

PHENYLKETONURIA IN MICHIGAN

BACKGROUND

Phenylketonuria (PKU) is an inherited disorder of phenylalanine metabolism. Phenylalanine is an amino acid, one of the building blocks of proteins, and is present in many foods. If a newborn with PKU does not receive prompt treatment, phenylalanine levels in blood increase, causing brain damage and mental retardation. To avoid these negative health outcomes, people with PKU need to avoid certain foods to maintain a low-phenylalanine diet.

Newborn screening (NBS) for PKU began in the 1960s when Dr. Robert Guthrie developed the bacterial inhibition assay to diagnose PKU by determining the level of phenylalanine in a drop of a baby's blood placed on a strip of filter paper. In 1965, following Dr. Guthrie's lead, Dr. Stanley Read at the Michigan Department of Public Health and Dr. Richard Allen at the University of Michigan introduced NBS for PKU to Michigan and almost immediately turned what had been a devastating, genetic disorder into a condition manageable by a low-protein diet.

Women with PKU must closely follow the low-phenylalanine diet to maintain appropriate levels of blood phenylalanine both before and during pregnancy. If a woman has high blood phenylalanine levels during pregnancy, the risk of spontaneous abortion, mental retardation, microcephaly, and/or congenital heart disease in the child is increased.

Following the cohort of patients with PKU diagnosed through NBS in Michigan is challenging. However, we can utilize statewide databases to evaluate the prevalence of PKU among newborns and the birth outcomes of women with PKU.

STATEWIDE DATABASES

The NBS Follow-up Program maintains databases with initial screening results and additional information on patients referred to the four NBS-funded medical management centers, such as the Children's Hospital of Michigan Metabolic Clinic (CHMMC). The CHMMC is responsible for the diagnosis and medical management of all newborns with any of the 42 metabolic disorders detected by NBS, including PKU. The clinic also provides biochemical and molecular genetic diagnostic laboratory services. The CHMMC sends information about confirmatory results for patients with PKU to the NBS Follow-up Program. We used this database to provide information on the 2009 cohort of newborns identified with PKU.

The CHMMC also sends data on pregnancy outcomes for women with PKU who live in Michigan at the time of pregnancy or who request medical management from CHMMC and live out of state. Recording of phenylalanine blood levels is incomplete, so we are not able to assess diet-compliance before and during pregnancy. We used this database to learn more about the pregnancy experiences of women with PKU who were born from 1965-1992.

The Michigan Inpatient Database (MIDB) is a database of hospital information collected by the Michigan Health & Hospital Association (MHA). Each hospital in the state reports data to the MHA, and the MHA aggregates the reported data. The Michigan Department of Community Health purchases the MIDB from the MHA. The Division for Vital Records and Health Statistics at the Michigan Department of Community Health routinely links the MIDB with live births records to create a linked file of hospital discharge records for mothers with deliveries. We used the 1999-2008 linked maternal discharge dataset to investigate birth outcomes among women with PKU.

WHAT DO WE KNOW ABOUT THOSE WITH PHENYLKETONURIA?

In 2009, 115,292 resident newborns were screened in Michigan. Of those, 15 newborns were diagnosed with PKU; the detection rate was 1:7,686 newborns screened (Table 1). Of patients with PKU in the 2009 birth cohort, 40% had classic PKU, 20% had mild PKU, and the remaining 40% had benign hyperphenylalaninemia.

Table 1. Phenylketonuria Screening, Michigan, 2009

PKU Subtype	Confirmed (N)	Detection Rate
Classic	6	1:19,215
Mild	3	1:38,431
Hyperphenylalaninemia	6	1:19,215
Total	15	1:7,686



For PKU cases diagnosed from 1965-1992 through NBS, information was found on 55 women who had 94 pregnancies (Table 2). Approximately one-third of the pregnancies occurred in women

with classic PKU, one-third in women with mild PKU, and one-third in women with hyperphenylalaninemia.

Nearly one-third (N=30, 31.9%) of pregnancies ended in abortion (13 therapeutic and 17 spontaneous), and 64 (68.1%) ended in live birth. Of the 64 live births, no information was found for 20 (31.3%) (Table 3). As maternal PKU subtype increased in severity, the percentage of normal live births decreased; 56% of newborns to mothers with hyperphenylalaninemia were normal compared to 24% of newborns to mothers with classic PKU. Only 2 of the 64 live offspring were diagnosed with PKU (one classic PKU and one hyperphenylalaninemia); both infants were born to a mother with hyperphenylalaninemia.

Using the 1999-2008 linked file of maternal discharge records and live births, 15 women had a diagnosis of PKU. Due to the small number of deliveries, we were not able to examine birth outcomes.

Table 2. Pregnancies for women born 1965-1992 with PKU, by subtype, Michigan

	Classic PKU		Mild PKU		Hyperphenylalaninemia		Total
	N	%	N	%	N	%	
Women	25	45.5	13	23.6	17	30.9	55
Pregnancies	35	37.2	28	29.8	31	33.0	94

Table 3. Live births outcomes for women born 1965-1992 with PKU, by subtype, Michigan

	Classic PKU		Mild PKU		Hyperphenylalaninemia		Total	
	N	%	N	%	N	%	N	%
Normal	5	23.8	9	50.0	14	56.0	28	43.8
Microcephaly	8	38.1	4	22.2	2	8.0	14	21.9
No info.	8	38.1	5	27.8	7	28.0	20	31.3
PKU-affected	0	0	0	0	2	8.0	2	3.1
Total	21	100	18	100	25	100	64	100

CONCLUSIONS AND FUTURE DIRECTIONS

Due to the potentially increased prevalence of microcephaly among offspring of women with mild and classic PKU compared to women with hyperphenylalaninemia, we are challenged to include pre-conception and inter-conception health assessment with NBS long-term follow-up strategies and standards of care. Furthermore, continuing education of both patients and providers about the life-time challenges and needs of patients with disorders diagnosed through NBS is becoming one of the long-term follow-up strategies.

In order to assess the effectiveness of continued education and health assessments, the Michigan NBS Follow-up Program plans to continue utilizing NBS data, including data from the CHMMC, and other databases to assess the prevalence of NBS disorders throughout the life span and evaluate birth outcomes to women with those disorders, including PKU.

ABOUT NEWBORN SCREENING FOLLOW-UP IN MICHIGAN

The Michigan Newborn Screening Program screens newborns in the state for 49 disorders, including PKU. The screening is performed within the Division of Chemistry and Toxicology in the Bureau of Laboratories. The NBS Follow-up Program, located in the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology within the Bureau of Epidemiology, oversees short and long-term follow-up of infants identified through the program. Follow-up begins with referring these infants to one of four NBS-funded medical management centers for diagnosis and treatment. The Follow-up Program maintains short and long-term follow-up databases for monitoring and evaluation. Education, training, and quality assurance measures are also responsibilities of the Follow-up Program.

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