

# Maternal Phenylketonuria and Tetrahydrobiopterin



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## INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive disorder of amino acid metabolism characterized by elevated phenylalanine (Phe) levels, which are teratogenic. In the maternal PKU syndrome, fetuses may be exposed to elevated Phe levels during development. Although the offspring usually do not suffer from PKU after birth, children born to mothers with untreated PKU generally suffer from microcephaly, developmental delay, and occasionally congenital heart disease. The Maternal PKU Collaborative Study found that maternal blood Phe levels >600  $\mu\text{mol/L}$  are often associated with poor fetal outcomes, while levels of 120–360  $\mu\text{mol/L}$  throughout gestation are associated with normal or near-normal outcomes. In practice, a Phe-restricted diet alone may not always produce sufficiently low Phe levels to promote normal fetal development. Tetrahydrobiopterin (6R-BH<sub>4</sub>) has been approved for use in the treatment of 6R-BH<sub>4</sub>-responsive PKU and has been designated as Pregnancy Category C. Several case reports exist for the successful use of 6R-BH<sub>4</sub> in pregnant women. Thus the safety and efficacy of 6R-BH<sub>4</sub> for pregnant PKU patients requires further study. A single treatment center provided 6R-BH<sub>4</sub> to expecting mothers with PKU, and here we detail the use of individualized 6R-BH<sub>4</sub> therapy in 5 new cases of PKU patients during pregnancy, providing additional support for the use of 6R-BH<sub>4</sub> with a Phe-restricted diet.

## OBJECTIVE

The objective of this study was to evaluate the safety and efficacy of 6R-BH<sub>4</sub> treatment for pregnant women with PKU in the prevention of maternal PKU syndrome.

## METHODS

6R-BH<sub>4</sub> (Kuvan [N=2]; Schirk's formulation [N=3]) was used with a Phe-restricted diet in 5 pregnant women with PKU. Blood Phe levels were monitored during pregnancy and 6R-BH<sub>4</sub> dosage was adjusted accordingly (Table 1). Head circumference, length, and weight were measured at birth. Infants were also screened for hyperphenylalaninemia (HPA) and followed for neurological or cardiac sequelae of maternal PKU syndrome.

## RESULTS

Blood Phe was maintained close to recommended levels during pregnancy (Figure 1a–e; Table 2). Five full-term infants were delivered (Table 3) without evidence of neurological or cardiac problems associated with maternal PKU. All infants were HPA-negative at screening.

## DISCUSSION

A Phe-restricted diet supplemented with 6R-BH<sub>4</sub> can be useful in lowering blood Phe to recommended levels in PKU patients who are 6R-BH<sub>4</sub>-responsive. In all 5 cases presented in this report, individualizing the dose of oral 6R-BH<sub>4</sub> treatment was used safely during pregnancy and resulted in control of blood Phe levels, most notably in the third trimester (Table 2). Furthermore, each of these women successfully delivered infants without microcephaly, cardiac or neurological problems, or any other evidence of Phe toxicity associated with maternal PKU (Table 3). Two of the pregnancies (TC2 and JF1) were complicated by severe nausea and vomiting, while CJ2, MK, and VW did not experience any of these symptoms. This suggests that the nausea and vomiting experienced by TC2 and JF1 may have been related to the patient's pregnancy as opposed to the treatment with 6R-BH<sub>4</sub>. Post-natal developmental assessments at regular time intervals are warranted to confirm healthy neurological development and can be performed as the infants age.

## CONCLUSION

A Phe-restricted diet supplemented with 6R-BH<sub>4</sub> was successful in maintaining blood Phe at recommended levels during pregnancy without detrimental effect on development of the unborn child. Further observations with larger sample sizes such as described in the PKU Demographics and Outcomes Registry (PKUDOS) will clarify the degree of benefit and safety of 6R-BH<sub>4</sub> in this patient population.

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Figure 1a: BH<sub>4</sub> dosing regimen with corresponding blood Phe levels in pregnant PKU subject (CJ2)

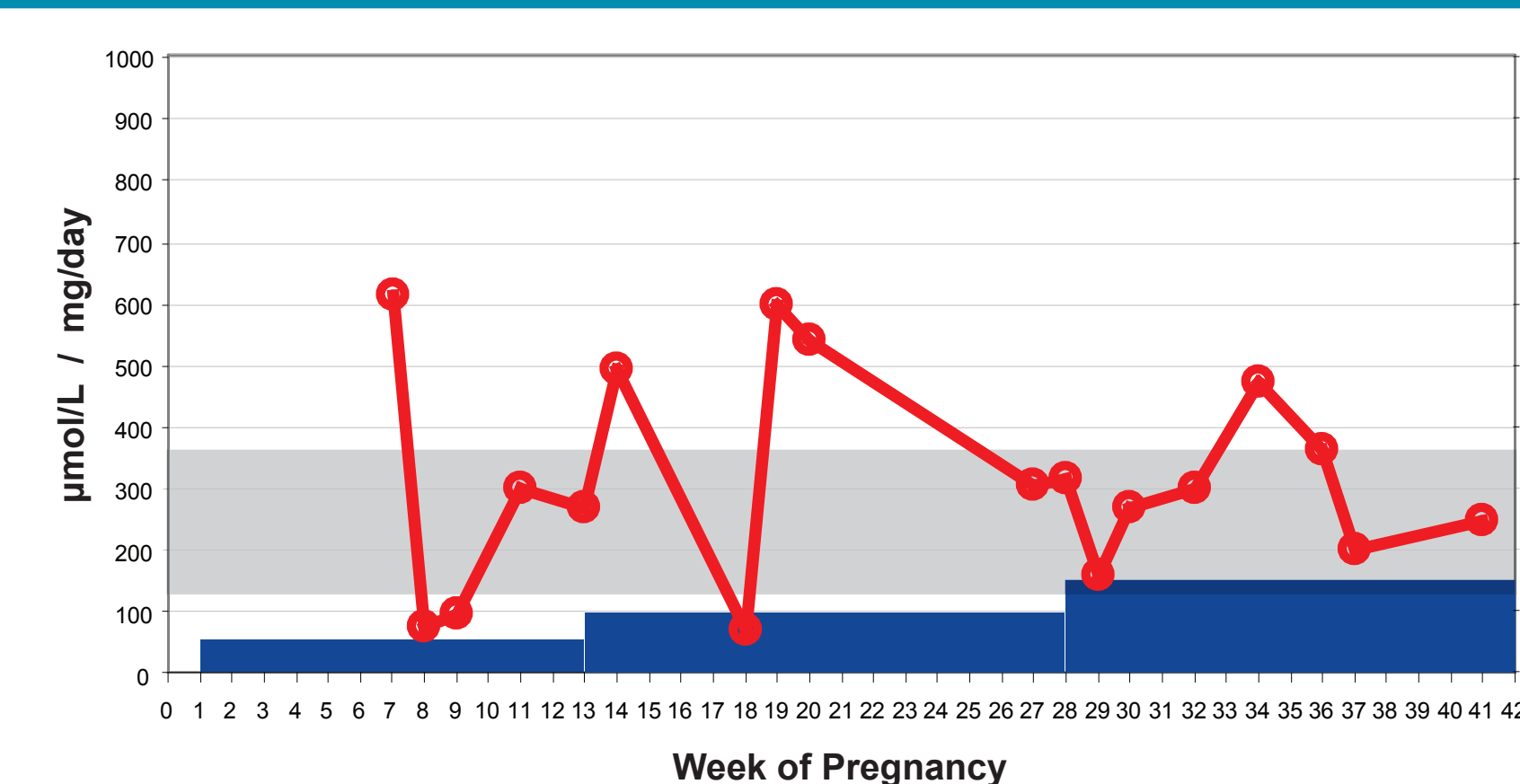


Figure 1b: BH<sub>4</sub> dosing regimen with corresponding blood Phe levels in pregnant PKU subject (TC2)

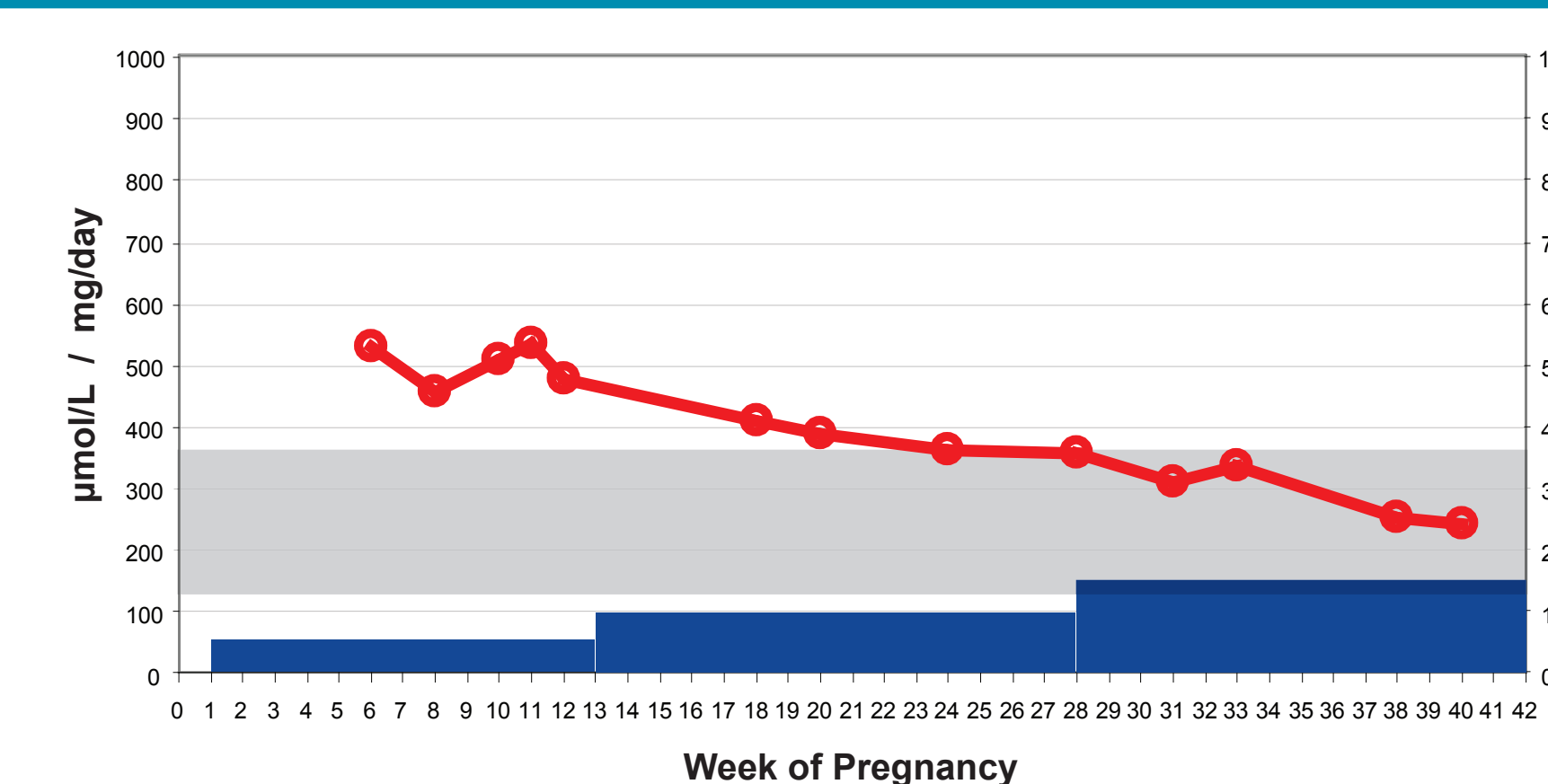


Figure 1c: BH<sub>4</sub> dosing regimen with corresponding blood Phe levels in pregnant PKU subject (JF1)

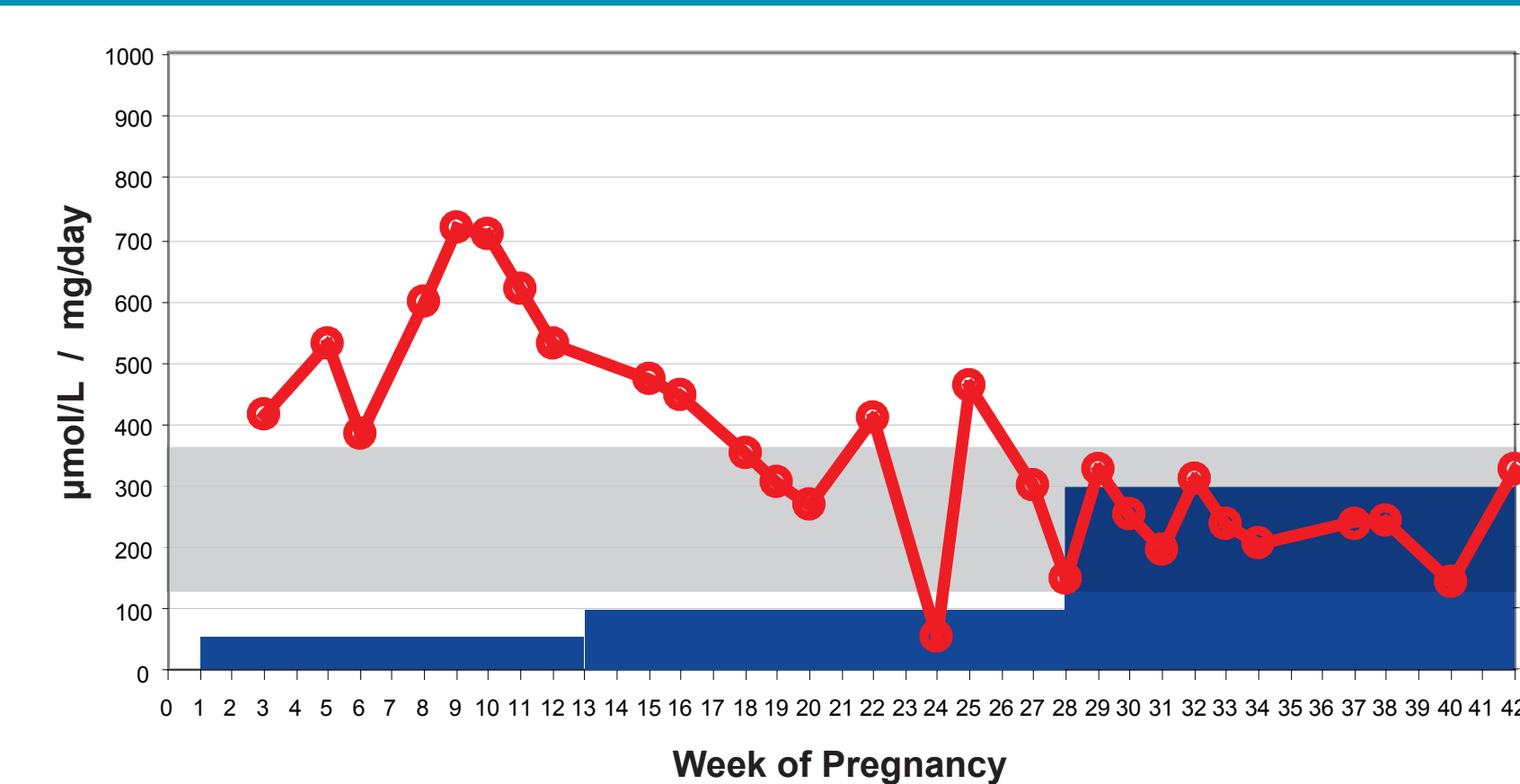


Figure 1d: BH<sub>4</sub> dosing regimen with corresponding blood Phe levels in pregnant PKU subject (MK)

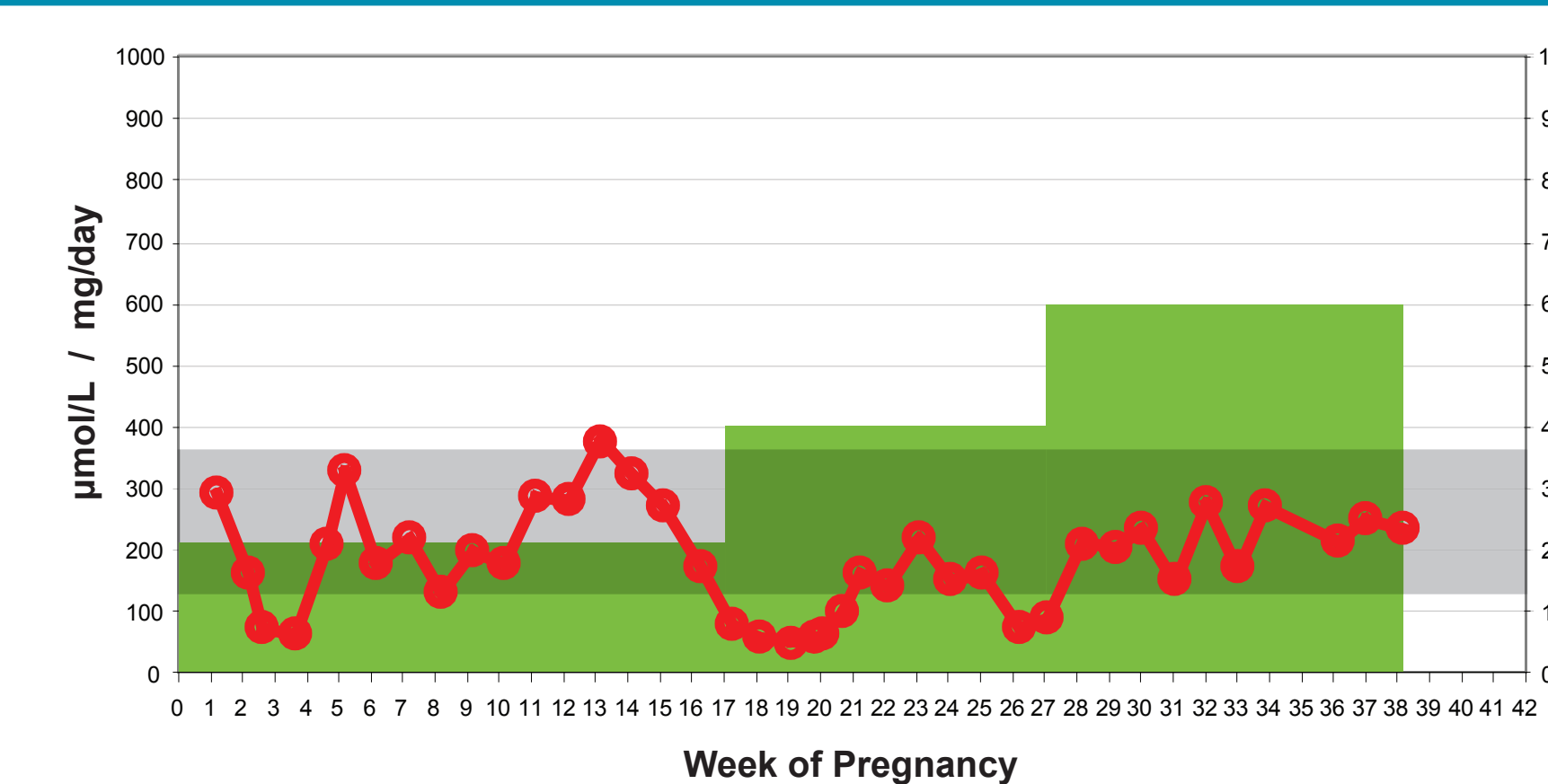


Figure 1e: BH<sub>4</sub> dosing regimen with corresponding blood Phe levels in pregnant PKU subject (VW)

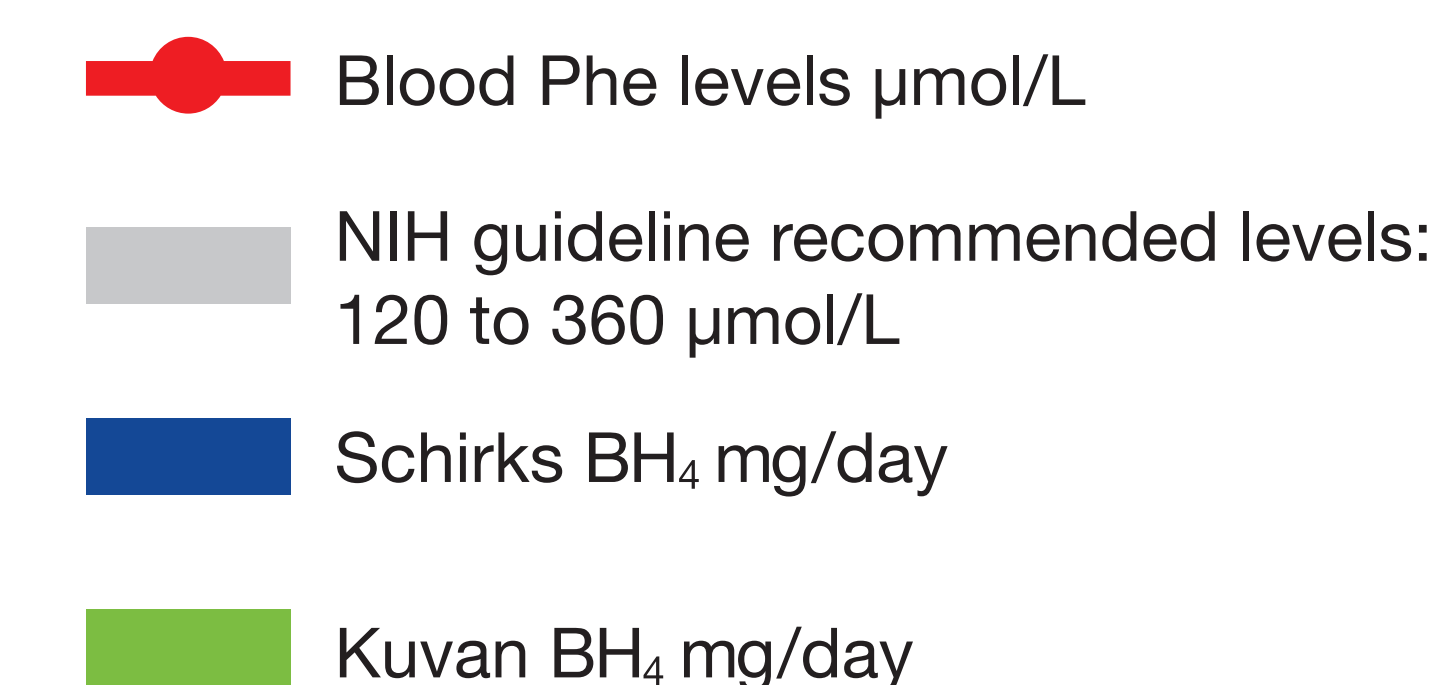
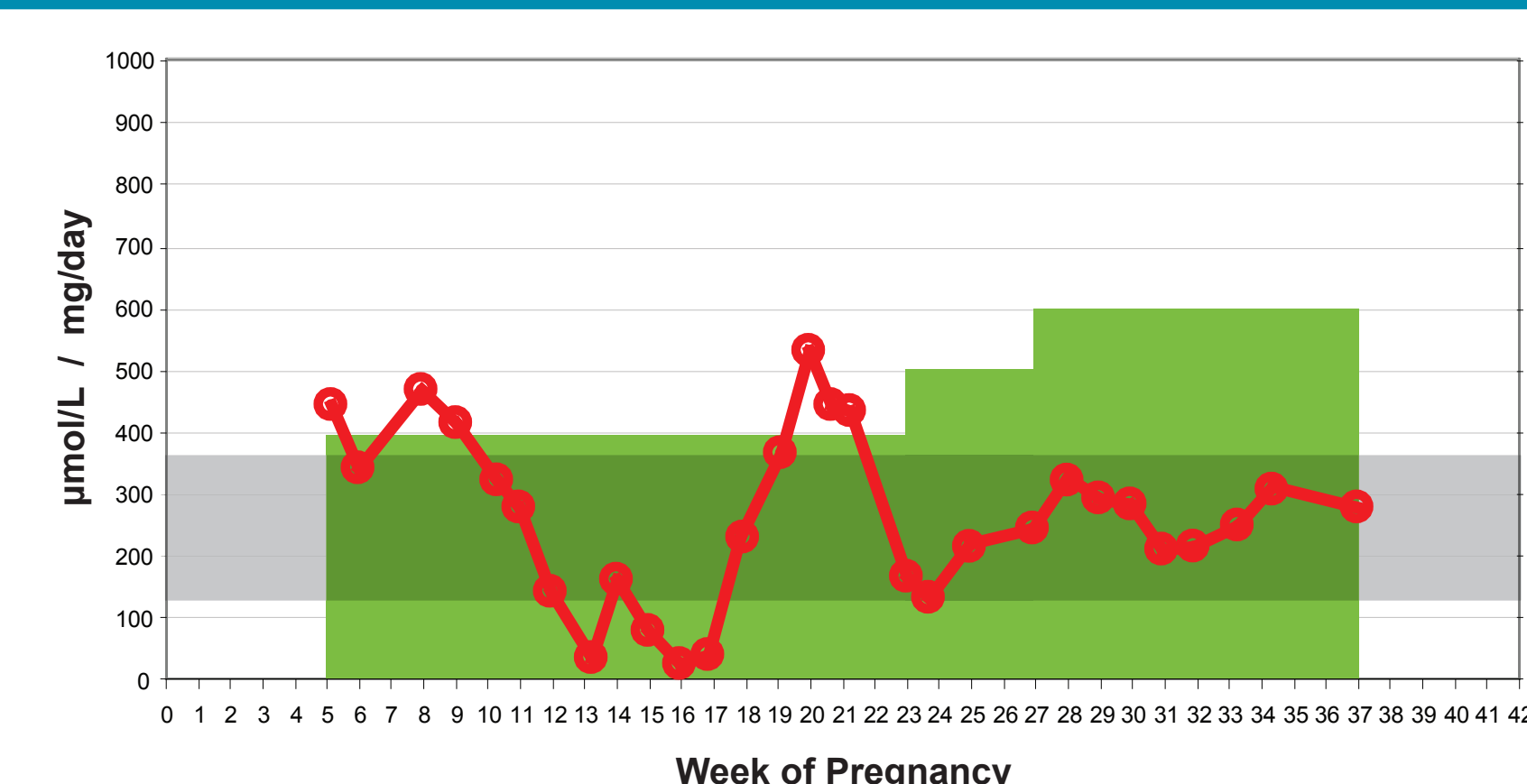


Table 1: 6R-BH<sub>4</sub> treatment information

Mother's initials/ Pregnancy number	CJ2	TC2	JF1	MK	VW
6R-BH <sub>4</sub> start date	Patient taking 6R-BH <sub>4</sub> prior to conception	6R-BH <sub>4</sub> started at 6 weeks of pregnancy	6R-BH <sub>4</sub> started at 4 weeks of pregnancy	Patient taking 6R-BH <sub>4</sub> prior to conception	6R-BH <sub>4</sub> started at 5 weeks of pregnancy
6R-BH <sub>4</sub> dose, 1 <sup>st</sup> trimester	50 mg/day	50 mg/day	50 mg/day	200 mg/day	400 mg/day
6R-BH <sub>4</sub> , 2 <sup>nd</sup> trimester	100 mg/day	100 mg/day	100 mg/day	400 mg/day (started week 17) 600 mg/day (started week 27)	500 mg/day (started week 23) 600 mg/day (started week 27)
6R-BH <sub>4</sub> , 3 <sup>rd</sup> trimester	150 mg/day	150 mg/day	300 mg/day	600 mg/day	600 mg/day

Table 2: Mean maternal Phe levels during pregnancy ( $\mu\text{mol/L}$ )

Mother's initials/ Pregnancy number	CJ2	TC2	JF1	MK	VW
1 <sup>st</sup> trimester	270 (5 values; range 74–611)	502 (5 values; range 456–536)	562 (8 values; range 381–720)	216 (14 values; range 67–381)	344 (7 values; range 143–466)
2 <sup>nd</sup> trimester	401 (5 values; range 68–600)	386 (3 values; range 360–409)	340 (9 values; range 54–470)	139 (16 values; range 54–327)	222 (14 values; range 23–534)
3 <sup>rd</sup> trimester	289 (8 values; range 156–470)	299 (5 values; range 240–359)	237 (11 values; range 137–326)	224 (10 values; range 151–278)	271 (8 values; range 210–325)

Table 3: Infant characteristics

Mother's initials/ Pregnancy number	CJ2	TC2	JF1	MK	VW
Gender	Male	Female	Female	Female	Female
Birth weight (g)	3440 (50 <sup>th</sup> –75 <sup>th</sup> percentile)	3446 (50 <sup>th</sup> –75 <sup>th</sup> percentile)	3260 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	3175 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	3055 (10 <sup>th</sup> –25 <sup>th</sup> percentile)
Length (cm)	53.5 (75 <sup>th</sup> –90 <sup>th</sup> percentile)	46.7 (10 <sup>th</sup> –25 <sup>th</sup> percentile)	48 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	48.3 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	48 (25 <sup>th</sup> –50 <sup>th</sup> percentile)
Head circumference (cm)	36.5 (50 <sup>th</sup> –75 <sup>th</sup> percentile)	35.5 (50 <sup>th</sup> –75 <sup>th</sup> percentile)	34 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	34 (25 <sup>th</sup> –50 <sup>th</sup> percentile)	35 (25 <sup>th</sup> –50 <sup>th</sup> percentile)