, Guttler F, et al. 2001 Congenital Heart Disease in Maternal Phenylketonuria: Report from the Maternal PKU Collaborative Study; Pediatric Research; 49: 636-642.*

Using the international, multi-center, prospective cohort enrolled in the Maternal PKU Collaborative Study, all hyperphenylalaninemic women known to the participating centers who were either planning pregnancy or who were pregnant during the study period were compared to normal women at the same centers. Outcomes for the 572 pregnancies of women with PKU or non-PKU Mild Hyperphenylalaninemia (MHP) enrolled were: 79 voluntary terminations, 75 spontaneous abortions, 3 ectopic pregnancies, and 3 stillbirths, resulted leaving 412 live births (416 offspring, due to four sets of twins). Ninety-nine unaffected women were enrolled resulting in 100 live-born offspring.

Maternal phenylalanine hydroxylase (PAH) genotypes were determined from blood samples, and offspring mutations were identified by PCR amplification of DNA. Treatment with a phenylalanine (phe) restricted diet was initiated before conception or as early as possible after conception in women whose phe levels were >600 and “metabolic control” was defined as a blood phe  $\leq$  600 micromolar. Women had their basal phe level (APL) assigned based on the highest of 2 or 3 levels while on an unrestricted diet when not pregnant. They also had blood phe levels assessed while on dietary treatment during pregnancy. Offspring were examined at birth, 6 months, and annually thereafter.

Congenital heart disease (CHD) was identified and confirmed by postnatal echocardiography or autopsy in 34 offspring of women with PKU and one offspring of a mother with non-PKU MHP. The mothers of these offspring had APL  $\geq$  900 micromolar and did not achieve metabolic control before 8 weeks gestation. The 34 affected offspring from PKU pregnancies represent 14% of the 235 participating women with PKU. Only one of the 100 control offspring (1%) had

CHD, which is similar to the population frequency of CHD (0.8%). No cases of CHD occurred among the 131 offspring of women with APL <900 micromolar or in which metabolic control was achieved prior to 8 weeks gestation. The mother with MHP had an APL of 516 micromolar and received no treatment during pregnancy. This represented 2% of the 50 offspring from mothers with untreated MHP.

The most frequent defect was coarctation of the aorta (20%) followed by tetralogy of Fallot (17%). Other defects included patent ductus arteriosus (14%), hypoplastic left heart syndrome (11%), and ventricular septal defect (11%). Both coarctation and hypoplastic left heart were overrepresented compared to their prevalence in children with CHD in the general population. The single control offspring with CHD has a ventricular septal defect. Although the majority of these defects are amenable to prenatal diagnosis by ultrasound, only 10 of the 35 offspring with CHD were identified

| Mothers<br>APL<br>(micromolar) | 900 – 1200 | 1201 – 1500 | 1501 – 1800 | 1801 - 3000 |
|--------------------------------|------------|-------------|-------------|-------------|
| Total number                   | 30         | 46          | 49          | 51          |
| % w/ CHD<br>offspring (n)      | 13% (4)    | 7% (3)      | 18% (9)     | 33% (17)    |

Table 1. Frequencies of at risk mothers with treated maternal PKU (APL  $\geq$ 900 micromolar and not in metabolic control by the 8<sup>th</sup> week gestation) who bore offspring with CHD, categorized by APL

Regarding maternal control, those with APL >1800 micromolar who did not achieve control by the 8<sup>th</sup> week were significantly overrepresented among those who bore offspring with CHD. More than 50% of the mothers bearing offspring with CHD had an APL >1800, and 33% of those with an APL >1800 had offspring with CHD.

From these data, having an APL >1800 and not being in metabolic control by week 8 of gestation confers a 1:3 risk for having a child with CHD. Even with an APL of 1501 – 1800, without achieving metabolic control, the risk is still almost 1:5. All but one instance of CHD occurred when the APL was  $\geq 900$  micromolar and metabolic control was not achieved by week 8 of gestation. The 14% rate of CHD in offspring from this group is comparable to the 12-15% frequency seen in untreated PKU with levels  $\geq 1000$  micromolar reported in a previous international survey, and the 2% occurrence of CHD in the MHP group is comparable to the 2.6% rate seen in untreated pregnancies with Phe <900 micromolar in the same international survey reported by Lenke in 1980.

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