

# The First Study of Successful Pregnancies in Chinese patients with Phenylketonuria

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## Research article

**Keywords:** Maternal phenylketonuria, Dietary treatment, Pregnancy, Offspring outcomes, sapropterin dihydrochloride, BH4

**Posted Date:** August 4th, 2019

**DOI:** <https://doi.org/10.21203/rs.2.12397/v1>

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**Version of Record:** A version of this preprint was published at BMC Pregnancy and Childbirth on April 28th, 2020. See the published version at <https://doi.org/10.1186/s12884-020-02941-9>.

## Abstract

Since the inception of newborn screening programs in China in the 1990s, pregnancy among patients with inherited, metabolic disorders has become more common. This study explores the management and outcomes of planned, full-term pregnancies in patients with phenylketonuria (PKU). Married patients from 2012 to 2017 were enrolled to receive prenatal counseling and their partners were screened for heterozygous genes of phenylalanine hydroxylase (PAH). Daily intake of phenylalanine (Phe), blood Phe, obstetrical data, and offspring outcomes (e.g. developmental quotients [DQs]) were recorded. None of the paternal parents were heterozygous for PAH. A total of 6 neonates were successfully delivered, 5 males and 1 female. The mean  $\pm$ SD (range) age of the mother at delivery was 26.3 $\pm$ 4.7 (range:21.1-32.5) years old. The mean duration of Phe control before pregnancy was 5.5 $\pm$ 1.3 (range:3.1-6.5) months. During pregnancy, the proportion of time during which blood Phe concentrations were within the clinically-recommended target range (120–360  $\mu$ mol/L) was 63.2-83.5%. For the two babies born to patients with <70% of their pregnancy within the blood Phe target range, both birth weight and DQs were lower than the other four births. This is the first report of women in China with PKU who successfully gave birth to clinically healthy babies. Infant outcomes were related to maternal blood Phe management prior to and during pregnancy. In maternal PKU patients with poor compliance to dietary treatment, sapropterin dihydrochloride (6R-BH<sub>4</sub>) may be an option to improve the management of blood Phe levels.

## Introduction

Phenylketonuria (PKU) is a rare, inherited, metabolic disease, usually caused by a deficiency of phenylalanine hydroxylase (PAH), causing elevated blood phenylalanine (Phe) levels (hyperphenylalaninemia; HPA) which can lead to mental retardation and neuropsychological abnormalities (Blau 2010). Early diagnosis and adequate metabolic management of blood Phe levels greatly improved the prognosis and quality of life of PKU patients (Blau 2010, Guthrie 1963). Hence, the newborn screening (NBS) program for detection of HPA was first introduced in the 1960s in western countries and has been available in China since 1990's (Chen 1983, Shi 2012), when a pilot plan was implemented (Mei 2013). In the past 30 years, a number of Chinese patients with PKU have benefitted from disease management and resulted in nearly normal intellectual and physical development (Shen 2016). Some of the female PKU patients have now reached childbearing age. However, due to cultural issues, marriage is less common in female PKU patients in China. Pregnant patients with PKU are associated with an increased risk of complications, as elevated Phe in pregnancy is associated with teratogenic effects and poor birth outcomes (Lenke 1980, Koch 2003). There is high risk of microcephaly, facial dysmorphism, mental retardation, and intrauterine and/or postnatal growth restriction. More importantly, elevated maternal blood Phe is particularly related to the embryogenesis of heart defects (Lenke 1980). These effects may be prevented with proper nutritional supplements and management of blood Phe levels prior to and throughout pregnancy (Widaman 2003, Langendonk 2012). The suggested target range for blood Phe is 120–360  $\mu$ mol/L, as established by the Maternal Phenylketonuria Collaborative Study (MPKUCS) (Koch 2003, Andersson 2013). Moreover, blood Phe variability within that range should also be avoided in order to obtain optimal offspring outcomes (Widaman 2003, Maillot 2008).

There is little research in the literature to describe pregnancy outcomes to help guide physicians and obstetricians in the management of pregnant women with rare diseases in China. One patient of methylmalonic aciduria (MMA) and homocystinuria, cblC type, in China has been reported to deliver a clinically healthy child (Liu 2015). Herein, we describe the pregnancy, delivery, and offspring outcomes for ten patients with PKU in China, along an evaluation of the effect of the timing and duration of diet, routine nutritional assessment, and other medical interventions.

## Patients And Methods

### Patients and pregnancy

All PKU patients married between 2012 and 2017 were recalled to receive prenatal counseling and screening for heterozygous genes of PAH in their partners. In order to obtain the best pregnancy outcomes, patients received education and instructions on the calculation of Phe intake, which would help them to maintain blood Phe within the clinically-acceptable blood Phe target range (120–360  $\mu$ mol/L) while sustaining adequate nutrition for the developing fetus. Gestational variables included the timing of the introduction of the Phe-restricted diet, weight gain, gestational age, pregnancy complications, and blood Phe concentrations (both

pre-conception and during pregnancy). The study protocol and data collection instruments were approved by the ethical review boards of China-Japan Friendship Hospital. A signed informed consent was obtained prior to the interview.

## Visits and/or interviews

Mothers were interviewed in person (if patients were in or near Beijing), by telephone, WeChat (a popular social media platform in China), or referred to local centers (if outside Beijing). Their current diets and other medical concerns were discussed during the interviews. Usual care consisted of bi-weekly to monthly communication with a metabolic nutritionist to review diet, weight and weight gain, dietary Phe intake calculations, and calorie counts. Dietary changes were based on the results of metabolic control, which could be derived from fasting plasma Phe concentrations and weight gain.

## Fasting plasma Phe concentration

Fasting blood Phe concentrations were suggested to be measured weekly at their local hospital prior to conception and twice a week during pregnancy; all data were recorded in their pregnancy diaries. Blood Phe was measured with high-pressure liquid chromatography (HPLC), using tandem mass spectrometry. An overall review of all those results was conducted in order to assess the mothers' adherence to diet during pregnancy.

## Nutrition

Throughout their planned conception and pregnancy, patients were asked to keep a daily record of all food and beverages consumed, from which synthetic protein, Phe, calorie, and fluid intake could be derived. Changes in body weight were also recorded. Laboratory examinations included plasma amino acids, hemoglobin and hematocrit, prealbumin, and iron. A nutritionist reviewed the data and gave advice to the maternal patients every two weeks.

## Offspring outcomes

Offspring outcome variables at birth consisted of gender, weight, length, and occipitofrontal circumference (OFC). The physical and neuropsychometric assessments for offspring were carried out routinely after birth. Intellectual assessments—development quotient (DQ) were carried out using the Gesell Child Developmental Age Scale (Conoley 1995).

## Statistical analysis

Descriptive analysis of demographic characteristics was conducted with calculation of means and standard deviations for continuous variables, and proportions for categorical variables. Data was expressed as mean  $\pm$ SD unless indicated otherwise.

## Results

### Patients' demographics

As one of the national centers in China, our unit has diagnosed and treated more than 2,930 patients with HPAs since 1984. By the end of 2017, a total of 172 female patients reached 20 years of age, but only 10 of them were remarried. Four of 10 were diagnosed by NBS, 5 were diagnosed symptomatically within their 1st year of life, and one was diagnosed at 26 years of age after delivering a baby with a congenital anomaly. The patients originated from Shanxi, Tianjin, Hebei, Shandong provinces and Beijing municipality and were all of Han nationality. None of their partners carried PAH heterozygous genes. In terms of educational attainment, two of the mothers graduated from middle school, three graduated from high school, and one attended college. The sample demographics are listed in Table 1.

## Pregnancy, delivery and infant outcomes

By the end of 2017, six of the 10 women had become pregnant: 4 of them had 1 pregnancy, one had 2 pregnancies, and one had 3 pregnancies. The mean age at pregnancy was  $26.3 \pm 4.7$  years and all patients had initiated a Phe-restricted diet during pre-conception. The condition during pregnancy was generally normal without anemia, gestational hypertension, or other severe complications (Table 2). Five of the deliveries were vaginal, while 1 was delivered by cesarean section. The mean blood Phe levels were:  $478.3 \pm 181.6 \mu\text{mol/L}$ ,  $193.7 \pm 84.8 \mu\text{mol/L}$ , and  $151.4 \pm 96.9 \mu\text{mol/L}$  for the first, second, and third trimester, respectively. Maternal weight change was  $11.5 \pm 2.6$  ( $9.2-15.0$ ) kg. Hemoglobin and hematocrit values were normal.

The six maternal patients with PKU successfully delivered 6 babies, 5 males and 1 female. The mean gestation period was  $38.2 \pm 0.6$  ( $37.4-39.1$ ) wks. Table 3 summarizes the effect of treatment in terms of birth weight, length, and OFC-B. The mean birth weight, mean birth length and mean OFC-B were  $2888.3 \pm 388.1$  (range:  $2350.0-3300.0$ ) g,  $49.7 \pm 2.3$  (range:  $46.6-53.0$ ) cm, and  $33.4 \pm 1.1$  (range:  $31.5-34.5$ ) cm respectively. All offspring were full-term babies with no congenital heart defects or other severe malformations (Table 3). Mean blood Phe levels were maintained within the targeted range for the 3rd trimester of pregnancy (Fig. 1).

*Patient 1:* Patient No. 1 was from Tianjin and had mild PKU. She was the first patient from our clinic who married. The mutation was c.1238G>C(p.R413P)/c.1238G>C(p.R413P). She was on a Phe-restricted diet 3.1 months prior to becoming pregnant. She learned how to count dietary protein and Phe intake from each meal during the 3 months and wrote 3 diaries during pregnancy. Baseline blood Phe was  $489.7 \mu\text{mol/L}$ . She lived in Tianjin city and came to the clinic every 2 weeks. Blood Phe levels were mostly stable during all 3 trimesters of her pregnancy. The mean proportion of blood Phe levels per trimester that were within the recommended range were 55.6%, 73.9% and 95.5% during the 1st trimester, 2nd trimester and 3rd trimester, respectively. After a full-term pregnancy, she gave birth to a healthy, male baby weighing 3050g and measuring 52cm in length. The infant was well developed physically and mentally, the latest DQ was 88.2.

*Patient 2:* Patient No. 2 came from Shanxi province. Her mutation was c.728G>A(p.R243Q)/c.838G>A(p.E280K). She initiated dietary treatment 5.0 months prior to becoming pregnant. Baseline blood Phe was  $523.9 \mu\text{mol/L}$ . Even though dietary management education was provided, she and her family didn't fully believe in it during the first period of pregnancy. Because of the financial burden, she didn't have frequent blood examinations at hospital visits. This patient had high blood Phe concentrations during her first trimester ( $605.4-908.1 \mu\text{mol/L}$  for 6 weeks) which resulted in a dramatic fluctuation of blood Phe when comparing the first to the third trimester. The proportion of her blood Phe levels per trimester that were within the recommended range were 36.2%, 66.3% and 92.7%, respectively. She delivered a male baby on 38<sup>+1</sup>W with a low birth weight: 2350g, birth length: 46.6cm, and a remarkably smaller OFC-B 31.5cm. The infant had mild language and fine motor development delays and a DQ of 80.6 during the last interview at nearly 3 years of age.

*Patient 3:* Patient No. 3 was late diagnosed at 28 years old, when she delivered a baby with cardiac anomalies of **Tetralogy of Fallot**. Her initial blood Phe was  $1278.0 \mu\text{mol/L}$  with the mutation c.728G>A(p.R243Q)/c.728G>A(p.R243Q). She lived in rural area of Hebei Province and had exhibited yellow hair color from childhood. She had 8 years of education, but failed to graduate from middle school. She could communicate on simple daily issues, but the Wechsler Adult Intelligence Scale (WAIS) indicated moderate mental retardation. She married at 26 years of age. Her second pregnancy was electively aborted due to lack of blood Phe control. She came to our hospital for genetic counseling and started dietary treatment 6 months before her third pregnancy. Baseline blood Phe was  $622.1 \mu\text{mol/L}$ . In order to decrease the Phe level quickly, she kept a very strict diet and limited protein intake. The fetus demonstrated intrauterine growth restriction because of the poor nutritional status in the first trimester. After correction on the second and trimester, she delivered a male baby on 38<sup>+4</sup>, birth weight: 2480g. The baby exhibited feeding difficulties in the first six months and the weight was 6950g at 1 year of age. After correction of feeding pattern, he reached 9000g at 19 months. The latest DQ was 85.7.

*Patient 4:* Patient No. 4 was a native of Beijing and baseline blood Phe was  $460.3 \mu\text{mol/L}$ . Her mutation was c.1222C>T(R408W)/c.975C>G(Y325X). She was the only one of the patients who attended college. She married at 29 years of age and implemented dietary treatment immediately after marriage. She balanced nutrition and Phe level very during frequent inquiries and visits with a specialist in obstetrics and metabolic diseases. Blood Phe levels were within the recommended range 87.5% of the time during

pregnancy. A healthy female baby was delivered on 39+1Wks by Cesarean section. The infant was followed-up every month during the first six months and every 3 months thereafter. She demonstrated normal growth and development milestones and obtained a DQ score of 98.8.

*Patient 5:* The first pregnancy of patient 5 was naturally aborted because of the arrested fetal development at 9 weeks. She came from Shandong Province. She had a second pregnancy after dietary treatment for 5.9 months. Her mutation was c.1238G>C(p.R413P)/c.782G>A(p.R261Q). She lived in Jinan city where there is a local metabolic center. She visited a local specialist every 1–2 weeks and visited our clinic every 1–2 months. The whole pregnancy went smoothly and she maintained 80.2% of blood Phe levels within the recommended range. She gave birth to a male baby on 37+3Wks. The infant was feeding well and growth data was around 60% percentile from birth to 1 year old. The latest DQ was 92.5.

*Patient 6:* Patient 6 had maternal PKU and was from Shandong province. Her gene mutation was c.1068C>A(p.Y356X)/c.1045T>G(p.S349A). She was one of the patients from our clinic who married the latest. She was on Phe-restricted diets 6.5 months prior to becoming pregnant. Baseline Phe was 348.6 μmol/L. She received consultations from a local center and our clinic. Blood Phe levels were controlled very well, which were maintained within the recommended range 89.5% of the time, and was the most stable patient at our clinic. She gave birth to a healthy male baby on 37+6Wks. The infant physically developed well with 8.9 kg of weight and 69.7 cm of the length at 7.3 months of age. The latest DQ was 96.2.

## Discussion

Even though several reports on maternal management of inherited diseases in western countries have been published (Andersson 2013, Aubard 2000, Levy 2003), a new group of patients in China, identified by NBS with HPA, have just reached child-bearing age. Maternal PKU is one of the prominent examples. To our knowledge, this study is the first report of a group of pregnant women with PKU and their offspring outcomes in China. Their lessons of management are of great importance for the future.

The Maternal PKU Collaborative Study reported microcephaly, facial dysmorphism, congenital heart defects, and intrauterine and postnatal growth retardation in the offspring of women with PKU (Lenke 1980, Koch 2003). Indeed, Patient No. 3 was first diagnosed with PKU after she gave birth to a baby with cardiac anomalies of **Tetralogy of Fallot** following a pregnancy with no dietary management of blood Phe levels. These complications can be prevented if a low-phenylalanine diet is maintained prior to, and throughout, pregnancy.

In this study, six maternal patients started a Phe-restricted diet 3.1–6.5 months before conception and successfully delivered 6 healthy babies, demonstrating that metabolic control during pregnancy is beneficial. Previous papers have discussed the effect of variations in blood Phe concentrations on offspring outcomes. They found strong negative correlations with IQ scores at 4, 8 and 14 years and variability of the Phe concentrations, revealing that not only should the blood Phe concentrations be kept within the suggested range, they should be kept as consistent as possible (Maillot 2008). Our study also demonstrated the similar trend of the DQ with variation of blood Phe levels. Patients No. 2 and No. 3, whose proportion of time within the target range lower than 70%, had progeny with lower DQs than the four other offspring.

Although patients with HPA conditions were strongly encouraged to seek frequent counseling from our metabolic nutritionist to achieve optimum metabolic control, there are still women who live in rural areas who failed to come to clinic or were unable to follow-up in a timely manner, such as patients No. 2 and Patient No. 3. MPKUCS recommended twice-weekly blood Phe measurements before conception and thrice-weekly measurements afterwards (Koch 2003, Widaman 2003). However, we are aware that Patient No. 3 was monitored every 2–3 weeks in the second trimester and Patient No. 2 was examined as infrequently as monthly during the whole conception period, despite considerable fluctuations in blood Phe concentrations. The frequency of monitoring blood Phe levels or interview visits was clearly inadequate, which resulted in a high fluctuation of blood Phe levels and impairment to the offspring. The birth weight of the two babies born to these subjects was lower than 2500g, 2350g and 2480g, respectively. Patient No. 3 also presented postnatal feeding difficulties and growth retardation in the first year, which had been reported by the MPKUCS (Maillot 2008, Platt 2000). Upon investigation, we found the reasons for inadequate monitoring were multifactorial: (1) a multi-disciplinary team comprised of a biochemical geneticist and a nutritionist, are only available in large cities while local hospitals are short of these experienced professionals, and patients cannot receive immediate advice at nearby health

centers; (2) Besides pregnant patients' adherence to metabolic control, the ability of the mothers with PKU to balance dietary treatment with sufficient prenatal nutrition was of great concern in this study. In order to keep the Phe concentration within the normal range, patient No.3 was too strict with her diet, which resulted in heavy hyperemesis gravidarum and intrauterine growth restriction within the first trimester. She had weight loss of 5kg during the first trimester and failed to increase weight until the third trimester; (3) Financial burden of pregnancy. As we published before (Wang 2017), patients suffer a heavy financial burden in many provinces where there are no government reimbursement policies. The cost of frequent visits and examinations may deter regular follow-up (e.g. patient No.2); and (4) In maternal PKU patients with poor compliance to dietary treatment, sapropterin dihydrochloride (6R-BH<sub>4</sub>, Kuvan), may be an option to improve the management of blood Phe levels. However, the cost of sapropterin dihydrochloride was prohibitive to all 6 patients (and there are no approved indications for use during pregnancy), even though some of them had poor compliance to dietary treatment (Moseley 2009, Aldámiz-Echevarría 2014, Feillet 2017).

These results indicate that greater effort must be applied to assist women with PKU to remain on the diet during their reproductive years. A national association like MCPKUS and national guideline to optimize maternal PKU care are urgently needed in order to share experience and best practices between hospitals and practitioners. The goal of this information sharing is to increase awareness of metabolic conditions and factors on offspring outcomes. Rural PKU patients may be able to receive counseling from experienced geneticists and nutritionists over the web. More options for blood Phe control (such as 6R-BH<sub>4</sub>) should be considered and be available in clinic especially for the patients with poor compliance to dietary treatment (Aldámiz-Echevarría 2014, Feillet 2017).

## Declarations

## Acknowledgments

We thank all of women with PKU, their partners, and the children for their involvement in our Maternal PKU Program and provided personal information. We thank the staff of the newborn screening centers that were involved in the recruitment and data collection processes. We want to acknowledge the local centers of PKU. We also extend our sincere thanks to BioMarin Pharmacy Company for extensive supports and fruitful discussions with the manuscript.

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## Tables

### Table 1 Sample Demographics

Maternal patients with PKU(n=6)	Mean±SD, range or n (%)
Age at pregnancy(Yrs)	26.3±4.7
Educational attainments (Yrs)	12.1±2.1
Marital status	All Yes
Nationality	All Han
Initial Phe concentration(μmol/L)	1095.8-2342.9
Classification	Classical PKU(5) Mild PKU (1)
Diet pre- or after conception	All pre-conception

**Table 2 Issues to be considered when a woman with an inherited disorder of metabolism plans a pregnancy**

Patient No.	Initial Phe Conc.	Age at pregnancy(Yrs)	Treatment before pregnancy(months)	The proportion of time(%)	Previous Negative events *	Mode of delivery	Weight gain During pregnancy	origin
1	1089.7	28.3	3.1	75.0	1	vaginal delivery	12.0	Tianjin
2	1210.8	21.1	5.0	66.7	0	vaginal delivery	9.2	Shanxi
3	1278.0	32.5	6.0	35.1	2 negative events*	vaginal delivery	9.5	Hebei
4	1755.7	30.2	6.3	87.5	0	Cesarean section	9.3	Beijing
5	1937.3	21.6	5.9	80.2	1	vaginal delivery	15.0	Shandong
6	1574.0	23.9	6.5	78.7	0	vaginal delivery	14.2	Shandong

\*the first pregnancy was natural aborted, the second pregnancy was elected to terminate because of no control of blood Phe.

☒ (by telephone or we-chat)

**Table 3 Offspring demographics and Developmental Quotients (DQs)**

Offspring No.	Gestational age	Age (months)	Gender	Birth weight	Birth Length	Head circumference	DQs
1	38+2	38.2	male	3050	50.2	34.0	84.2
2	38+1	34.0	male	2350	46.6	31.5	76.8
3	38+4	19.3	female	2480	48.0	33.0	79.0
4	39+1	14.7	female	2950	48.9	33.3	92.5
5	37+3	14.5	male	3300	51.5	34.5	86.3
6	37+6	7.3	male	3200	53.0	34.0	90.2

# Figures

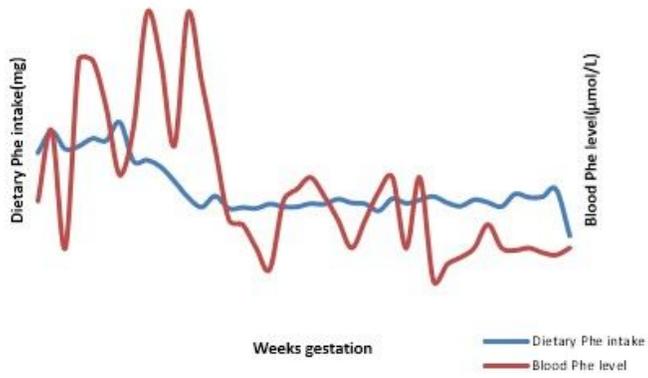


Figure 1

Blood Phe level and dietary Phe intake in a pregnant woman with well-controlled PKU.