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Short Communication

Characteristics and outcomes of pregnancies among women with phenylketonuria from the NBS Connect registry

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ABSTRACT

Women with phenylketonuria (PKU) should maintain blood phenylalanine (phe) concentration within the recommended range before and during pregnancy to prevent maternal PKU syndrome (MPKUS) in their offspring. Women who gave birth to children with MPKUS symptoms were more likely to report elevated phe concentration before pregnancy, and barriers to accessing components of their dietary management during pregnancy, including blood phe testing, medical food, modified low-protein foods, and healthcare visits with PKU specialists.

1. Introduction

Phenylketonuria (PKU, OMIM 261600) is a rare inherited (autosomal recessive) metabolic disorder in which the affected person has a reduced or eliminated function of phenylalanine hydroxylase (PAH), an enzyme that converts the essential amino acid phenylalanine (phe) to tyrosine (tyr) [1]. This results in an increased concentration of phe and a decreased concentration of tyr in the body. Untreated, PKU results in progressive, irreversible cognitive impairment and other sequelae [2].

Treatment of PKU includes restriction of dietary protein from natural sources that are high in phe (eg, meat, fish, eggs, dairy, seeds, and nuts). To ensure enough protein for growth and development, medical foods rich in phe-free amino acids are prescribed. In addition, modified low-protein foods are commercially available to supplement the diet. Blood spots on filter papers are routinely used to measure the concentration of phe in the patient's blood to assess how well they are managing their diet. In the United States (US), the goal of nutritional management of PKU is to maintain lifelong blood phe concentrations between 120 and 360 μmol/L [1,3].

Because of the challenging nature of the dietary management of PKU, many patients abandon their prescribed diet in adolescence or adulthood. Women with PKU who do not maintain phe concentrations within the recommended range before and during pregnancy have an increased risk of a constellation of birth defects in their offspring, including heart defects and cognitive impairment, known as maternal PKU syndrome (MPKUS) [4]. Attitudes toward treatment, knowledge about the impact of elevated phe concentration during pregnancy, social support, and access to medical foods, modified low-protein foods, and blood phe concentration testing are all factors that have been shown to impact the risk of MPKUS [5–8].

In this paper, we report on maternal demographic and pregnancy-related characteristics of 17 pregnancies among women with PKU in the US, along with MPKUS-related outcomes in offspring.

2. Methods

Newborn Screening (NBS) Connect was a web-based self-report patient registry in existence from 2012 to 2019. Development of the registry and survey methodology was previously described [9,10]. Data collection and analysis via the NBS Connect registry was approved by the Emory University Institutional Review Board.

In 2018, NBS Connect integrated a 33-item survey to collect data on pregnancies, including diet compliance, challenges, experiences, and birth outcomes. The survey questions that were used in this report are provided in the Supplemental File 1. For the purposes of this descriptive analysis, children of these pregnancies were categorized as having symptoms of MPKUS if the mother reported one of more of the following: low birthweight, small for gestational age, heart defect, other birth defects, or development delay.

3. Results

Twelve women with PKU completed the pregnancy-related survey as part of the NBS Connect Registry. The average age at the time of the

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survey was 37.0 years (se = 10.0, range = 23–52). All 12 participants were white, and two were Latina/Hispanic. All 12 participants resided in the US. In total, 20 pregnancies were reported: seven women reported having had one pregnancy, five women reported two pregnancies, and one reported three pregnancies. Three of the pregnancies resulted in terminations or miscarriage. No additional data were available for three of the pregnancies. Out of the 14 reported pregnancies that resulted in live birth outcomes, six resulted in infants with MPKUS symptoms (five singletons and one set of twins), and eight resulted in infants with no MPKUS symptoms. The reported MPKUS symptoms included low birthweight ($n = 3$), small for gestational age ($n = 4$), cleft lip/palate ($n = 1$), heart defect ($n = 2$), developmental problems with motor skills (n = 1), developmental problems with cognitive skills (n = 2), and other (n = 1).

Characteristics of the mothers of liveborn infants and their pregnancies are shown in Table 1. The mothers of infants without MPKUS symptoms were slightly older at the time of birth (mean = 39.3 years, se = 10.1) than were mothers of infants with MPKUS symptoms (mean = 35.6 years, se = 6.7). Half (50.0%) of the mothers of infants with no symptoms of MPKUS reported barriers to health insurance coverage or reimbursement for blood phe concentration testing, PKU specialist visits, medical food, or modified low-protein food. Mothers of infants with MPKUS symptoms were more likely to report barriers to one or more of these essential components of PKU management (66.7%). Among the pregnancies that resulted in infants without MPKUS symptoms, 62.5% of the mothers were connected to PKU medical specialists before the pregnancy began, which is slightly more than among pregnancies which resulted in infants with MPKUS symptoms (50%). For pregnancies which resulted in an infant with MPKUS symptoms, mothers were more likely to report elevated blood phe concentration at the time they learned they were pregnant (66.6%) compared to pregnancies which resulted in infants with no MPKUS symptoms (37.5%). One woman reported never reaching recommended blood phe concentration before or during a pregnancy which resulted in a live birth infant with no MPKUS symptoms. Two women were taking sapropterin before pregnancy. One discontinued use during pregnancy and reported MPKUS symptoms in her offspring, while the other continued use during pregnancy and reported no MPKUS symptoms in her offspring.

Three women reported more than one pregnancy with a live birth. All three of these women reported MPKUS symptoms in their first pregnancies and no symptoms in their second pregnancies. One woman had a total of three pregnancies that resulted in three live births, with her first and third child displaying evidence of MPKUS symptoms.

4. Discussion

Miscarriages or terminations were reported in three of the seventeen pregnancies for which data were available, consistent with the 28% fetal loss rate reported in the Maternal Phenylketonuria Collaborative Study [11]. Six out of fourteen babies born to women with PKU demonstrated symptoms of MPKUS. While the numbers are too small to reach statistical significance, there are important trends in the data reported by women with PKU who have had children. Pregnancies which resulted in infants with MPKUS symptoms were more likely to have been associated with barriers to access to care and other components of the medically-managed low-phe diet. Most women did not have phe concentrations within the recommended range prior to pregnancy.

One woman reported never reaching recommended blood phe concentration before or during her pregnancy which resulted in a live birth with no MPKUS symptoms. It is possible to have blood phe concentrations above the recommended range, and still have a child without MPKUS [4]. The risk of MPKUS symptoms depends on the concentration of phe during the pregnancy as well as the timing of elevated phe concentration [4], and actual phe concentration during pregnancy was not captured in our study. While barriers were reported in the survey, it is not clear whether or not the barriers had a direct impact on ability to

Table 1
Maternal characteristics and medical outcomes in 15 children from 14 pregnancies.

	By Participant	
Demographics	PKUS Symptoms in one or more offspring ($n = 5$)	No PKUS Symptoms in offspring (n = 5)
Education, n (%)		
High School	2 (40.0)	3 (60.0)
4-year college	1 (20.0)	1 (20.0)
Graduate	1 (20.0)	1 (20.0)
Missing	1 (20.0)	0 (0.0)
Health Insurance Status, n (%)		
Private, employer-based	1 (20.0)	3 (60.0)
Government-based	4 (80.0)	1 (20.0)
None	0 (0.0)	1 (20.0)
	By Pregnancy	
Characteristics	**Livebirth – MPKUS Symptoms ($n = 6$)[a]**	**Livebirth – No MPKUS Symptoms ($n = 8$)**
Age of mother at delivery, n (%)		
16–19 years	1 (16.7)	0 (0.0)
20–34 years	4 (66.6)[b]	6 (75.0)
35 or more years	1 (16.7)	2 (25.0)
When learned of pregnancy		
<6 weeks after last menstrual period	5 (83.3)[b]	7 (87.5)
6–8 weeks after last menstrual period	1 (16.7)	1 (12.5)
Received MPKUS counseling, n (%)	5 (83.3)[b]	7 (87.5)
Yes, before pregnancy	1 (16.7)	1 (12.5)
Yes, after becoming pregnant		
PKU specialist contacted, n (%)		
Never stopped regular care	3 (50.0)[b]	5 (62.5)
In 1st trimester	3 (50.0)	3 (37.5)
Phe blood concentration when learned of pregnancy		
120–360 μmol/L	2 (33.4)	3 (37.5)
> 360 μmol/L	4 (66.6)[b]	3 (37.5)
Unknown or missing answer	0 (0.0)	2 (25.0)
Phe blood concentration within recommended range		
Before pregnancy	3 (50.0)[b]	3 (37.5)
< 6 weeks after last menstrual period	1 (16.6)	3 (37.5)
6–8 weeks after last menstrual period	2 (33.4)	1 (12.5)
Never reached recommended range	0 (0.0)	1 (12.5)
Problems with coverage/ reimbursement of[c], n (%)	1 (16.7)	1 (12.5)
Blood phe testing	0 (0.0)	1 (12.5)
PKU specialist visits	1 (16.7)	0 (0.0)
Medical food	4 (66.6)	2 (25.0)
Modified low-protein food	2 (33.4)[b]	4 (50.0)
No problems		
Medical food supplementation, n (%)	5 (83.3)[b]	7 (87.5)
Before pregnancy	6 (100.0)[b]	8 (100.0)
During pregnancy		
Sapropterin use, n (%)		
Before pregnancy	1 (16.7)	1 (12.5)
During pregnancy	0 (0.0)	1 (12.5)
Gestation, n (%)		
40 weeks	2 (33.3)	5 (62.5)
36–39 weeks	3 (50.0)[b]	3 (37.5)
< 36 weeks	1 (16.7)	0 (0.0)

[a] Includes 6 pregnancies that resulted in 7 livebirths (5 singletons and one pair of twins).
[b] Includes one pregnancy that resulted in livebirth twins.
[c] Participants had option to select all that apply.

achieve phe concentrations in the recommended range.

Several women reported MPKUS symptoms in their offspring despite having phe concentrations in the recommended range prior to pregnancy. It is not clear if the symptoms were due to factors other than MPKUS, as some of the symptoms can have many different etiologies. The data in this study were based on self-report, without confirmation from medical records or further clinical investigation. Self-report can be limited by recall and reporting biases. However, further investigation into such reports is warranted. The interpretation of these data is also limited by the small sample size. Despite these limitations, the results suggest that women with PKU continue to struggle with access to components of medical nutrition therapy for PKU which are critical for prevention of MPKUS, and that patient registries can be a valuable source of information about patient experiences. Further research could help assess the impact of barriers, such as lack of health insurance coverage of medical foods, on the prevalence of MPKUS. Legislation of medical nutrition equity might help remove some of the barriers affecting the reproductive health of women with PKU in the US. To optimize the outcomes of children born to women with PKU, it is vital that patients with PKU receive not only access to resources but also comprehensive services, including support from a well-trained workforce and social networks.

CRediT authorship contribution statement

Aileen Kenneson: Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis. **Margite I. Borth:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Rani H. Singh:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available upon request subject to the institution's data sharing requirements.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101092.

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