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Maternal phenylketonuria: an update on intervention compliance, challenges to staying compliant, and child outcomes from patient-reported survey data in the Newborn Screening Connect patient registry

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An abstract of
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Abstract

Maternal phenylketonuria: an update on intervention compliance, challenges to staying compliant, and child outcomes from patient-reported survey data in the Newborn Screening Connect patient registry

By
Margite Isabella Borth

BACKGROUND: Maternal phenylketonuria (mPKU) syndrome has been a known complication for pregnant women with PKU for a few decades now. Pregnant women with PKU who do not follow a low phenylalanine (phe) diet can end up having a variety of detrimental child outcomes like cognitive impairments and heart defects. Women with PKU can have successful pregnancies with proper diet interventions; however, despite the known implications and available resources on mPKU syndrome, these cases are still very much prevalent.

METHODS: Newborn Screening Connect is the first web-based, self-reported patient registry for metabolic disorders. The mPKU pregnancy surveys collects data on treatment/diet, medical history, medications, and outcomes from women with PKU who have been pregnant. Descriptive statistics on these data will be reported to provide an update on treatment compliance and child outcomes from those who reported live births. Also, women who reported multiple pregnancies will be further investigated to assess any differences between pregnancies.

RESULTS: We received surveys that described 17 pregnancies from 12 women, resulting in 15 livebirths. In this sample, 43% of livebirths reportedly had symptoms of mPKU syndrome. All women consumed medical food during all pregnancies, but those who reported no symptoms were more likely to report adherence challenges. Use of modified low-protein foods and additional dietary supplements were more commonly reported by those who did who reported no symptoms. Three women reported more than one pregnancy that resulted in a live birth. All three reported mPKU syndrome symptoms in their first pregnancy and no symptoms in their second pregnancy.

CONCLUSION: Phe blood levels seem to have been under control throughout most pregnancies and most followed their prescribed diets; however, mPKU symptoms were still prevalent. Other nutritional inadequacies must be furthered studied on how they can exacerbate mPKU syndrome. Cost was the most common issue reported on being able to adhere to diet. Women who reported more than one pregnancy seem to have improved child health outcomes in subsequent pregnancies.

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Introduction

Phenylketonuria and Newborn Screening

Phenylketonuria (PKU, OMIM 261600) is a rare metabolic inherited disorder in which the affected person does not have the functioning enzyme to convert phenylalanine (phe) to tyrosine [1]. This results in increased levels of phenylalanine and decreased levels of tyrosine in the body. Phenylalanine is an essential amino acid that is found naturally in most everyday foods. Treatment of PKU consists of restriction of dietary protein from natural sources that are high in phenylalanine (such as meat, fish, eggs, dairy, seeds and nuts). In order to ensure enough non-phenylalanine protein for growth and development, medical foods rich in phenylalanine-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 amount of phenylalanine in the patient's blood in order to assess how well they are managing their diet.

In the United States, newborn screening initiatives began in the 1960s [2]. Today, the genetic disorders that are screened for vary state by state, but each one screens for at least 29 disorders and PKU is screened for in every state due to it being one of the most common inherited metabolic disorders [3]. The incidence of PKU in newborns in the United States is about 1 in 16,500 newborns [4]. This number can vary depending on the race and ancestry with higher rates among Whites and lower rates among African Americans. Newborns do not usually show any symptoms; therefore, newborn screening has made early PKU detection possible.

If PKU is not detected early and diet intervention is not implemented immediately, high phenylalanine blood levels can become toxic and disrupt brain functions resulting in cognitive impairment [1]. More recent studies have also shown that the lack of tyrosine in their diets may also have an impact on neuropsychological function [5]. Up until recently, PKU patients could

only control their phenylalanine blood levels through diet intervention. Now, there are a couple of FDA approved drugs where phenylalanine is metabolized with the assistance of an exogenous enzyme or cofactor. Efficacy of these drugs are case by case and can highly depend on the patient's mutation(s) [6]. However, these drug treatments have not been approved for higher risk PKU patients, including women who are pregnant [7].

Maternal Phenylketonuria Syndrome

With improved medical interventions and better overall quality of life, women with PKU and their healthcare providers are faced with managing their condition during pregnancy. *Maternal phenylketonuria (mPKU) syndrome has been a known complication for pregnant women with PKU for a few decades now. Pregnant women with PKU who do not follow a low phenylalanine diet can end up having a variety of detrimental child outcomes like cognitive impairments and heart defects [8]. Women with PKU can have successful pregnancies with proper diet interventions; however, despite the known implications and available resources on mPKU syndrome, these cases are still very much prevalent.* With the same number of babies being exposed to mPKU as babies being born with PKU it is imperative that medical professionals and practitioners are aware of the challenges pregnant women with PKU come across to stay on diet [9].

The American College of Obstetricians and Gynecologists recommends women with PKU have phenylalanine blood levels below 360 μmol/L at least three months before conception and maintain levels in the range of 120-360 μmol/L throughout pregnancy for proper fetal development to reduce the risk of adverse effects associated with mPKU syndrome [10]. Studies have shown that women who achieved phenylalanine blood levels of 360 mmol/l or below just

one month before conception still saw mPKU syndrome symptoms despite being in range during pregnancy [11]. Because pregnancies of women with PKU are considered high-risk, standard of care procedures in PKU, like blood spots to monitor blood phenylalanine concentrations, are done more frequently than when the patient is not pregnant [11]. *The literature has shown barriers, including practical difficulties with implementing the diet and financial restraints, that could prevent women from following a proper low phenylalanine diet and regular visits to medical practitioners [12]. Identifying and understanding these challenges is an important step in addressing the issues women with PKU have throughout their pregnancies.*

Past studies have focused on women's overall and average diet control information throughout a pregnancy and specific outcomes of a child from medical records. The Maternal Phenylketonuria International Collaborative Study (MPKUCS) is the largest mPKU observational study that has taken place. A total of 382 women with hyperphenylalaninemia (HPA), including those with PKU, were enrolled between 1988 and 2002 and completed 572 pregnancies. This study focused on the child outcomes of these pregnancies and concluded that optimal birth outcomes occurred when maternal blood phenylalanine levels were in control pre- and periconception [13]. Other studies, including case studies, have also confirmed this finding with emphasis on the importance of early dietary control [14-17].

Newborn Screening Connect Patient Registry

The Newborn Screening (NBS) Connect patient registry was launched in 2012 and served as an internet-based support network for parents, guardians, and individuals with inherited metabolic disorders (IMDs), including PKU [18]. NBS Connect captured and analyzed information related to IMDs in an effort to assess gaps in service, access to care, develop best

standards of practice for clinical management, and connect families to research opportunities. The information related to IMDs was captured through a variety of surveys available to patients or parents/guardians. This registry was available to those with IMDs worldwide. Researchers can also have access to this de-identified data after administrative approval.

In 2018, NBS Connect integrated a mPKU survey to collect data on diet compliance, challenges, experiences, child outcomes, and postpartum details. This was one of the first surveys to provide self-reported data from women with PKU who have had pregnancies, including those who have had more than one pregnancy, to the research community.

Study Rationale

Maternal PKU diet compliance and child outcomes have not been assessed in this population for some years now. Challenges and barriers on attaining early dietary control per nutrition guidelines are much less studied in this population. One interview-based study conducted on 24 women who were pregnant between 1998 and 2002 found diet treatment and psychological barriers that included dislike of formula, long commutes to clinics, need to take off work for multiple clinic visits, desire to interact with other women with PKU, lack of confidence in obstetric knowledge about maternal PKU, and poor adherence to pre-pregnancy recommendations, despite awareness of maternal PKU pregnancy-related risks [19]. Additionally, there are no studies assessing and comparing mPKU syndrome outcomes and diet intervention in a sample of women who have had multiple pregnancies.

This manuscript will fill this gap in the literature by providing an update on the characteristics that have been published, such as child outcomes and when and if dietary control was obtained, as well as data on sources of protein intake, current information on any

challenges women may have faced throughout the pregnancy, and side by side comparisons of pregnancy characteristics in women that had more than one pregnancy. It will also be unique as it will be the first to include data from a self-reported patient registry, NBS Connect.

Methods

Data Collection and Extraction

Data collection was executed through the NBS Connect patient registry online portal. Female PKU patients who were already registered in the NBS Connect registry were made aware of the mPKU survey through the NBS Connect newsletter and emails. Women who were already registered or who registered after the survey was integrated had the survey available to them for completion if they reported being pregnant in the past at time of NBS Connect registration. If a woman reported multiple pregnancies, one survey for each pregnancy was available.

Responses from the following questions were extracted into excel from the NBS Connect patient registry researcher portal. The same questions that asked about a patient's first pregnancy were also asked about subsequent pregnancies in a succeeding survey for those who reported multiple pregnancies. For a list of possible responses to these questions and the full survey questions, please see the Appendix A.

Pregnancy History
- How many pregnancies have you had?
- How many live births resulted from these pregnancies?

Pregnancy - Social History
- Are you aware of the NPKUA mentoring program for women with PKU who are pregnant or are new mothers?
- Would you like to be involved in the NPKUA mentoring program for women with PKU who are pregnant or are new mothers?

1st Pregnancy Detail
- When did you learn you were pregnant the FIRST time?
- What was your plasma/blood phenylalanine level at the time you learned you were pregnant?
- Did you receive counseling about the consequences of high blood phenylalanine levels during your FIRST pregnancy?
- After learning you were pregnant the FIRST time, when did you contact a PKU specialist and return to clinic?
- How old were you when you found out you were pregnant the FIRST time?

1st Pregnancy - Treatment/Diet
- After learning you were pregnant the FIRST time, when did you resume the diet prescribed by your clinical team?

- After learning you were pregnant the FIRST time, and you resumed a prescribed diet, when did your plasma/blood phenylalanine levels first reach the recommended range of 120-360 µmol/Liter (or 2-6 mg/dL)?
- What were your usual plasma/blood phenylalanine levels during your FIRST pregnancy?
- Check all components of the diet you followed BEFORE your FIRST pregnancy. Note: Natural protein means foods that contain protein or phenylalanine.
- Check all components of the diet you followed DURING your FIRST pregnancy. Note: Natural protein means foods that contain protein or phenylalanine.
- Did you follow the diet prescribed by your clinical team DURING your FIRST pregnancy?
- Did you use specially modified low protein food products DURING your FIRST pregnancy?
- Did you take medical food (formula) DURING your FIRST pregnancy?
- Did you have any of the following problems taking your prescribed medical food (formula) DURING your FIRST pregnancy? (Select all that apply.)
- Did you take any other supplements BEFORE your FIRST pregnancy? (Select all that apply.)
- Did you take any other supplements DURING your FIRST pregnancy? (Select all that apply.)
- Did you take any other supplements AFTER your FIRST pregnancy? (Select all that apply.)

1st Pregnancy - Medical History

- Were you hospitalized during your FIRST pregnancy for any reason other than for delivery? If yes, please provide the reason for the hospitalization. (Select all that apply.)
- If you had ultrasounds during your FIRST pregnancy, were any abnormalities seen in the baby? (Select all that apply.)
- During your FIRST pregnancy, were you exposed to tobacco, alcohol, or drugs (other than those prescribed by your doctor)?
- Did you have blood essential fatty acid analysis done just before or during the FIRST pregnancy?
- DURING your FIRST pregnancy, did you take medication for depression, anxiety, ADHD, or ADD?
- Did you see a PKU specialist during your FIRST pregnancy? (Select all that apply.)
- During your FIRST pregnancy, were you followed by an obstetrician specializing in high risk pregnancies?
- During your FIRST pregnancy, did you have a problem getting coverage or reimbursement for any of the following? (Select all that apply.)
- What was the outcome of your FIRST pregnancy?
- When was your baby from your FIRST pregnancy born?
- Did you have any complications during labor or during delivery of your FIRST pregnancy? (Select all that apply.)
- At birth, was your baby from your FIRST pregnancy within normal ranges for length, weight, head circumference and APGAR scores? (Select all that apply.)
- Were any birth defects noted in your baby from your FIRST pregnancy after delivery? (Select all that apply.)
- Check all components of the diet you are following now AFTER your FIRST pregnancy. Note: Natural protein means foods that contain protein or phenylalanine.
- Are you now, or did you breastfeed your baby from your FIRST pregnancy?

- As your baby from your FIRST pregnancy has grown, are there any developmental problems? (Select all that apply.)

Data Analysis

For the questions about plasma phenylalanine levels, answers given in the mg/dL format were converted to μmol/L. Plasma phenylalanine levels were categorized into three ranges (<120 μmol/L, 120-360 μmol/L, >360 μmol/L) and unknown. Some supplements were collapsed into the 'other' category. These included omega-3 fatty acids (DHA), omega-6 fatty acids, vitamin D, calcium, iron, folic acid, vitamin B12, and other.

Most demographics data of mothers were collected at time of enrollment to NBS Connect registry, except for awareness of NPKUA mentoring program. Symptoms of mPKU syndrome in children included low birthweight, small for gestational age, cleft lip/palate, heart defects, motor skill delays, cognitive skill delays, and an 'other' option.

All completed surveys were extracted via excel and included in this analysis. Two women reported three pregnancies but only completed one survey and one woman reported two pregnancies but only completed one survey. Pregnancies that were terminated or lost by miscarriage were excluded from tables 2-7. Additionally, questions that were skipped over were categorized into unknown/no answer.

Descriptive statistics, including frequencies, percentages, means, and standard errors, were calculated via excel. Further statistical analysis was not performed due to the small sample size.

NBS Connect patient registry data collection and analysis was approved by the Emory University Institutional Review Board (IRB00052505).

Results

Study Participants

Demographic characteristics and pregnancy outcomes of women who completed at least one NBS Connect mPKU survey are shown in Table 1. All participants were from the US and age averaged in the mid-thirties ranging from 23 years to 53 years at the time of the survey. Only two women identified as Caucasian, Latino/Hispanic with the remainder as Caucasian, not Latino/Hispanic. Although none participated in it, 83% of women reported they were aware of the National PKU Alliance (NPKUA) mentoring program. A total of 12 women self-reported at least one pregnancy with seven women reporting only one pregnancy, five women reporting two pregnancies and one reporting three pregnancies. There were two women who reported terminations (one first and only pregnancy, one first pregnancy and a live birth as her second). One participant reported a miscarriage as her first pregnancy and a live child outcome as her second pregnancy. Out of the 14 pregnancies that resulted in live birth outcomes, six pregnancies were reported to have shown mPKU syndrome symptoms with one resulting in twins, and eight pregnancies were reported to have no mPKU syndrome outcomes. Demographics of all women are reported along with them being stratified by pregnancy outcome. Distributions of each characteristic are quite equivalent throughout each pregnancy outcome except for health insurance status. Women that reported pregnancies that resulted in mPKU syndrome symptoms were more likely (66.6%) to be enrolled in government regulated health insurances while those who did not report mPKU syndrome symptoms were more likely to have health insurance from an employer (62.5%).

Table 1. Demographic characteristics and pregnancy outcome of women who completed the NBS Connect mPKU survey(s)

		By Pregnancy		
			Live birth outcome	
Characteristics	**Total Women (n=12)**	**Termination/ Miscarriage (n=3)**	**Evidence of mPKU syndrome symptoms[1] (n=7)**	**No evidence of mPKU syndrome symptoms[1] (n=8)**
Age in years, mean (standard error)	36.98 (9.95)	35.93 (15.88)	35.6 (6.69)	39.31(10.09)
Race/Ethnicity, n (%)				
Caucasian, Latino/Hispanic	2 (16.6)	0 (0.0)	2 (33.3)	2 (25.0)
Caucasian, Not Latino/Hispanic	10 (83.4)	3 (100.0)	4 (66.7)[2]	6 (75.0)
Education, n (%)				
High School	6 (50.0)	2 (66.7)	2 (33.3)	3 (37.5)
4-year college	2 (16.7)	0 (0.0)	1 (16.7)	2 (25.0)
Graduate	3 (25.0)	1 (33.3)	2 (33.3)	3 (37.5)
Unknown	1 (8.3)	0 (0.0)	1 (16.7)[2]	0 (0.0)
Health insurance status, n (%)				
Employer	7 (58.4)	2 (66.7)	2 (33.3)[2]	5 (62.5)
Medicaid	2 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)
Medicare	1 (8.3)	1 (33.3)	0 (0.0)	1 (12.5)
Federal	1 (8.3)	0 (0.0)	2 (33.3)	1 (12.5)
None	1 (8.3)	0 (0.0)	0 (0.0)	1 (12.5)
Aware of NPKUA[3] mentoring program, n (%)				
Yes, involved	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes, never involved	10 (83.3)	2 (66.7)	5 (83.3)[2]	7 (87.5)
No	2 (16.7)	1 (33.3)	1 (16.7)	1 (12.5)

[1]Child with evidence of mPKU syndrome symptoms include low birthweight, small for gestational age, birth defects, low APGAR scores, and developmental delays
[2]represents one pregnancy that resulted in live twins
[3]NPKUA= National PKU Alliance

Intervention compliance, challenges to staying compliant and live child outcomes

Medical characteristics of pregnancies and phenylalanine blood levels throughout the pregnancy and live child outcomes of women who completed at least one NBS Connect mPKU survey are shown in Tables 2 and 3. Distributions in Table 2 differed the most between women who reported mPKU symptoms and those who reported no symptoms on never stopping regular care with a PKU specialist (50% vs 62.5%), having high risk pregnancy OB care (50% vs 87.5%), abnormalities seen in ultrasound (100% vs 0%), problems with coverage/reimbursements in at least one resource or service (66.6% vs 25%), and having

delivery complications (83.3% vs 12.5%). From the 15 live births reported, 46.7% showed evidence of mPKU syndrome symptoms. Symptoms reported include low birthweight (50.0%), small for gestation age (50.0%), cleft lip/palate (16.7%), heart defects (33.4%), and development problems (50%). Women who reported mPKU symptoms were more likely to report high phenylalanine blood levels when they learned they were pregnant (66.6%); however, at least 50% of participants, the same percentage as those who reported no mPKU syndrome symptoms, had usual phenylalanine blood levels within recommended range throughout their pregnancy (Table 3). One woman reported never reaching recommended blood phe levels before or during pregnancy with a result of a live birth with no mPKU syndrome symptoms.

Table 2. Medical characteristics and child outcome of women who completed the NBS Connect mPKU survey(s) and reported a live birth outcome

Characteristics	**Live Birth Outcome**	
	Evidence of mPKU syndrome symptoms[1] (n=7)	**No evidence of mPKU syndrome symptoms[1] (n=8)**
Age of mother, n (%)		
16-19 years	1 (16.7)	0 (0.0)
20-34 years	4 (66.6)[3]	6 (75.0)
> 35 years	1 (16.7)	2 (25.0)
Received maternal PKU counseling, n (%)		
Yes, before pregnancy	5 (83.3)[3]	7 (87.5)
Yes, after becoming pregnant	1 (16.7)	1 (12.5)
PKU specialist contacted, n (%)		
Never stopped regular care	3 (50.0)[3]	5 (62.5)
1st trimester	3 (50.0)	3 (37.5)
PKU specialist contacted[2], n (%)		
Genetic Counselor	3 (50.0)	4 (50.0)
Geneticist	5 (83.3)[3]	6 (75.0)
Metabolic Nutritionist/ Dietitian	6 (100.0)[3]	5 (62.5)
Nurse Practitioner	0 (0.0)	1 (12.5)
Other	0 (0.0)	1 (12.5)
Followed by high-risk pregnancy OB, n (%)		
No	3 (50.0)[3]	1 (12.5)
Yes	3 (50.0)	7 (87.5)
Hospitalized for other than delivery, n (%)		
No	4 (66.6)	6 (75.0)
Yes	2 (33.4)[3]	0 (0.0)
Unsure	0 (0.0)	1 (12.5)
Abnormalities in ultrasound, n (%)		
Small for gestational age	5 (83.3)[3]	0 (0.0)
Other	1 (16.7)	0 (0.0)
None	0 (0.0)	8 (100.00)
Exposure to tobacco, alcohol, and/or drugs during pregnancy, n (%)		
No	6 (100.0)[3]	8 (100.00)
Yes	0 (0.0)	0 (0.0)
Blood essential fatty acid analysis, n (%)		
No	0 (0.0)	2 (25.0)
Yes	1 (16.7)	0 (0.0)
Unsure	5 (83.3)[3]	6 (75.0)
Take medications for anxiety, depression, ADD, ADHD, n (%)		
No	5 (83.3)[3]	8 (100.00)
Yes	1 (16.7)	0 (0.0)

Problems with coverage/reimbursement of[2], n (%)		
Blood testing	1 (16.7)	1 (12.5)
Genetic testing	0 (0.0)	0 (0.0)
PKU specialist clinic visits	0 (0.0)	1 (12.5)
Medical food	1 (16.7)	0 (0.0)
Modified low protein food	4 (66.6)	2 (25.0)
No problems	2 (33.4)[3]	4 (50.0)
Unsure	0 (0.0)	1 (12.5)
Gestation, n (%)		
Full term (40 weeks)	2 (33.3)	5 (62.5)
36-39 weeks	3 (50.0)[3]	3 (37.5)
< 36 weeks	1 (16.7)	0 (0.0)
Delivery complications[2], n (%)		
Emergency C-section	3 (50.0)[3]	0 (0.0)
Pre-eclampsia/eclampsia	0 (0.0)	1 (12.5)
Other	3 (50.0)	0 (0.0)
None	1 (16.7)	7 (87.5)
Type of mPKU symptoms[2]		
Low birthweight	3 (50.0)	-
Small for gestation age	3 (50.0)[3]	-
Cleft lip/palate	1 (16.7)	-
Heart defects	2 (33.4)	-
Developmental problems		
Motor skills	1 (16.7)	-
Cognitive skills	2 (33.4)	-
Unsure	1 (16.7)	-
Other	1 (16.7)	-

[1]Child with evidence of mPKU syndrome symptoms include low birthweight, small for gestational age, birth defects, low APGAR scores, and developmental delays
[2]participant had option to select all that apply
[3]represents one pregnancy that resulted in live twins

Table 3. Phenylalanine blood levels throughout the pregnancy and child outcome of women who completed the NBS Connect mPKU survey(s) and reported a live birth outcome

	Live Birth Outcome	
Characteristics	**Evidence of mPKU syndrome symptoms[1] (n=7)**	**No evidence of mPKU syndrome symptoms[1] (n=8)**
Learned pregnant after last menstrual cycle, n (%)		
< 6 weeks	5 (83.3)[2]	7 (87.5)
6-8 weeks	1 (16.7)	1 (12.5)
Phe blood levels when learned pregnant, n (%)		
120-360 µmol/L	2 (33.4)	3 (37.5)
> 360 µmol/L	4 (66.6)[2]	3 (37.5)
Unknown/No Answer	0 (0.0)	2 (25.0)
Phe blood levels returned to recommended range, n (%)		
Levels already in recommended range	3 (50.0)[2]	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)
Usual Phe blood levels, n (%)		
1st trimester		
< 120 µmol/L	0 (0.0)	1 (12.5)
120-360 µmol/L	5 (83.3)[2]	4 (50.0)
> 360 µmol/L	1 (16.7)	1 (12.5)
Unknown/No Answer	0 (0.0)	2 (25.0)
2nd trimester		
< 120 µmol/L	0 (0.0)	0 (0.0)
120-360 µmol/L	5 (83.3)[2]	6 (75.0)
> 360 µmol/L	1 (16.7)	0 (0.0)
Unknown/No Answer	0 (0.0)	2 (25.0)
3rd trimester		
< 120 µmol/L	1 (16.7)	0 (0.0)
120-360 µmol/L	3 (50.0)[2]	5 (62.5)
> 360 µmol/L	1 (16.7)	1 (12.5)
Unknown/No Answer	1 (16.6)	2 (25.0)

[1]Child with evidence of mPKU syndrome symptoms include low birthweight, small for gestational age, birth defects, low APGAR scores, and developmental delays
[2]represents one pregnancy that resulted in live twins

Intervention and diet components followed before, during, and after pregnancy and live child outcomes of women who completed at least one NBS Connect mPKU survey are shown in Table 4. One woman who reported mPKU symptoms reported taking Kuvan (sapropterin dhydrochloride, a pharmaceutical treatment for PKU) before and after her pregnancy but not throughout it. Another woman reported taking Kuvan before, during and after her pregnancy and reported no symptoms. Even though 100% of participants consumed medical food during the

pregnancy, there was a drop to 66.6% of consumption after pregnancy in those who reported mPKU symptoms compared to a drop to 87.5% in those who reported no symptoms. In general, problems with consumption of medical food throughout pregnancy were similar in distribution between the two groups; however, 25% and 50% of those who reported no mPKU symptoms expressed issues with cost and nausea/vomiting, respectively compared to 0% and 16.7% in those who reported mPKU symptoms. Modified low-protein foods were more commonly consumed consistently throughout a pregnancy in those who reported no mPKU symptoms, 62.5% compared to 50%. Fifty percent of those who reported mPKU symptoms and 25% who reported no symptoms did not consume any dietary supplements before, during or after her pregnancy. Additionally, there was a higher proportion of women who reported taking dietary supplements before and after pregnancy in participants who reported no mPKU symptoms.

Table 4. Intervention components followed before, during, and after pregnancy and child outcome of women who completed the NBS Connect mPKU survey(s) and reported a live birth outcome

Characteristics	**Live Birth Outcome**	
	Evidence of mPKU syndrome symptoms[1] (n=7)	**No evidence of mPKU syndrome symptoms[1] (n=8)**
Components followed before pregnancy[2], n (%)		
Medical Food	5 (83.3)[4]	7 (87.5)
No meat	1 (16.7)	2 (25.0)
Phe/Natural protein restriction	3 (50.0)*	3 (37.5)
Simplified Diet	2 (33.4)*	4 (50.0)
Kuvan	1 (16.7)	1 (12.5)
No restriction	1 (16.7)	0 (0.0)
Resumed diet, n (%)		
Before becoming pregnant	5 (83.3)[4]	6 (75.0)
< 6 weeks after last menstrual period	1 (16.7)	1 (12.5)
6-8 weeks after last menstrual period	0 (0.0)	1 (12.5)
Components followed during pregnancy[2], n (%)		
Medical Food	6 (100.0)[4]	8 (100.0)
No meat	1 (16.7)	1 (12.5)
Phe/Natural protein restriction	4 (66.6)[4]	4 (50.0)
Simplified Diet	3 (50.0)	3 (37.5)
Kuvan	0 (0.0)	1 (12.5)
No restriction	0 (0.0)	0 (0.0)

Components followed after pregnancy[2], n (%)		
Medical Food	4 (66.6)[4]	7 (87.5)
No meat	1 (16.7)	3 (37.5)
Phe/Natural protein restriction	3 (50.0)[4]	2 (25.0)
Simplified Diet[3]	3 (50.0)[4]	2 (25.0)
Kuvan	1 (16.7)	2 (25.0)
No restriction	0 (0.0)	0 (0.0)
Followed diet prescribed, n (%)		
Yes, never discontinued	4 (66.6)[4]	3 (37.5)
Yes, after learning pregnant	2 (33.4)	4 (50.0)
Yes, discontinued after pregnancy	0 (0.0)	1 (12.5)
Medical Food (formula), n (%)		
Yes, always used	4 (66.6)	5 (62.5)
Yes, after learning pregnant	0 (0.0)	2 (25.0)
Yes, but discontinued after pregnancy	1 (16.7)	1 (12.5)
Partially before and during pregnancy	0 (0.0)	0 (0.0)
Not before or during pregnancy	0 (0.0)	0 (0.0)
Other	1 (16.7)[4]	0 (0.0)
Problems with consuming medical food[2], n (%)		
Cost	0 (0.0)	2 (25.0)
Dislike taste	1 (16.7)	2 (25.0)
Dislike odor	0 (0.0)	1 (12.5)
Dislike texture	1 (16.7)	0 (0.0)
Dislike amount required	2 (33.4)	2 (25.0)
Heartburn	1 (16.7)	1 (12.5)
Inconvenience	2 (33.4)	1 (12.5)
Nausea/vomiting	1 (16.7)[4]	4 (50.0)
No problems	2 (33.4)	2 (25.0)
Modified low-protein foods, n (%)		
Yes, always used	1 (16.7)	2 (25.0)
Yes, after learning pregnant	1 (16.7)	2 (25.0)
Yes, discontinued after pregnancy	1 (16.7)	1 (12.5)
Partially before and during pregnancy	2 (33.2)	1 (12.5)
Not before or during pregnancy	0 (0.0)	1 (12.5)
Other	1 (16.7)[4]	0 (0.0)
Unknown/No Answer	0 (0.0)	1 (12.5)
Supplements consumed before[2], n (%)		
Tyrosine	0 (0.0)	0 (0.0)
Multivitamin	0 (0.0)	1 (12.5)
Prenatal	0 (0.0)	3 (37.5)
Other	0 (0.0)	1 (12.5)
None	3 (50.0)	2 (25.0)
Unknown/No Answer	3 (50.0)[4]	3 (37.5)
Supplements consumed during[2], n (%)		
Tyrosine	2 (33.4)[4]	1 (12.5)
Multivitamin	2 (33.4)	1 (12.5)
Prenatal	2 (33.4)	5 (62.5)
Other	3 (50.0)[4]	4 (50.0)
None	3 (50.0)	2 (25.0)
Unknown/No Answer	0 (0.0)	1 (12.5)

Supplements consumed after[2], n (%)		
Tyrosine	0 (0.0)	0 (0.0)
Multivitamin	0 (0.0)	1 (12.5)
Prenatal	0 (0.0)	1 (12.5)
Other	1 (16.7)[4]	0 (0.0)
None	3 (50.0)	2 (25.0)
Unknown/No Answer	2 (33.4)	4 (50.0)

[1]Child with evidence of mPKU syndrome symptoms include low birthweight, small for gestational age, birth defects, low APGAR scores, and developmental delays
[2]participant had option to select all that apply
[3]Simplified Diet: restricting high phe or high natural protein foods but allowing most fruits and vegetables
[4]represents one pregnancy that resulted in live twins

Intervention compliance, challenges to staying compliant and live child outcomes among women who reported more than one pregnancy with a live birth outcome

Out of the 12 women, three reported more than one pregnancy with a live birth. All three of these women reported mPKU symptoms in their first pregnancies and no symptoms in their second pregnancies. One woman had a total of three pregnancies that resulted in live births with her first and third child displaying evidence of mPKU symptoms.

Medical characteristics and child outcomes of this subsample of women are shown in Table 5. The mPKU symptoms reported by these women include low birthweight, small for gestational age, and cognitive skills problems. Differences between first and second pregnancies were greatest in type of PKU specialist contacted, abnormalities in ultrasounds, problems with coverage/reimbursements in at least one resource or service, and delivery complications. None of these women were seeking genetic counselor care in their first pregnancy compared to two who did seek this care in their second pregnancy. All three women reported fetal abnormalities in their first pregnancy, and the one in her third pregnancy, compared to none in their second pregnancy. Problems with coverage/reimbursement were seen more in second pregnancies and delivery complications were seen more in first pregnancies.

Table 5. Medical characteristics and child outcome of women who completed the NBS Connect mPKU survey(s) and reported more than one pregnancy that resulted in a live birth

Characteristics	Live Birth Outcome		
	First Pregnancy (n=3)	Second Pregnancy (n=3)	Third Pregnancy (n=1)
Age of mother			
16-19 years	1	0	0
20-34 years	2	3	0
> 35 years	0	0	1
Received maternal PKU counseling			
Yes, before pregnancy	3	3	1
Yes, after becoming pregnant	0	0	0
PKU specialist contacted			
Never stopped regular care	2	2	1
1st trimester	1	1	0
PKU specialist contacted[1]			
Genetic Counselor	0	2	1
Geneticist	3	3	1
Metabolic Nutritionist/ Dietitian	3	3	1
Nurse Practitioner	0	0	0
Followed by high-risk pregnancy OB			
No	1	1	1
Yes	2	2	0
Hospitalized for other than delivery			
No	2	3	1
Yes	1	0	0
Abnormalities in ultrasound			
Small for gestational age	2	0	1
Other	1	0	0
None	0	3	0
Blood essential fatty acid analysis			
No	0	1	0
Yes	0	0	0
Unsure	3	2	1
Take medications for anxiety, depression, ADD, ADHD			
No	3	3	1
Yes	0	0	0
Problems with coverage/reimbursement of[1]			
Blood testing	0	1	0
Genetic testing	0	0	0
PKU specialist clinic visits	0	1	0
Medical food	0	0	0
Modified low protein food	1	2	1
No problems	2	0	0

Gestation			
Full term (40 weeks)	1	2	1
36-39 weeks	2	1	0
Delivery complications[1]			
Emergency C-section	1	0	0
Pre-eclampsia/eclampsia	0	1	0
Other	1	0	1
None	1	2	0
mPKU symptoms[1]			
Low birthweight	1	0	1
Small for gestation age	1	0	0
Cleft lip/palate	0	0	0
Heart defects	0	0	0
Developmental problems			
Motor skills	0	0	0
Cognitive skills	1	0	0
Unsure	0	0	0
Other	0	0	1
None	0	0	0

[1]participant had option to select all that apply

Table 6 shows phenylalanine blood levels throughout each pregnancy in woman who reported more than one pregnancy with a live birth outcome. One woman reported phenylalanine blood levels above the recommended range when she discovered she was pregnant and stated her levels returned to being in range between 6-8 weeks after last menstrual period. All three women with multiple live births reported having usual phenylalanine blood levels in range throughout all pregnancies. Intervention components followed before, during, and after the pregnancies of women who completed more than one NBS Connect mPKU survey and reported more than one pregnancy that resulted in a live birth are shown in Table 7. All women reported consuming medical food before and during all pregnancies; however, medical food was consumed more consistently in second pregnancies. Women were also a bit more consistent and compliant on consuming modified low protein foods in their second pregnancies. The woman who had three pregnancies did not consume dietary supplements in any of her pregnancies. One woman took a multivitamin and another a prenatal vitamin before their second pregnancy, but did not take any

dietary supplements in their first pregnancy. One woman consumed a tyrosine supplement during her first pregnancy and did not for her second pregnancy.

Table 6. Phenylalanine blood levels throughout the pregnancy of women who completed the NBS Connect mPKU survey(s) and reported more than one pregnancy that resulted in a live birth

Characteristics	**Live Birth Outcome**		
	First Pregnancy (n=3)	**Second Pregnancy (n=3)**	**Third Pregnancy (n=1)**
Learned pregnant after last menstrual cycle			
< 6 weeks	2	3	1
6-8 weeks	1	0	0
Phe blood levels when learned pregnant			
120-360 µmol/L	2	1	1
> 360 µmol/L	1	2	0
Phe blood levels returned to recommended range			
Levels already in recommended range	2	0	1
< 6 weeks after last menstrual period	0	3	0
6-8 weeks after last menstrual period	1	0	0
Usual Phe blood levels			
1st trimester			
< 120 µmol/L	0	1	0
120-360 µmol/L	3	2	1
> 360 µmol/L	0	0	0
2nd trimester			
< 120 µmol/L	0	0	0
120-360 µmol/L	3	3	1
> 360 µmol/L	0	0	0
3rd trimester			
< 120 µmol/L	1	0	0
120-360 µmol/L	2	3	1
> 360 µmol/L	0	0	0

Table 7. Intervention components followed before, during, and after pregnancy of women who completed the NBS mPKU survey(s) and reported more than one pregnancy that resulted in a live birth

Characteristics	Live Birth Outcomes		
	First Pregnancy (n=3)	Second Pregnancy (n=3)	Third Pregnancy (n=1)
Components followed before pregnancy[1]			
Medical Food	3	3	1
No meat	0	0	0
Phe/Natural protein restriction	1	1	1
Simplified Diet	2	3	0
Kuvan	0	0	0
No restriction	0	0	0
Resumed diet			
Before becoming pregnant	3	3	1
< 6 weeks after last menstrual period	0	0	0
6-8 weeks after last menstrual period	0	0	0
Components followed during pregnancy[1]			
Medical Food	3	3	1
No meat	0	0	0
Phe/Natural protein restriction	3	2	1
Simplified Diet[2]	1	2	0
Kuvan	0	0	0
No restriction	0	0	0
Components followed after pregnancy[1]			
Medical Food	2	3	1
No meat	0	1	0
Phe/Natural protein restriction	2	0	1
Simplified Diet	2	2	1
Kuvan	0	0	0
No restriction	0	0	0
Followed diet prescribed			
Yes, never discontinued	3	1	1
Yes, after learning pregnant	0	2	0
Yes, discontinued after pregnancy	0	0	0
Partially before and during pregnancy	0	0	0
Not before or during pregnancy	0	0	0
Medical Food (formula)			
Yes, always used	1	3	1
Yes, after learning pregnant	0	0	0
Yes, but discontinued after pregnancy	0	0	0
Partially before and during pregnancy	1	0	0
Not before or during pregnancy	0	0	0
Other	1	0	0

Problems with consuming medical food[1]			
Cost	0	2	0
Dislike taste	0	0	0
Dislike odor	0	0	0
Dislike texture	0	0	0
Dislike amount required	1	1	1
Heartburn	0	0	0
Inconvenience	1	1	1
Nausea/vomiting	1	1	0
No problems	1	0	0
Modified low-protein foods			
Yes, always used	0	1	0
Yes, after learning pregnant	1	1	0
Yes, discontinued after pregnancy	0	0	0
Partially before and during pregnancy	1	1	1
Not before or during pregnancy	0	0	0
Other	1	0	0
Supplements consumed before[1]			
Tyrosine	0	0	0
Multivitamin	0	1	0
Prenatal	0	1	0
Other	0	0	0
None	1	1	1
Unknown	2	1	0
Supplements consumed during[1]			
Tyrosine	1	0	0
Multivitamin	1	1	0
Prenatal	1	1	0
Other	2	1	0
None	1	1	1
Unknown	0	1	0
Supplements consumed after[1]			
Tyrosine	0	0	0
Multivitamin	0	0	0
Prenatal	0	0	0
Other	1	0	0
None	1	1	1
Unknown	1	2	0

[1]participant had option to select all that apply

[2]Simplified Diet: restricting high phe or high natural protein foods but allowing most fruits and vegetables

Discussion

Results Summary

From our sample of pregnancies that resulted in live births (n=14), 43% reported evidence of mPKU syndrome symptoms. At least one ultrasound abnormality and at least one delivery complication was reported by all six pregnancies who reported mPKU syndrome symptoms. Phenylalanine blood levels when participants learned they were pregnant were more likely to report levels above recommended range if they reported mPKU syndrome symptoms; however, usual phenylalanine blood levels ranges were similar between the two groups throughout pregnancy. All women consumed medical food during all pregnancies, but those who reported no adverse child outcomes were more likely to report issues in consuming medical food, specifically issues with nausea/vomiting and costs. Modified low-protein foods were more commonly consumed consistently throughout pregnancies by those who did who reported no symptoms. Additional dietary supplements were also more likely consumed by those who reported no symptoms.

Three women reported more than one pregnancy that resulted in a live birth. Each of these women reported mPKU syndrome symptoms in their first pregnancy and no symptoms in their second pregnancy and usual phenylalanine blood levels in the recommended range throughout pregnancy for all pregnancies. Medical food and modified low protein foods were reported to be consumed more consistently in second pregnancies. Two women reported to have taken supplements before their second pregnancy, but not before their first, and one consumed tyrosine during her first pregnancy, but not during her second.

Diet adherence and phenylalanine blood levels

Studies, including MPKUCS, show that achieving recommended phenylalanine blood concentrations (less than 360 μmol/L before pregnancy and between 120-360 μmol/L during pregnancy) with a phenylalanine-restricted diet significantly decreases morbidity in the offspring of women with PKU [13]. In this study, the majority of women who reported mPKU syndrome symptoms also reported blood phenylalanine levels that were above recommended range before pregnancy and in recommended range throughout the pregnancy. Also, in general, these participants reported that they followed their prescribed diet before and throughout the pregnancy. Even though a few women who reported no symptoms were not in recommended range when they learned they were pregnant, they were able to achieve phenylalanine control sooner than those who reported mPKU symptoms. Women who reported no mPKU symptoms reported at a higher proportion in consistently consuming modified low-protein foods during pregnancy and taking supplements before pregnancy. Modified low-protein foods are low in protein and high in energy which may help prevent catabolic weight loss and elevated phenylalanine levels due to nausea/vomiting during pregnancy [20]. Other nutrients, aside from phenylalanine, have been much less studied on how they might contribute to or exacerbate mPKU syndrome. In our population, only women who reported no mPKU symptoms consumed additional supplements like multivitamins and prenatal vitamins before becoming pregnant. Many times, a phenylalanine-restricted diet can create other nutritional insufficiencies of which the medical provider and patient might not be aware of, such as low tyrosine [21]. Further research is needed on how additional nutritional inadequacies before and during pregnancy contribute to mPKU syndrome outcomes when women have controlled blood phenylalanine levels.

In terms of intervention initiation, we found that 79% of pregnancies reported resuming diet before becoming pregnant while the remaining 21% reported resuming their prescribed diet during their first trimester with similar distributions among the two groups. In the MPKUCS, 25.9% of pregnancies were in dietary control before conception, about 50% of the women with HPA were in dietary control during the first trimester, 9.1% were in dietary control in the second trimester, and 0.7% were in dietary control in the third [13]. There was a higher prevalence of early diet intervention from women in our sample than in the MPKUCS. Our higher results could be due to small sample size or recall bias.

One woman reported never reaching recommended blood phe levels before or during pregnancy which resulted in a live birth with no mPKU syndrome symptoms. It is possible to have blood phenylalanine levels above the recommended range, and still have a child that doesn't have any of the symptoms of mPKU that the survey asked about [11]. According to Prick (2012), the rate of symptoms in untreated pregnancies are small for gestational age (19%), microcephaly (46%), congenital heart disease (6.6%), intellectual or development disability (47%), and facial dysmorphology (50%). The risk of these symptoms depends on level of phenylalanine during pregnancy, and actual phenylalanine blood levels were not captured in this population [11]. This woman could have been only slightly above the recommended range.

mPKU syndrome symptoms

We reported low birthweight (50%), small for gestational age (50%), developmental problems (50%) and heart defects (33.4%) as the most common mPKU syndrome symptoms in our population. In terms of birth measurements, pregnancies in the MPKUCS that achieved control phenylalanine levels pre-conception or during the first trimester on average fell in the

55th percentile for length and 35th percentile for weight [13]. However, two pregnancies, out of 15 live births in our study resulted in CHD while only one, out of 187 pregnancies, resulted in CHD among the women who achieved metabolic control by 10 weeks of pregnancy in the MPKUCS. A follow up study to the MPKUCS found that there is a higher risk for CHD in the groups where women had a lower natural protein and medical food intake, regardless of blood phenylalanine levels [22]. The two women in our sample who reported CHD also reported consuming medical foods, modified low-protein foods and followed a simplified diet during pregnancy. However, this survey does not capture amount of natural protein intake or amount of medical food intake. Additional data on quantity of natural protein and medical food would be needed to support the previous study's findings. One of these women did report taking various supplements during pregnancy but not before. This again reiterates that further research is needed on additional nutritional micronutrients before and during pregnancy.

Other medical complications

Ultrasound abnormalities and delivery complications were by far the characteristics in which the two group's distributions differed the most. Ultrasounds abnormalities were reported in all pregnancies that showed evidence of mPKU outcomes and none of those that reported no symptoms. Delivery complications were seen in 100% of pregnancies that showed evidence of mPKU outcomes, with an emergency cesarean section being the most common, and only one of eight pregnancies in those that reported no symptoms. In the general population, an estimated 14 in every 1000 women hospitalized for delivery in the United States experienced severe maternal morbidity [23]. One follow-up study to MPKUCS found that ultrasound abnormalities did occur in mPKU patients even when they are following a prescribed diet [24]. However, delivery

complications among this population are much less studied and not described in the literature. In our study, one cesarean section resulted from complications with a twin birth delivery. About one in three twin deliveries are performed through cesarean section in the United States [25]. Details on the other two cesarean sections were not given by the participants. More data would need to be collected from these participants in order to assess reasoning for emergency cesarean section.

Diet adherence challenges

Women in this sample reported challenges in regard to adhering to recommendations despite the advancement in the knowledge of completing successful pregnancies. Challenges reported included problems with coverage/reimbursement of services and resources and problems with consumption of medical foods. In this sample, 57% of pregnancies had at least one issue with coverage/reimbursement of resources and services and 71% of pregnancies reported at least one problem associated with consumption of medical food. One study by Chatterjee (2008), had 91% of pregnant women with a chronic disease report out of pocket costs [26]. Women who reported mPKU symptoms reported problems with coverage/reimbursements at a higher proportion with lack of coverage in modified low-protein foods being the most common issue. Modified low-proteins are not required to be covered by public health insurance and many private health insurance companies [27]; therefore, it makes sense why this was an issue in terms of coverage. On the contrary, women who reported no mPKU symptoms reported issues with consuming medical foods at a higher proportion than those who did report symptoms. This could be from consuming medical food more frequently in order to adhere to diet recommendations.

Drug treatments

Some of these issues and complications could be prevented with the addition of medication. One woman in this sample reported taking a sapropterin dihydrochloride drug treatment (Kuvan) while pregnant. She did not keep track of her phenylalanine levels while pregnant but did follow a phenylalanine-restricted diet. She reported no mPKU syndrome symptoms. Even though medications like sapropterin dihydrochloride have not been approved by the FDA for the use by pregnant women, other case studies have shown no additional adverse effects from women that take this during pregnancy when implemented under medical supervision and these medications can decrease mPKU syndrome outcomes [28-30]. Pegvaliase is a newer drug that does not depend on the patient's mutation as much as sapropterin dihydrochloride for efficacy. As of now, it has only been studied on pregnant PKU mice and has been shown to reduce mPKU syndrome severity in the offspring [31]. Having a drug treatment option could decrease the burden of mPKU syndrome outcomes when combined with a diet intervention with the possibility of increasing diet diversity to prevent other nutritional inadequacies.

Women who reported more than one pregnancy

In this study, out of five women who reported more than one pregnancy, three reported more than one pregnancy with a live birth outcome. All three of these women reported mPKU syndrome symptoms outcomes in their first child and none reported any adverse outcomes in their second child. Most of these women achieved phenylalanine control per guidelines and followed their prescribed diet in their first and second pregnancies. Due to the small sample size, we could not assess if the outcome improvements from first to second pregnancies are

statistically significant. However, there is a clear observational pattern in improvement of outcomes from first to second pregnancy. Again, characteristic frequencies differed the most in ultrasound abnormalities and delivery complications between first a second pregnancies. Symptoms reported in first pregnancies included low birthweight, small for gestational age and cognitive problems. Medical foods and modified-low protein foods were more consistently consumed during second pregnancies and a couple of women took supplements before their second pregnancy but not their first. Problems with consuming medical foods were again more frequent in second pregnancies. However, even though problems with coverage/reimbursements were seem more frequent in second pregnancies, the biggest issue again was lack of coverage in modified low-protein foods. More details on their diets before and during the pregnancies would need to be assessed to study other nutritional components.

Additional support for PKU women

The National PKU Alliance implemented a mPKU mentoring program in 2012 in which a mentor-mentee relationship is established between two women with PKU, one being pregnant or planning to become pregnant and the other having already experienced a successful pregnancy [32]. Women with PKU who have had successful pregnancies are free to become a mentor. Past surveys have shown that pregnant women with PKU would like to have more interaction with other PKU women [19]. However, with this resource available, 83.3% of our participants were aware of this program but were not involved. It could be possible that the 17% were not aware of the program because they completed their pregnancy before the program was implemented. More data would need to be collected to assess why women were reluctant to participate or even if they had the ability to participate at the time of their pregnancies.

Strengths and Limitations

The last report on mPKU intervention and child outcomes was published on February 2015 [33]. This study reports an update on current diet compliance, phenylalanine control, child outcomes, and challenges women might face in order to adhere to diet. Additionally, this is the first study to capture self-reported data from women with PKU who had more than one pregnancy.

Even though 91.7% of women reported to have some type of health insurance at the time of NBS Connect registration, that status might not reflect insurance status at time of pregnancy. This data was self-reported, and participants had to recall details on their pregnancies and recollection of some details might not be accurate. This survey does not capture time of pregnancy dates and whether the pregnancy was planned. The survey also does not accommodate responses for those who have had multiple child pregnancy. Other limitations include small sample size, and the possibility of selection bias (perhaps those with poor control during pregnancy were less likely to participate in the survey). Also, when women reported that they achieved control of their phe levels before pregnancy, we don't know if it was at least three months before pregnancy or immediately before pregnancy. Further statistical analyses were not able to be performed due to the small sample size.

Conclusion

Even though we were only able to carry out descriptive statistics on our sample, there are some observations that should be noted. First, even when phenylalanine control is achieved before pregnancy and pregnant PKU patients follow their prescribed diets, adverse child outcomes are still prevalent. Other nutritional inadequacies must be furthered studied on how

they can exacerbate mPKU syndrome. Second, challenges to being able to adhere to their prescribed diet are prevalent as well, specifically with costs and lack of insurance coverage being the main issues. Finally, women who have more than one pregnancy seem to have improved child health outcomes in subsequent pregnancies. Larger, prospective studies are needed to better understand these issues in this high-risk and understudied population.

References

1. Cunningham, G.C., *Phenylketonuria. Early detection, diagnosis and treatment.* Calif Med, 1966. **105**(1): p. 1-7.
2. Guthrie, R., *The origin of newborn screening.* Screening, 1992. **1**: p. 5-15.
3. Therrell, B.L., et al., *Current status of newborn screening worldwide: 2015.* Semin Perinatol, 2015. **39**(3): p. 171-87.
4. Therrell, B.L., Jr., et al., *Inborn errors of metabolism identified via newborn screening: Ten-year incidence data and costs of nutritional interventions for research agenda planning.* Mol Genet Metab, 2014. **113**(1-2): p. 14-26.
5. Clacy, A., R. Sharman, and J. McGill, *Depression, anxiety, and stress in young adults with phenylketonuria: associations with biochemistry.* J Dev Behav Pediatr, 2014. **35**(6): p. 388-91.
6. Blau, N. and N. Longo, *Alternative therapies to address the unmet medical needs of patients with phenylketonuria.* Expert Opin Pharmacother, 2015. **16**(6): p. 791-800.
7. Markham, A., *Pegvaliase: First Global Approval.* BioDrugs, 2018. **32**(4): p. 391-395.
8. Forbes, N.P., et al., *Maternal phenylketonuria.* Nurs Outlook, 1966. **14**(1): p. 40-2.
9. Resta, R., *Generation n + 1: Projected numbers of babies born to women with PKU compared to babies with PKU in the United States in 2009.* Am J Med Genet A, 2012. **158a**(5): p. 1118-23.
10. *Committee opinion no: 636: Management of women with phenylketonuria.* Obstet Gynecol, 2015. **125**(6): p. 1548-50.
11. Prick, B.W., W.C. Hop, and J.J. Duvekot, *Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: pregnancy complications and neonatal sequelae in untreated and treated pregnancies.* Am J Clin Nutr, 2012. **95**(2): p. 374-82.
12. Koch, R., F. Trefz, and S. Waisbren, *Psychosocial issues and outcomes in maternal PKU.* Mol Genet Metab, 2010. **99 Suppl 1**: p. S68-74.
13. Koch, R., et al., *The Maternal Phenylketonuria International Study: 1984-2002.* Pediatrics, 2003. **112**(6 Pt 2): p. 1523-9.
14. Matalon, K.M., P.B. Acosta, and C. Azen, *Role of nutrition in pregnancy with phenylketonuria and birth defects.* Pediatrics, 2003. **112**(6 Pt 2): p. 1534-6.
15. Widaman, K.F., *Phenylketonuria in Children and Mothers: Genes, Environments, Behavior.* Curr Dir Psychol Sci, 2009. **18**(1): p. 48.
16. Guttler, F., et al., *Impact of the phenylalanine hydroxylase gene on maternal phenylketonuria outcome.* Pediatrics, 2003. **112**(6 Pt 2): p. 1530-3.
17. Koch, R., *Maternal phenylketonuria: the importance of early control during pregnancy.* Arch Dis Child, 2005. **90**(2): p. 114-5.
18. Osara, Y., et al., *Development of newborn screening connect (NBS connect): a self-reported patient registry and its role in improvement of care for patients with inherited metabolic disorders.* Orphanet J Rare Dis, 2017. **12**(1): p. 132.
19. Brown, A.S., et al., *Barriers to successful dietary control among pregnant women with phenylketonuria.* Genet Med, 2002. **4**(2): p. 84-9.
20. Singh, R., et al., *Recommendations for the nutrition management of phenylalanine hydroxylase deficiency.* Genetics in Medicine, 2014. **6**(2): p. 121-131.
21. van Spronsen, F.J., et al., *Phenylketonuria: tyrosine supplementation in phenylalanine-restricted diets.* Am J Clin Nutr, 2001. **73**(2): p. 153-7.

22. Yano, S., et al., *Maternal Phenylketonuria International Collaborative Study revisited: evaluation of maternal nutritional risk factors besides phenylalanine for fetal congenital heart defects.* J Inherit Metab Dis, 2014. **37**(1): p. 39-42.
23. Prevention, C.f.D.C.a. *Severe maternal morbidity in the United States*. 2017; Available from: https://www.cdc.gov/reproductivehealth/maternalinfanthealthseverematernalmorbidity.html#anchor_SMM.
24. Levy, H.L., et al., *Fetal ultrasonography in maternal PKU.* Prenat Diagn, 1996. **16**(7): p. 599-604.
25. Lee, H.C., et al., *Trends in cesarean delivery for twin births in the United States: 1995-2008.* Obstet Gynecol, 2011. **118**(5): p. 1095-101.
26. Chatterjee, S., M. Kotelchuck, and U. Sambamoorthi, *Prevalence of chronic illness in pregnancy, access to care, and health care costs: implications for interconception care.* Womens Health Issues, 2008. **18**(6 Suppl): p. S107-16.
27. Wilson, K., P. Charmchi, and B. Dworetzky, *State Statutes & Regulations on Dietary Treatment of Disorders Identified Through Newborn Screening*, N.C.C.f.t.R.G.S. Collaboratives and C. Center, Editors. 2016.
28. Aldamiz-Echevarria, L., et al., *A new case of maternal phenylketonuria treated with sapropterin dihydrochloride (6R-BH4).* Gynecol Endocrinol, 2014. **30**(10): p. 691-3.
29. Feillet, F., et al., *Use of sapropterin dihydrochloride in maternal phenylketonuria. A European experience of eight cases.* J Inherit Metab Dis, 2014. **37**(5): p. 753-62.
30. Grange, D.K., et al., *Sapropterin dihydrochloride use in pregnant women with phenylketonuria: an interim report of the PKU MOMS sub-registry.* Mol Genet Metab, 2014. **112**(1): p. 9-16.
31. Zeile, W.L., et al., *Maternal phenylketonuria syndrome: studies in mice suggest a potential approach to a continuing problem.* Pediatr Res, 2018. **83**(4): p. 889-896.
32. National PKU Alliance. *The Maternal PKU Mentor Program*. 2014 April 5, 2019]; Available from: http://adultswithpku.org/Mentor-Programs/Maternal-PKU-Mentor-Program.
33. Waisbren, S.E., et al., *Maternal Phenylketonuria: Long-term Outcomes in Offspring and Post-pregnancy Maternal Characteristics.* JIMD Rep, 2015. **21**: p. 23-33.

Appendix A

*if a participant selected more than one pregnancy, questions 5.2.1-5.9.8 would be repeated in succeeding surveys as Maternal PKU Pregnancy 2, Maternal PKU Pregnancy 3, etc.

Maternal PKU Pregnancy 1 (if applicable)

Pregnancy History

5.1.1 How many pregnancies have you had?

1
2
3
4 or more

5.1.2 How many live births resulted from these pregnancies?

0
1
2
3
4 or more

Pregnancy - Social History

5.2.1 Are you aware of the NPKUA mentoring program for women with PKU who are pregnant or are new mothers?

Yes, I am aware of this program but have not been involved
Yes, I am, or have been, involved in this program
No, I have not heard of this program

5.2.2 Would you like to be involved in the NPKUA mentoring program for women with PKU who are pregnant or are new mothers?

Yes
No
Not currently pregnant or new mother
Unsure

1st Pregnancy Detail

5.3.1 When did you learn you were pregnant the FIRST time?

Less than 6 weeks after last menstrual period
6 - 8 weeks after last menstrual period
9 - 12 weeks after last menstrual period
Over 12 weeks after last menstrual period

5.3.2 What was your plasma/blood phenylalanine level at the time you learned you were pregnant?
Please select your response in either µmol/liter or mg/dL

Answers	**Answer Columns**	**Answer Columns**
Plasma/Blood phenylalanine level	µmol/liter	mg/dL
	Unknown	Unknown
	Less than 120	Less than 2
	120 - 360	2 - 6
	361 - 600	7 - 10
	601 - 840	11 - 14
	841 - 1200	15 - 20
	Over 1200	Over 20

5.3.3 Did you receive counseling about the consequences of high blood phenylalanine levels during your FIRST pregnancy?

Yes, before pregnancy
Yes, after becoming pregnant
No
Unsure

5.3.4 Did you receive counseling about your baby's risk of having PKU during your FIRST pregnancy?

Yes
No
Unsure

5.3.5 After learning you were pregnant the FIRST time, when did you contact a PKU specialist and return to clinic?

Did not contact
During 1st trimester
During 2nd trimester
During 3rd trimester
Never stopped regular care by a PKU specialist

5.3.6 How old were you when you found out you were pregnant the FIRST time?

15 years or younger
16 - 19 years
20 - 34 years
35 years or older

5.3.7 Has the baby's father had genetic testing/mutation analysis performed?

Yes
No
Unsure

5.3.8 If yes, is he willing to share his results?

Yes
No
Unsure
Not applicable

5.3.9 The father's results are:
Examples:
p.R408W
IVS10- 11G>A
p.I65T
c.1315+1G>A
EX6_IVS6del
p.N133_Q134Rfs
p.X453_453+2del

Mutation 1
Mutation 2

1st Pregnancy - Treatment/Diet

5.4.1 After learning you were pregnant the FIRST time, when did you resume the diet prescribed by your clinical team?

Before becoming pregnant
Less than 6 weeks after last menstrual period
6 - 8 weeks after last menstrual period
9 - 12 weeks after last menstrual period
Over 12 weeks after last menstrual period
Did not resume prescribed diet
Unsure

5.4.2 After learning you were pregnant the FIRST time, and you resumed a prescribed diet, when did your plasma/blood phenylalanine levels first reach the recommended range of 120-360 µmol/Liter (or 2-6 mg/dL)?

Levels were already in recommended range
Less than 6 weeks after last menstrual period
6 - 8 weeks after last menstrual period
9 - 12 weeks after last menstrual period
2nd trimester
3rd trimester
Never reached recommended range

5.4.3 What were your usual plasma/blood phenylalanine levels during your FIRST pregnancy?

Answers	Answer Columns	Answer Columns
1st Trimester	µmol/liter	mg/dL
2nd Trimester	Unknown	Less than 2
3rd Trimester	Less than 120	2 - 6
	120 - 360	7 - 10
	361 - 600	11 - 14
	601 - 840	15 - 20
	841 - 1200	Over 20
	Over 1200	

5.4.4 Check all components of the diet you followed BEFORE your FIRST pregnancy.
Note: Natural protein means foods that contain protein or phenylalanine.

Did not restrict phe or natural protein
Kuvan
Medical food (formula)
No meat, but otherwise no further phe or natural protein restriction
Phe or natural protein restriction
"Simplified Diet" (restricting high phe or high natural protein foods but allowing most fruits and vegetables)

5.4.5 Check all components of the diet you followed DURING your FIRST pregnancy.
Note: Natural protein means foods that contain protein or phenylalanine.

Did not restrict phe or natural protein
Kuvan
Medical food (formula)
No meat, but otherwise no further phe or natural protein restriction
Phe or natural protein restriction
"Simplified Diet" (restricting high phe or high natural protein foods but allowing most fruits and vegetables)

5.4.6 If you took Kuvan before or during your FIRST pregnancy, when did you start taking it?

Before pregnancy, then stopped during pregnancy
Before pregnancy, and continued during pregnancy
During pregnancy, but not before
Not applicable/did not take Kuvan

5.4.7 Which of the following best describes your usual prescribed protein or phenylalanine intake from food at the BEGINNING of your FIRST pregnancy?
Choose your answer from the column that best shows your method of measurement/counting.

Answers	**Answer Columns**	**Answer Columns**	**Answer Columns**
Prescribed Intake	Grams protein / day	Mg phe / day	Phe Exchanges
	Unknown	Unknown	Unknown
	No prescription	No prescription	No prescription
	0	0 - 50	0 - 3.5
	1	51 - 100	3.6 - 7.0
	2	101 - 150	7.1 - 10.5
	3	151 - 200	10.6 - 14.0
	4	201 - 250	14.1 - 17.5
	5	251 - 300	17.6 - 21.0
	6	301 - 350	21.1 - 24.5
	7	351 - 400	24.6 - 28.0
	8	401 - 450	28.1 - 31.5
	9	451 - 500	31.6 - 35.0
	10	501 - 550	35.1 - 38.5
	11	551 - 600	38.6 - 42.0
	12	601 - 650	42.1 - 45.5
	13	651 - 700	45.6 - 49.0
	14	701 - 750	49.1 - 52.5
	15	751 - 800	52.6 - 56.0
	16	801 - 850	56.1 - 59.5
	17	851 - 900	59.6 - 63.0
	18	901 - 950	63.1 - 66.5
	19	951 - 1000	> 66.5
	20	> 1000	
	> 20		

5.4.8 Which of the following best describes your usual prescribed protein or phenylalanine intake from food at the time of delivery (the END of your FIRST pregnancy)?

Choose your answer from the column that best shows your method of measurement/counting.

Answers	Answer Columns	Answer Columns	Answer Columns
Prescribed intake	Grams protein / day	Mg phe / day	Phe Exchanges
	Unknown	Unknown	Unknown
	No prescription	No prescription	No prescription
	0	0 - 50	0 - 3.5
	1	51 - 100	3.6 - 7.0
	2	101 - 150	7.1 - 10.5
	3	151 - 200	10.6 - 14.0
	4	201 - 250	14.1 - 17.5
	5	251 - 300	17.6 - 21.0
	6	301 - 350	21.1 - 24.5
	7	351 - 400	24.6 - 28.0
	8	401 - 450	28.1 - 31.5
	9	451 - 500	31.6 - 35.0
	10	501 - 550	35.1 - 38.5
	11	551 - 600	38.6 - 42.0
	12	601 - 650	42.1 - 45.5
	13	651 - 700	45.6 - 49.0
	14	701 - 750	49.1 - 52.5
	15	751 - 800	52.6 - 56.0
	16	801 - 850	56.1 - 59.5
	17	851 - 900	59.6 - 63.0
	18	901 - 950	63.1 - 66.5
	19	951 - 1000	Over 66.5
	20	Over 1000	
	Over 20		

5.4.9 Did your prescribed intake of natural protein (phenylalanine) increase DURING your FIRST pregnancy?

Yes, during 1st trimester
Yes, during 2nd trimester
Yes, during 3rd trimester
No
Unsure
Not applicable

5.4.10 Did you follow the diet prescribed by your clinical team DURING your FIRST pregnancy?

Yes, after learning of pregnancy (but not before conception)
Yes, during pregnancy but discontinued after pregnancy
Yes, never discontinued diet
Not before or during pregnancy
Only partially before and during pregnancy
Other
Unsure
Not applicable

5.4.11 Did you use specially modified low protein food products DURING your FIRST pregnancy?

Yes, after learning of pregnancy (but not before conception)
Yes, during pregnancy but discontinued after pregnancy
Yes, I have always used specially modified low protein foods
Not before or during pregnancy
Only partially before and during pregnancy
Other
Unsure
Not applicable

5.4.12 Did you take medical food (formula) DURING your FIRST pregnancy?

Yes, after learning of pregnancy (but not before conception)
Yes, during pregnancy but discontinued after pregnancy
Yes, I have always taken medical food
Not before or during pregnancy
Only partially before and during pregnancy
Other
Unsure
Not applicable

5.4.13 Did you take Glytactin medical food (formula) DURING your FIRST pregnancy? (Select all that apply.)

No
BetterMilk Lite De-lite
BetterMilk
Build powder stick
Complete 10
Complete 15
Restore
Restore Lite
Restore Lite powder sticks
Restore powder sticks
Ready To Drink (RTD) 10
Ready To Drink (RTD) 15
Unsure

5.4.14 Did you take PhenylAde medical food (formula) DURING your FIRST pregnancy? (Select all that apply.)

No
Essential DM, Cans
Essential DM, Pouches
GMP Mix-In, Pouches
GMP, Cans
GMP, Pouches
MTE AA Blend, Cans
MTE AA Blend, Pouches
PheBLOC Powder, LNAAs
PheBLOC Tablets, LNAAs
Phenylade 40, Pouches
Phenylade 60, Cans
Phenylade 60, Pouches
Unsure

5.4.15 Which medical food (formula) did you take DURING your FIRST pregnancy? (Select all that apply.)

Camino Pro PKU Drink
Camino Pro PKU Sorbet Stix
Lanaflex
Lophlex Powder

Lophlex LQ
NeoPhe
Periflex Advance
Periflex LQ
Phenactin Plus Ready To Drink (RTD)
Phenex-1
Phenex-2
Phenylfree 1
Phenylfree 2
Phenylfree 2 HP
Phlexy Vits
Phlexy-10
Phlexy-10 Tablets
PKU Cooler 10
PKU Cooler 15
PKU Cooler 20
PKU Easy Microtabs
PKU Express 10
PKU Express 15
PKU Express 20
PKU Gel
PKU Sphere 20
PreKUnil
XPhe Maxamum Sachets
XPhe Maxamum Cans
None of these
Unsure

5.4.16 Did you have any of the following problems taking your prescribed medical food (formula) DURING your FIRST pregnancy? (Select all that apply.)

Had no problems taking the medical food (formula)
Cost
Dislike taste
Dislike odor
Dislike texture
Dislike amount required
Heartburn of pregnancy
Inconvenience

Nausea/vomiting
Other

5.4.17 Did you take any other supplements DURING your FIRST pregnancy? (Select all that apply.)

Tyrosine
Multi vitamin and mineral supplement
Prenatal vitamin/mineral
Omega-3 Fatty Acids (DHA)
Omega-6 Fatty Acids
Vitamin D
Calcium
Iron
Folic acid
Vitamin B12
Unsure
Other
None

1st Pregnancy - Medical History

5.5.1 Were you hospitalized during your FIRST pregnancy for any reason other than for delivery?

Yes
No
Unsure

5.5.2 If yes, please provide the reason for the hospitalization. (Select all that apply.)

Not applicable
Unknown
Agoraphobia (a type of anxiety disorder in which you fear and avoid places or situations that might cause you to panic and make you feel trapped, helpless or embarrassed)

Anxiety
Blood phe levels above recommended range
Depression
Diabetes/gestational diabetes
High blood pressure/pre-eclampsia
Illness not related to PKU
Injury
Nausea related to pregnancy
Other complications of pregnancy
Other - unrelated to pregnancy

5.5.3 If you had ultrasounds during your FIRST pregnancy, were any abnormalities seen in the baby? (Select all that apply.)

Yes, the baby was small for gestational age (small for stage of pregnancy)
Yes, the baby's head was small (microcephaly)
Yes, heart defects were seen
Yes, unusual facial features were seen
No abnormalities were seen
No ultrasounds were done
Unsure
Other

5.5.4 During your FIRST pregnancy, were you exposed to tobacco, alcohol, or drugs (other than those prescribed by your doctor)?

Yes
No
Unsure

5.5.5 Did you have blood essential fatty acid analysis done just before or during the FIRST pregnancy?

Yes - Normal result
Yes - Abnormal result
No
Unsure

5.5.6 DURING your FIRST pregnancy, did you take medication for depression, anxiety, ADHD, or ADD?

Yes
No
Unsure

1st Pregnancy Medication

5.6.1 Which of these medications did you take for depression, anxiety, ADHD, or ADD during your FIRST pregnancy? (Select all that apply.)

Abilify (aripiprazole)
Adderall
Adderall XR
Anafranil (clomipramine)
Asendin (amoxapine)
Ativan (lorazepam)
Aventyl (nortriptyline)
Buspar (buspirone)
Citalopram (celexa)
Clozaril (clozapine)
Concerta
Cymbalta (duloxetine)
Daytrana
Depakote (divalproex sodium)
Desoxyn
Desyrel (trazodone)
Dexedrine (dextroamphetamine)
Dexmethylphenidate
Dextrostat
Effexor (venlafaxine)
Elavil (amitriptyline)
Emsam (selegiline)
Eskalith (lithobid lithium carbonate)
Fanapt (iloperidone)
Focalin
Focalin XR

Geodon (ziprasidone)
Haldol (haloperidol)
Invega (paliperidone)
Klonopin (clonazepam)
Lamictal (lamotrigine)
Lexapro (escitalopram)
Librium (chlordiazepoxide)
Lithium citrate
Loxitane (loxapine)
Ludiomil (maprotiline)
Luvox (fluvoxamine)
Marplan (isocarboxazid)
Mellaril (thioridazine)
Metadate CD
Metadate ER
Methylin
Methylphenidate
Moban (molindone)
Nardil (phenelzine)
Navane (thiothixene)
Neurontin (gabapentin)
Norpramin (desipramine)
Orap (pimozide)
Oxazepam
Pamelor (nortriptyline)
Parnate (tranylcypromine)
Paxil (paroxetine)
Permitil, Prolixin (fluphenazine)
Perphenazine
Pexeva (paroxetine mesylate)
Pristiq (desvenlafaxine)
Prozac (fluoxetine)
Remeron (mirtazapine)
Risperdal (risperidone)
Ritalin
Ritalin LA
Ritalin SR
Sarafem (fluoxetine hydrochloride)
Seroquel (quetiapine)
Sinequan (doxepin)
Stelazine (trifluoperazine)

Strattera (atomoxetine)
Surmontil (trimipramine)
Symbyax (fluoxetine and olanzapine)
Tegretol (carbamazepine)
Thorazine (chlorpromazine)
Tofranil (imipramine)
Tofranil-PM (imipramine pamoate)
Topamax (topiramate)
Tranxene (clorazepate dipotassium)
Trileptal (oxcarbazepine)
Valium (diazepam)
Vivactil
Vyvanse (lisdexamfetamine)
Wellbutrin (bupropion Hcl)
Xanax (alprazolam)
Zoloft (sertraline)
Zyprexa (olanzapine)
None of these
Unsure
Other (please specify)

1st Pregnancy - Insurance

5.7.1 Did you see a PKU specialist during your FIRST pregnancy? (Select all that apply.)

No
Genetic Counselor
Geneticist
Metabolic Nutritionist/Dietitian
Nurse Practitioner
Physician Assistant
Social Worker
Unsure
Other (please specify)

5.7.2 During your FIRST pregnancy, were you followed by an obstetrician specializing in high risk pregnancies?

Yes
No
Unsure

5.7.3 During your FIRST pregnancy, did you have a problem getting coverage or reimbursement for any of the following? (Select all that apply.)

Blood testing
G-tubes or other medical equipment
Genetic testing/mutation analysis
High risk obstetrics care
Kuvan (BH4)
Lab work other than blood phe testing
Large neutral amino acids (LNAA)
Medical food (formula)
PKU specialist clinic visits
Specially modified low protein foods
No, did not have this problem
Unsure

1st Pregnancy Outcome

5.8.1 What was the outcome of your FIRST pregnancy?

Live birth
Miscarriage
Still birth
Termination

1st Pregnancy - Postpartum

5.9.1 When was your baby from your FIRST pregnancy born?

Full term (40 weeks)
36 - 39 weeks
32 - 35 weeks
Less than 32 weeks

5.9.2 Did you have any complications during labor or during delivery of your FIRST pregnancy? (Select all that apply.)

No complications
Emergency C-section
Fetal distress
Gestational diabetes
HELLP syndrome
Placenta previa
Pre-eclampsia/eclampsia (high blood pressure)
Other (please specify)

5.9.3 At birth, was your baby from your FIRST pregnancy within normal ranges for length, weight, head circumference and APGAR scores? (Select all that apply.)

Yes, normal range for all birth parameters
No, low birth weight
No, small for gestational age (low length and weight)
No, small head circumference (microcephaly)
No, low APGAR scores
Unknown

5.9.4 Were any birth defects noted in your baby from your FIRST pregnancy after delivery? (Select all that apply.)

No birth defects
Cleft lip or palate
Heart defect
Small head circumference (microcephaly)
Unusual facial features
Other

5.9.5 Check all components of the diet you are following now AFTER your FIRST pregnancy.
Note: Natural protein means foods that contain protein or phenylalanine.

Did not restrict phe or natural protein
Kuvan
Medical food (formula)
No meat, but otherwise no further phe or natural protein restriction
Phe or natural protein restriction
"Simplified Diet" (restricting high phe or high natural protein foods but allowing most fruits and vegetables)

5.9.6 Are you now, or did you breastfeed your baby from your FIRST pregnancy?

Yes
No
Partially (combination of breast milk and infant formula)

5.9.7 Does your baby from your FIRST pregnancy have PKU?

Yes
No
Unsure

5.9.8 As your baby from your FIRST pregnancy has grown, are there any developmental problems? (Select all that apply.)

No, my child has no developmental problems
Yes, my child was delayed in sitting, crawling or walking (motor skill delay)
Yes, my child was delayed in speaking (early cognitive delay)
Yes, my child has difficulty learning
Yes, my child has behavior problems
Yes, my child has a diagnosis of ADD or ADHD
Unsure