

Two singleton pregnancies of phenylketonuric woman (p.R408W/p.R408W) on low phenylalanine diet resulting in healthy offspring: A recurrent lack of expected meaningful increase in phenylalanine tolerance during the third trimester

Dwie ciąży pojedyncze u chorej na fenyloketonurię (p.R408W/p.R408W) na diecie niskofenyloalaninowej zakończone urodzeniem zdrowego potomstwa – powtarzalny brak oczekiwanego znaczącego wzrostu tolerancji fenyloalaniny w III trymestrze ciąży

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Pielęgniarstwo i Zdrowie Publiczne, ISSN 2082-9876 (print), ISSN 2451-1870 (online)

Piel Zdr Publ. 2019;9(2):147–153

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Funding sources

None declared

Conflict of interest

None declared

Received on September 10, 2018

Reviewed on November 19, 2018

Accepted on December 11, 2018

This is a translated article.

Please cite the original

Polish-language version as

Żółkowska J, Hozyasz KK. Dwie ciąży pojedyncze u chorej na fenyloketonurię (p.R408W/p.R408W) na diecie niskofenyloalaninowej zakończone urodzeniem zdrowego potomstwa – powtarzalny brak oczekiwanego znaczącego wzrostu tolerancji fenyloalaniny w III trymestrze ciąży

Piel Zdr Publ. 2019;9(2):147–153. doi:10.17219/pzp/100660

DOI

10.17219/pzp/100660

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Abstract

The maternal phenylketonuria (PKU) syndrome is caused by high phenylalanine (Phe) level during pregnancy. Dietary treatment to control Phe concentration (low-Phe diet) can prevent sequelae like intellectual disability, microcephaly and birth defects. In this study, 2 singleton pregnancies resulting in healthy offspring in 1 woman with PKU are reported. A state of metabolic control was sustained both during the preconception period and pregnancy in the course of both pregnancies. In clinical practice, the empirical determination of Phe tolerance relies on frequent assessment of blood Phe concentrations in patients with PKU in relation to Phe intake assessed using food records. In contrast to predictions based on literature data stating that Phe tolerance intensively increases in the 3rd trimester and a low Phe tolerance may indicate fetal PKU, Phe tolerance in both pregnancies showed a low increase in the 3rd trimester and a more noticeable increase during the whole pregnancy: 453 mg (30.2%)/1,653 mg (551%) and 200 mg (12.5%)/1,560 mg (650%), respectively. Interestingly, the patterns of Phe increase were relatively similar only in the 2nd half of pregnancy. Further research on determinants of Phe tolerance in pregnant women with PKU is needed.

Key words: public health, phenylketonuria, phenylalanine tolerance, maternal-fetal interactions

Streszczenie

Duże stężenia fenyloalaniny (Phe) w ciąży są przyczyną fenyloketonurii matczynej (ang. *maternal phenylketonuria* – MPKU: upośledzenie umysłowe, małowłowie, wady wrodzone), któremu można zapobiec, stosując terapię dietą niskofenyloalaninową. Autorzy niniejszego artykułu przedstawili 2 ciąże pojedyncze (zakończone urodzeniem zdrowego potomstwa) pacjentki chorej na fenyloketonurię (PKU), która pozostawała w stanie wyrównania metabolicznego zarówno w okresie prekoncepcyjnym, jak i w ciąży. W praktyce klinicznej ocena tolerancji Phe opiera się na częstych oznaczeniach stężenia tego aminokwasu w powiązaniu z analizą jadłospisu. Zgodnie z danymi z piśmiennictwa autorzy oczekiwali znaczącego wzrostu tolerancji Phe w III trymestrze, gdyż jego brak uważa się za marker tej choroby także u płodu. Analizując wyniki badań pacjentki, zaobserwowano, że w pierwszej i drugiej ciąży tolerancja Phe w III trymestrze i podczas całej ciąży wzrosła odpowiednio o 453 mg (30,2%)/1653 mg (551%) i 200 mg (12,5%)/1560 mg (650%). Wzorzec zmian tolerancji Phe był podobny tylko w drugiej połowie obu ciąż. Niezbędne są dalsze badania nad czynnikami wpływającymi na homeostazę Phe w ciąży u chorych na PKU.

Słowa kluczowe: zdrowie publiczne, fenyloketonuria, tolerancja fenyloalaniny, oddziaływania matczyno-płodowe

The benefits of newborn PKU screening and treatment could be significantly curtailed if adequate resources, education, and funding are not available to follow and monitor women with PKU and their babies.

Robert Resta¹

Background

Detection of a case of phenylketonuria (PKU) in neonatal screening and the implementation of a low-phenylalanine diet is associated with the risk of maternal phenylketonuria (MPKU) in the offspring of a patient giving up dietary treatment after reaching adulthood. In unfavorable circumstances, one health problem may be replaced by another – a woman with PKU, who has been prevented from having limited intellectual and physical development that excludes reproduction, gives birth to sick offspring as a result of exposure to high concentrations of phenylalanine (Phe) amino acid.^{1–3} We now know that after the patient has given up treatment, a diet with limited Phe supply should be rigorously re-introduced during the contraception period and used under the supervision of a doctor and a dietician throughout the pregnancy.^{4–6} The supply of Phe increases rapidly as the concentration of this essential amino acid reaches a level below 120 $\mu\text{mol/L}$ (2 mg%) in the pregnant woman's blood.⁶ The general principles of prevention of MPKU are well known, but there is a lack of detailed analysis for predicting an increase in Phe tolerance in pregnant women, and some indications need to be critically evaluated,^{5,7} because, as experimental animal studies show, dietary restrictions can have very different consequences in the offspring.⁸ The desire to know the optimal, because of disease, preconceptive body mass index (BMI) in patients has not yet been the subject of analysis,⁶ despite the identification of physiological relationships between BMI of pregnant women and fetal metabolism,^{9,10} and the effect of glycemia on placental transfer.¹¹ Maternal metabolism of Phe is likely to be significantly supported by the fetus' maturing liver.⁷

In 2009, Kohlschütter et al.⁷ pointed out that the lack of the expected increase in Phe tolerance in the 3rd trimester may also be a marker of PKU occurrence in the fetus, an observation made by the latest European recommendations for the diagnosis and treatment of this disease.⁶ In 2 women with PKU described by Kohlschütter et al.⁷ who were correctly treated (genotypes: p.194del/p.P281L and p.165T/p.R408W), the tolerance of Phe increased in the 3rd trimester of pregnancy with an unencumbered fetus by 100% (900 mg) and 50% (500 mg).

The aim of the study was to present 2 pregnancies in a patient with PKU (using a low-Phe diet with good results), in which there was no radical increase in Phe tolerance at the end of each of them.

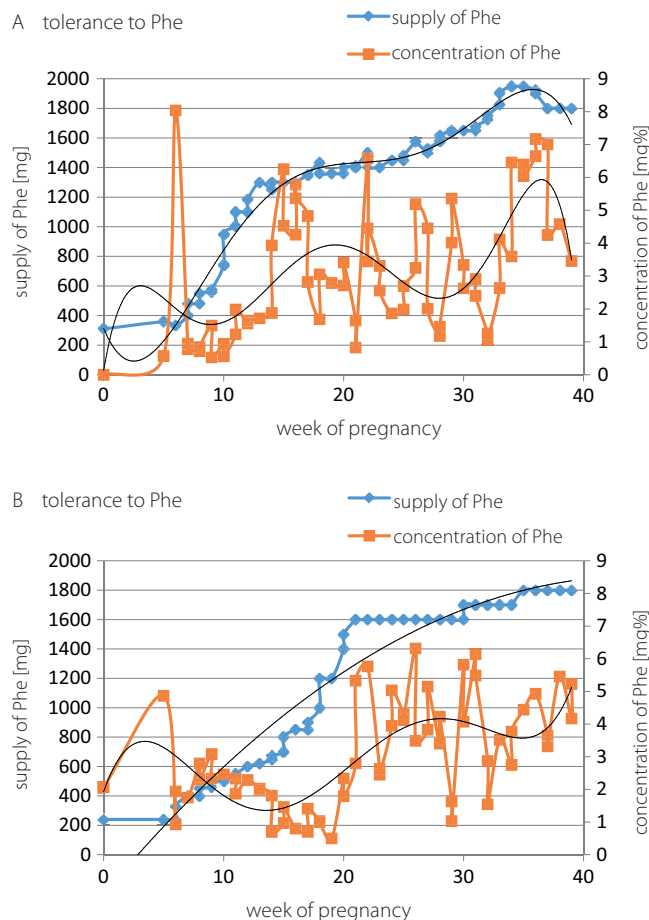
Case study

The patient was diagnosed with classic PKU and dietary treatment had been implemented in the neonatal period. The woman completed a vocational school and supplementary technical school for adults. At the age of 23 she got married. She did not have a miscarriage. She prepared herself properly for the 1st and 2nd pregnancy: for 2 years and 2 months she followed a diet that allowed her to maintain Phe concentration in the recommended range of 120–360 $\mu\text{mol/L}$ (2–6 mg%).⁶ At the time of both pregnancies she remained in a metabolic equilibrium state (Table 1), with BMI before pregnancy being lower than recommended (18.5–24.9¹²), especially in the 2nd pregnancy. Each week of pregnancy, blood Phe levels were measured twice or 3 times, and the patient was encouraged to send menus at least twice, which enabled the Phe supply to be quickly adjusted to the dynamically changing tolerance of this amino acid.

The ratio of birth weight of the offspring to weight gained by the woman in both pregnancies was similar (Table 1). The birth of healthy children took place in 40th week of pregnancy (Table 2). The birth weight of newborns was within the World Health Organization (WHO) recommended range of 3,100–3,600 g.¹³ Blood Phe con-

Table 1. Clinical data on 2 singleton pregnancies in the presented PKU patient resulting in live births**Tabela 1.** Charakterystyka 2 ciąż pojedynczych u pacjentki chorej na PKU

Data	Genotype p. R408W/p. R408W	
	1 st pregnancy	2 nd pregnancy
The patient's age when she got pregnant [years]	25	27
In vitro support procedure	no	no
Smoking during pregnancy	no	no
Body weight before pregnancy [kg]	49.9	46.6
BMI before pregnancy [kg/m ²]	17.8	16.6
Pregnant weight gain [kg]	19.1	19.4
BMI before childbirth [kg/m ²]	24.6	23.6
Weight gain in the 1 st trimester of pregnancy [kg]	3.1	3.4
BMI in the 1 st trimester of pregnancy [kg/m ²]	18.90	17.85
Birth weight ratio of the offspring to weight gain [%]	19	18
Phe concentration before pregnancy [μmol/L (mg%)]	34.2 (0.57)	124.2 (2.07)
Introduction of a low-Phe diet before pregnancy	yes	yes
Medicinal preparation	XP Maxamum, Milupa PKU3 tempora	XP Maxamum
% results of Phe >360 μmol/L (6 mg%) throughout pregnancy	14	3
% results of Phe <120 μmol/L (2 mg%) throughout pregnancy	37	29
Daily supply of protein from the medicinal preparation [g]	14 Hbd	58.5
	28 Hbd	79.5
	34 Hbd	86.5
	38 Hbd	93.5
	39 Hbd	93.5
Daily energy supply [kcal]	14 Hbd	2,104–2,656
	28 Hbd	2,505–3,015
	34 Hbd	2,273–3,140
	38 Hbd	3,307–3,519
	39 Hbd	2,729–3,054

**Fig. 1.** Phe tolerance during the 1st (A) and 2nd (B) pregnancy of the presented PKU patient**Ryc. 1.** Tolerancja Phe w ciąży pierwszej (A) i drugiej (B) u chorej na PKU

centrations and Phe tolerance are shown in Fig. 1. The ratio of Phe tolerance to weight of the pregnant woman was similar (in both pregnancies) outside the first few weeks (Fig. 1, Table 3). The ratio of Phe tolerance to birth weight and estimated fetal weight is shown in Table 4. In the 3rd trimester, there was only a slight increase in Phe tolerance, 30.2% and 12.5% in the 1st and 2nd pregnancy, respectively (Table 5). Throughout the 1st and 2nd pregnancy, tolerance of Phe increased to a maximum 5.5 and 6.5 times, respectively (Table 5). Between 33rd and 36th week of pregnancy, tolerance of Phe was higher by approx. 7–15% in the 1st pregnancy than in the 2nd. From 37th week, no differences in Phe tolerance were observed

Table 2. Birth measurements for completed pregnancies of the presented PKU patient**Tabela 2.** Zestawienie pomiarów urodzeniowych potomstwa pacjentki chorej na PKU

Pregnancy	Pregnancy week	Sex	Body weight [g; percentile] ^a	Body length [cm; percentile] ^a	Head circumference [cm; percentile]	Apgar score	Congenital defects, dysmorphic features	Phe in neonatal screening [μmol/L]	Status of a patient with PKU
1 st	40	female	3,600; >50	55; >97	34; <50	10	no	80.4 (1.34 mg%)	no
2 nd	40	male	3,450; <50	55; <97	33; 10	10	no	67.2 (1.12 mg%)	no

^a According to WHO standards.

Table 3. Estimated Phe tolerance and its ratio to weight of the presented pregnant woman in the 1st and 2nd pregnancy**Tabela 3.** Szacunkowa tolerancja Phe i jej stosunek do masy ciała ciężarnej w pierwszej i drugiej ciąży

Age of pregnancy [weeks]	1 st pregnancy			2 nd pregnancy		
	Phe concentration [μmol/L]	Phe tolerance [mg]	Phe/body weight ^c [mg/kg]	Phe concentration [μmol/L]	Phe tolerance [mg]	Phe/body weight ^c [mg/kg]
14	306 (236; 375) ^a	1,250 (1,200–1,300) ^b	23.6 (22.6–24.5)	76 (109–42) ^a	672 (643–700) ^b	13.44 (12.9–14)
28	164 (88; 241) ^a	1,615 (1,580–1,650) ^b	25.6 (25.1; 26.2)	228 (204; 254) ^a	1,600	25.8
39 ^c	336	1,800	26.1	282 (314; 250) ^a	1,800	27.3

^a Means of at least 2 indications^b Mean reconstruction of at least 2 menus.^c Ratio of tolerable intake of Phe to the current weight of the pregnant woman.^d Penultimate week of pregnancy.

in both pregnancies, also expressed as a ratio to estimated fetal weights (Fig. 1, Table 4).

After the birth of the 1st child, the control of Phe concentration deteriorated, while after the 2nd pregnancy, the patient practically gave up using the medicinal diet.

Discussion

In the discussed patient, the most common mutation (p.R408W) of the *PAH* gene encoding the phenylalanine hydroxylase enzyme was found in the homozygotic system.¹⁴ The age at which both pregnancies occurred fell in the optimal period of life for procreation^{15,16} and there was no nicotinism. According to the recommendations, the low-Phe diet was used not only during pregnancy, but also during preconception.^{6,17–19} Despite the lower tolerance of Phe at the beginning of the 2nd pregnancy, the final value of this parameter, including when converted to the weight of the pregnant woman and fetus, was almost identical to that of the 1st pregnancy. In the 3rd trimester, there was no radical increase in Phe tolerance, which cannot be explained in both cases by PKU in the fetus, as postulated by Kohlschütter et al.⁷ Observation of barely 12.5% increase in Phe tolerance in the 3rd trimester of the 2nd pregnancy is worth emphasizing, in comparison with only 20% increase in the 1st pregnancy, provided that we consider calculations of Phe tolerance in the last weeks of pregnancy (37th–39th week; Fig. 1) and not, as in Table 5, the maximum recorded value of 34th week of pregnancy. The small increase in Phe tolerance at the end of pregnancy in the described pregnant woman, who did not have any significant residual activity of the phenylalanine hydroxylase enzyme that could be stimulated,²⁰ combined with the birth of mature, healthy newborns (with regular body weight and Apgar scores of 10) stimulates an in-depth discussion on the role of the fetus liver in the metabolic equilibrium of a pregnant woman suffering from PKU. It is also worth noting that in the 3rd trimester of the 2nd pregnancy, the absolute increase in Phe

tolerance was 200 mg, i.e., comparable to the same period of pregnancy (pregnant genotype p.R408W/p.R261Q) with the fetus suffering from PKU (genotype p.R408W/p.R408W) described by Kohlschütter et al.⁷ In retrospective studies on the relationship between the characteristics of Phe concentration variability and the course of pregnancy in PKU, women's genotype was not taken into account.¹⁹ Widaman and Azen²¹ found that the severity of Phe concentration variability depends on the genotype and age of pregnant PKU patients receiving dietary treatment. In the patient described by the authors of this article, despite normal Phe concentrations in the perinatal period, weight deficiency before the 2nd pregnancy co-existed with a slower increase in Phe tolerance at the beginning of pregnancy. So far, the initiation of a therapeutic diet during the preconceptive period has been indicated as an important factor in favor of Phe tolerance in the 1st trimester of pregnancy, compared to its immediate implementation only after becoming pregnant.^{4,17,19} In healthy individuals, preconceptive BMI not within the recommended standard is a risk factor for abnormal pregnancy, including fetal organogenesis and growth, and postnatal neurodevelopmental disorders.^{22–24} The possibility of influencing Phe tolerance by previously unknown placental and maternal factors has also been signaled.¹⁹ It is likely that the creation of databases considering genotypes and anthropometric data of pregnant women and detailed records of changes in Phe tolerance will enable the regulation of increased Phe tolerance in pregnant women with PKU.

Like hyperphenylalaninemia, excessive restriction of Phe supply and low levels of this amino acid in pregnant woman's blood are a risk factor for intrauterine growth restriction.²⁵ Despite a high percentage of Phe measurements <120 μmol/L (<2 mg%), the birth length and body weight of newborns from both pregnancies were normal or exceeded 97th percentile. Relatively small birth circumference of the head of a boy from the 2nd pregnancy (approx. 10th percentile) was not associated with a high percentage of Phe measurements >360 μmol/L (>6 mg%).

Table 4. Estimated Phe tolerance and its ratio to fetal weight in the 1st and 2nd pregnancy**Tabela 4.** Szacunkowa tolerancja Phe w pierwszej i drugiej ciąży z uwzględnieniem masy ciała płodów

Age of pregnancy [weeks]	1 st pregnancy			2 nd pregnancy		
	Phe concentration [μmol/L]	Phe tolerance [mg]	Phe/weight of fetus ^c [mg/kg]	Phe concentration [μmol/L]	Phe tolerance [mg]	Phe/weight of fetus ^c [mg/kg]
22	237.3 (3.96) 207; 267.6 (3.45; 4.46)	1,450 (1,400–1,500)	2,900 (2,800–3,000)	346.2 (5.77)	1,600	2,909
25	178.8 (2.98) 162; 195 (2.7; 3.25)	1,465 (1,450–1,480)	2,092.85 (2,071.4–2,114.3)	252 (4.2) 258.6; 247.2 (4.31; 4.12)	1,600	2,133.3
29	261 (4.35) 321.6; 200.4 (5.36; 3.34)	1,636 (1,622–1,650)	1,422.6 (1,410.4–1,434.8)	79.8 (1.33) 97.2; 61.8 (1.62; 1.03)	1,600	1,333.3
30	166.2 (2.77) 157.8; 174.6 (2.63; 2.91)	1,650	1,269.2	294 (4.9) 349.2; 244.2 (5.82; 4.07)	1,650 (1,600–1,700)	1,178.6 (1,142.9–1,214.3)
31	109.8 (1.83) 75.6; 144 (1.26; 2.4)	1,675 (1,650–1,700)	1,116.7 (1,100–970.9–1,133.3)	348 (5.8) 368.4; 329.4 (6.14; 5.49)	1,700	1,062.5
32	166.2 (2.77) 174; 157.8 (2.9; 2.63)	1,725 (1,700–1,751)	1,014.7 (1,000–1,030)	132.6 (2.21) 172.2; 93 (2.87; 1.55)	1,700	944.4
33	231.6 (3.86) 247.2; 216 (4.12; 3.6)	1,830 (1,753–1,908)	963.2 (922.6–1,004.2)	211.2 (3.52)	1,700	850
34	385.8 (6.43)	1,950 (1,948–1,953)	928.6 (927.6–930)	195.6 (3.26) 165; 226.2 (2.75; 3.77)	1,700	755.5
35	381 (6.35) 362.4; 399 (6.04; 6.65)	1,950	829.8	266.4 (4.44)	1,800	720
36	425.4 (7.09) 430.2; 420.6 (7.17; 7.01)	1,924.5 (1,899–1,950)	740.2 (730.4–750)	295.8 (4.93)	1,800	666.7
37	264 (4.4) 255; 274.8 (4.25; 4.58)	1,800 (1,799–1,801)	631.6 (631.2–631.9)	209.4 (3.49) 219; 199.2 (3.65; 3.32)	1,800	610
38	207.6 (3.46)	1,801.5 (1,801–1,802)	590.65 (590.5–590.8)	327.6 (5.46)	1,800	571.4
39	336 (5.6)	1,800	553.8	282 (4.7) 313.8; 250.2 (5.23; 4.17)	1,800	537.3

^a Means of at least 2 indications.^b Mean reconstruction of at least 2 menus.^c Ratio of the Phe intake to the estimated weight of the fetus.**Table 5.** Increase in Phe tolerance during the course of pregnancy**Tabela 5.** Wzrost tolerancji Phe w różnych okresach ciąży

Pregnancy	Increase in Phe tolerance							
	1 st trimester		2 nd trimester		3 rd trimester		whole pregnancy	
	mg	%	mg	%	mg	%	mg	%
1 st	1,000 300→1,300	333.3	400 1,200→1,600	33.3	453 1,500→1,953	30.2	1,653 300→1,953	551
2 nd	410 240→650	170.8	957 643→1,600	148.8	200 1,600→1,800	12.5	1,560 240→1,800	650

The arrow marks the smallest and the largest calculation of Phe tolerance, not always coinciding with the calculations exactly at the beginning and end of a given trimester (Fig. 1).

Microcephaly, congenital heart defects and impaired intellectual development are the main symptoms of MPKU syndrome.^{17,18,25,26} Matalon et al.²⁷ showed a correlation between a small body weight increase (<70% of the recommended) of a pregnant woman with PKU and microcephaly in the offspring.

Education on the effects of unregulated Phe concentrations on the fetus from the time of contraception and preparation for pregnancy is invariably recommended for all women with PKU and other forms of hyperphenylalaninemia at childbearing age.^{6,19,28}

Conclusions

The different dynamics of increase of Phe tolerance at the beginning of both pregnancies suggests a significant influence of environmental factors in its formation. Frequent Phe concentration determinations are an essential tool for the care of a pregnant woman with PKU.

The repeated lack of radical increase in Phe tolerance in the 3rd trimester in the described patient without significant residual activity of the phenylalanine hydroxylase enzyme does not support the thesis about the fundamental role of the liver of the fetus not suffering from PKU in Phe homeostasis in advanced pregnancy.

One of the greatest achievements of preventive medicine, which is the introduction of obligatory neonatal screening for PKU, results in the necessity to conduct research on methods of care for patients struggling with this disease at the procreative age.

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References

- 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*. 2012;158A(5):1118–1123. doi:10.1002/ajmg.a.35312
- Guthrie R. Maternal PKU: A continuing problem. *Am J Public Health*. 1988;78(7):771. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1350330/?page=1>. Accessed on June 12, 2019.
- Prick BW, Hop WC, Duvekot JJ. Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: Pregnancy complications and neonatal sequelae in untreated and treated pregnancies. *Am J Clin Nutr*. 2012;95(2):374–382. doi:10.3945/ajcn.110.009456
- Lee PJ, Ridout D, Walter JH, Cockburn F. Maternal phenylketonuria: Report from the United Kingdom Registry 1978–97. *Arch Dis Child*. 2005;90(2):143–146. doi:10.1136/ad.2003.037762
- Brenton DP, Lilburn M. Maternal phenylketonuria. A study from the United Kingdom. *Eur J Pediatr*. 1996;155(Suppl 1):S177–S180.
- van Wegberg AM, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12:162. doi:10.1186/s13023-017-0685-2
- Kohlschütter B, Ellerbrok M, Merkel M, et al. Phenylalanine tolerance in three phenylketonuric women pregnant with fetuses of different genetic PKU status. *J Inher Metab Dis*. 2009;32(Suppl 1):S1–S4. doi:10.1186/s13023-017-0685-2
- Wang Y, Li SR, Zeng ZG, Du WG. Maternal food availability affects offspring performance and survival in a viviparous lizard. *Funct Ecol*. 2017;31:1950–1956. doi:10.1111/1365-2435.12903
- Lowe WL Jr, Bain JR, Nodzenski M, et al. Maternal BMI and glycaemia impact the fetal metabolome. *Diabetes Care*. 2017;40(7):902–910. doi:10.2337/dc16-2452
- Hellmuth C, Lindsay KL, Uhl O, et al. Association of maternal pre-pregnancy BMI with metabolomic profile across gestation. *Int J Obes (Lond)*. 2017;41(1):159–169. doi:10.1038/ijo.2016.153
- Jensen VF, Mølck AM, Lykkesfeldt J, Bøgh IB. Effect of maternal hypoglycaemia during gestation on materno-foetal nutrient transfer and embryo-foetal development: Evidence from experimental studies focused primarily on the rat. *Reprod Toxicol*. 2018;77:1–24. doi:10.1016/j.reprotox.2018.01.007
- Siega-Riz AM, Deierlein A, Stuebe A. Implementation of the New Institute of Medicine Gestational Weight Gain Guidelines. *J Midwifery Womens Health*. 2010;55(6):512–519. doi:10.1016/j.jmwh.2010.04.001
- Maternal anthropometry and pregnancy outcomes: A WHO collaborative study. *Bull World Health Organ*. 1995;73(Suppl 1):1–98.
- Bik-Multanowski K, Kałużny Ł, Mozrzyk R, et al. Molecular genetics of PKU in Poland and potential impact of mutations on BH4 responsiveness. *Acta Biochim Pol*. 2013;60(4):613–616. http://www.actabp.pl/pdf/4_2013/613.pdf. Accessed on June 12, 2019.
- Cabrera-Leon A, Lopez-Villaverde V, Rueda M, Moya-Garrido MN. Calibrated prevalence of infertility in 30- to 49-years-old women according to different approaches: A cross-sectional population-based study. *Hum Reprod*. 2015;30(11):2677–2688. doi:10.1093/humrep/dev226
- Deatsman S, Vasilopoulos T, Rhoton-Vlasak A. Age and fertility: A study of patient awareness. *JBRA Assist Reprod*. 2016;20(3):99–106. doi:10.5935/1518-0557.20160024
- Didycz B, Domagała L, Pietrzyk JJ. Zespół fenylketonurii matczynej – problem nadal aktualny. *Przegl Lek*. 2009;66:4–10. http://www.wple.net/plek/numery_2009/numer-1-2-2009/4-10.pdf. Accessed on June 12, 2019.
- Paprocka J, Jamroz E, Wiktor M, Marszał E. Maternal phenylketonuria. *Wiad Lek*. 2009;62(1):11–17.
- Maillot F, Lilburn M, Baudin J, Morley DW, Lee PJ. Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: The importance of variation in maternal blood phenylalanine. *Am J Clin Nutr*. 2008;88(3):700–705. doi:10.1093/ajcn/88.3.700
- Guldberg P, Rey F, Zschocke J, et al. A European Multicenter Study of Phenylalanine Deficiency: Classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype. *Am J Hum Genet*. 1998;63(1):71–79. doi:10.1086/301920
- Widaman KF, Azen C. Relation of prenatal phenylalanine exposure to infant and childhood cognitive outcomes: Results from the International Maternal PKU Collaborative Study. *Pediatrics*. 2003;112(6 Pt 2):1537–1543. <https://link.springer.com/article/10.1023/B:BOLI.0000045758.86492.54>. Accessed on June 12, 2019.
- Siega-Riz M, Adair LS, Hobel CJ. Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. *J Nutr*. 1996;126(1):146–153. doi:10.1093/jn/126.1.146
- Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma U. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. *Int J Obes (Lond)*. 2012;36(10):1312–1319. doi:10.1038/ijo.2012.143
- Jeric M, Roje D, Medic N, Strinic T, Mestrovic Z, Vucic M. Maternal pre-pregnancy underweight and fetal growth in relations to Institute of Medicine recommendations for gestational weight gain. *Early Hum Dev*. 2013;89(5):277–281. doi:10.1016/j.earlhumdev.2012.10.004
- Teissier R, Nowak E, Assoun M, et al. Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant. Maternal phenylketonuria: Low phenylalaninemia might increase the risk of intra uterine growth retardation. *J Inher Metab Dis*. 2012;35(6):993–999. doi:10.1007/s10545-012-9491-0
- Koch R, Gross Friedman EG, Wenz E, Jew K, Crowley C, Donnell G. Maternal phenylketonuria. *J Inher Metab Dis*. 1986;9(Suppl 2):159–168. https://link.springer.com/chapter/10.1007/978-94-009-4131-1_20. Accessed on June 12, 2019.

27. Matalon KM, Acosta PB, Azen C. Role of nutrition in pregnancy with phenylketonuria and birth defects. *Pediatrics*. 2003;112(6 Pt 2): 1534–1536. https://pediatrics.aappublications.org/content/112/Supplement_4/1534. Accessed on June 12, 2019.
28. American Academy of Pediatrics, Committee on Genetics. Maternal phenylketonuria. *Pediatrics*. 2001;107:427–428. <https://pediatrics.aappublications.org/content/122/2/445>. Accessed on June 12, 2019.