

Case report

Increased maternal phenylalanine concentration may influence not only fetal heart structural development but also cardiovascular function and pulmonary tissue development in humans – a case report



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Abstract

A case of the fetus exposed to elevated phenylalanine concentration, who presented structural and functional cardiovascular changes and pulmonary injury in uncontrolled phenylketonuria of the pregnant woman. Continued fetal echocardiographic monitoring in the third trimester of pregnancy allowed to present fetal functional cardiovascular abnormalities and suspect neonatal persistent pulmonary hypertension. To the best of our knowledge, prenatal detection of persistent pulmonary hypertension in the case of maternal phenylketonuria on the newborn has not been reported before, and increased phenylalanine might be an additional factor influencing pulmonary tissue development.

Key words: case report, pulmonary hypertension, fetal echocardiography, fetal, phenylketonuria.

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Introduction

In Poland phenylketonuria occurs in 1:8000 newborns. There are more than 600 mutations in the PAH gene that lead to elevated phenylalanine concentration in blood serum [1]. Early diagnosis of phenylketonuria may provide good clinical follow-up if a strict diet is maintained. Successful treatment of many children has enabled them to grow to adulthood and to start procreation. Nevertheless, phenylalanine abandonment

must be continued during pregnancy in these cases, as phenylalanine crosses the placenta to the fetus. Phenylalaninaemia in the pregnant woman causes intrauterine fetal growth restriction, hydrocephalus, mental retardation, and congenital heart defects [2]. Out of these abnormalities, congenital heart defects are the most dangerous because they may cause rapid and severe neonatal cardiovascular deterioration. We would like to present a case of the fetus exposed to elevated phenylalanine

Table 1. Fetal presentation of selected parameters- fetal echocardiographic monitoring

Parameter	32 nd week of gestation	33 rd week of gestation	35 th week of gestation
GA (LMP) [weeks + days]	32 + 1	33 + 5	35 + 5
EFW [g]	2049	2448	3078
Placenta [mm]	29	45	45
Cerebro-placental ratio	> 1	> 1	> 1
AP [mm]	41	35	45
AP L [mm]	44	46	52
HA/CA	0.32	0.4	0.4
LV [mm]	7.7	6.9	9.7
MV [mm]	1.9	3.6	5.2
RV [mm]	16.2	25	35
TV [mm]	11.1	21	31
Ao [mm]	5	5.4	6
MPA [mm]	11	12	12.5
PVs [cm/s]	33	57	
FO [mm, description]	6 (stiff)	patent (stiff)	stiff
FO index [%] [4]	32	25	
Functional anomalies (cardiac)	Disproportion, tricuspid insufficiency, myocardial hypertrophy, cardiomegaly, myocarditis	Disproportion, tricuspid insufficiency, myocardial hypertrophy, cardiomegaly, myocarditis, pulmonary hypertension	Disproportion, tricuspid insufficiency, myocardial hypertrophy, cardiomegaly, myocarditis, pulmonary hypertension
Functional anomalies (extracardiac)	Prominent gallbladder	Tortuous umbilical cord, prominent gallbladder	Tortuous umbilical cord, prominent gallbladder, hydrops testis

GA – gestational age, LMP – last menstrual period, AP – transversal fetal heart diameter, AP L – longitudinal fetal heart diameter, HA/CA – heart area divided by thorax area, LV – left ventricle diameter, MV – mitral valve diameter, RV – right ventricle diameter, TV – tricuspid valve diameter, Ao – aorta diameter, MPA – main pulmonary artery diameter, PVs – pulmonary veins peak systolic velocity, FO – foramen ovale diameter, FO index – foramen ovale index measured in atrial M-mode.

concentration, who was monitored prenatally by fetal echocardiography. We hope that our observations will provide better understanding of fetal pathological cardiovascular functional anomalies that in the future will result in more adequate and quicker treatment in these selected cases.

The study did not require ethical approval because it was retrospective descriptive study. The patient granted our request to publish her medical data for scientific purposes. The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The data was deidentified.

Case report

The case report involves was the second pregnancy of a 23-year-old woman. She had an early miscarriage less than 2 years before the second conception [3]. The patient was diagnosed in her childhood with phenylketonuria and did not stick to the recommended diet. Phenylalanine levels during her pregnancy were 13 mg/dl, with the normal values up to 2 mg/dl. The patient had a first-trimester ultrasound with no abnormality detected. Basic obstetric ultrasound in the 24th week of gestation was described as normal, and in the 32nd week

of gestation the obstetrician detected a congenital heart defect, so the patient was referred for fetal echocardiography to our tertiary fetal cardiology centre.

The fetus had echocardiographic examinations at 32, 33 + 5, and 35 + 5 weeks of gestation (Table 1) [4]. Fetal echocardiography was advised earlier than the 32nd week of gestation, but the parents decided not to follow medical recommendations. The final fetal echocardiographic diagnosis that was stated 30 days before birth was of a fetus with uncommon cardiovascular presentation: hypertrophy of RV, broad RVOT, narrow LVOT, skinny LV, hypoplastic Ao arch (Ao valve –1.89 Z-score, Ao ascending –2 Z-score, Ao isthmus –2.44 Z-score), and pulmonary hypertension highly expected.

Fetal atria: disproportion, stiff FO flap in the RA. In LA substantial forward pulmonary venous blood streams moderating FO flap movements (Figure 1).

Fetal ventricles: disproportion 2:1 (RV > LV), inhomogeneous myocardium echogenicity suggestive for fetal myocarditis with atypical TV (differential diagnosis TV dysplasia). TR to 3m/s. Abnormal ventricular contractility (Figure 2).

Fetal great arteries: MPA diameter > 95th centile (Figure 3). Ao < 95th centile. Broad RPA and LPA. Periodically reversal

flow in Ao arch. Crested spectrum of blood flow in MPA-pulmonary hypertension highly possible.

The newborn was born by spontaneous delivery at 39 weeks of gestation. The birthweight was 3400 g and Apgar score was 9 at one minute and 10 at 5 minutes of postnatal life. Neonatal echo confirmed hypoplastic left ventricle and hypoplastic aortic arch, abnormal right ventricle myocardium structure, restrictive foramen ovale, and pulmonary hypertension. The neonate had Norwood surgery on the 3rd day of postnatal life. Postoperative time was complicated by pneumonia (*Mycoplasma pneumoniae* and *Streptococci*) and 4 weeks later by sepsis (*Klebsiella pneumoniae*). Progressive deterioration of systemic ventricle was systematically observed. The right ventricle was described as hypokinetic, hypertrophied, and “lacunar”. Due to abnormal anatomy and function of the right ventricle the infant was disqualified from further cardiosurgical treatment. Finally, the baby died on the 110th day. The autopsy was not performed due to the parents’ wishes.

Discussion

Phenylketonuria may be successfully treated, but in some cases a strict diet is not followed [5]. Phenylalanine crosses the placenta and as a teratogen causes fetal abnormalities in the cardiovascular and pulmonary system. The pathophysiological role of phenylalanine on pulmonary circulation is still unclear. Tan *et al.* showed that elevated phenylalanine concentration induces pulmonary hypertension in rats through binding to calcium-sensing receptors [6]. It was also presented by Kaluarachchi *et al.* that in neonates with persistent pulmonary hypertension of the newborn (PPHT) there may be elevated phenylalanine concentration, but the precise mechanism has not been explained [7], and up to now there has not been such a fetal case presented to the authors’ knowledge. Their results were also confirmed by Steurer *et al.* [8].

Persistent pulmonary hypertension of the newborn may be predicted prenatally [9]. The best tool to monitor the fetal cardiovascular system is fetal echocardiography, because it enables us to describe not only fetal heart anatomy but also fetal heart function [10]. Prediction of PPHT is not an easy task and requires adequate experience and at least a few fetal echocardiography examinations (especially in the third trimester of pregnancy). In our case that was profoundly difficult because prenatal diagnosis was complex: the disproportion and dilation of MPA and right side of the fetal heart was probably caused by the abnormal fetal pulmonary tissue development and concomitant with features of evolving fetal hypoplastic left heart syndrome [3, 7]. The limitation of the case report is the lack of an autopsy.

Fetal prediction of PPHT may be highly important in cases with congenital heart defects. PPHT is a poor prognostic factor, and in some cases successful treatment of PPHT may be the only chance for a favourable outcome. That is why early intervention and treatment (even before neonatal symptoms, when detected prenatally) may improve the prognosis, but it should be preceded by fetal echocardiographic monitoring in a fetal cardiology referral centre.

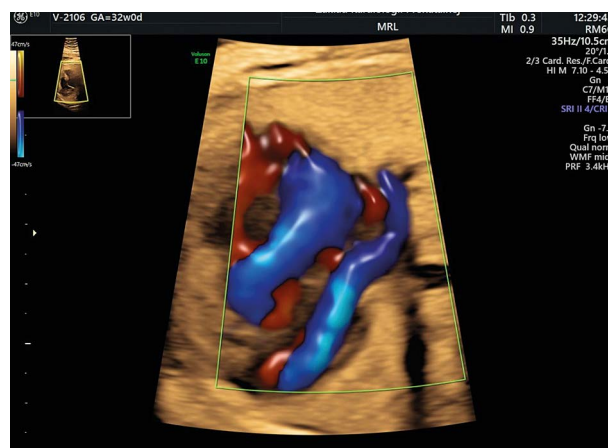


Figure 1. 32nd week of gestation. Four-chamber view. Significant disproportion. Dilated right side of the fetal heart. Narrow left ventricle with prominent pulmonary blood flow. Fetal cephalic position, fetal spine of left maternal side



Figure 2. Abnormal ventricular contractility presented by speckle tracking analysis. Fetal cephalic position, fetal spine of left maternal side



Figure 3. Dilated MPA (11 mm) and dilated RPA – pulmonary hypertension highly expected. No ductal constriction. Fetal cephalic position, fetal spine of left maternal side

Conclusions

Continued fetal echocardiography in the third trimester in fetal structural and functional cardiovascular changes allowed us to predict neonatal PPHT in uncontrolled phenylketonuria of a pregnant woman, which has never been reported previously.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Kawalec W, Grenda R, Kulus M. *Pediatrics*. Vol. I. PZWL, Warsaw 2018; 269.
2. Levy HL, Ghavami M. Maternal phenylketonuria: a metabolic teratogen. *Teratology* 1996; 53: 176-184.
3. Strzelecka I, Słodki M, Chrzanowski J, Rizzo G, Respondek-Liberska M. International Prenatal Cardiology Collaboration group. An investigation of the optimal inter-pregnancy interval following pregnancy with a fetus with congenital heart disease. *Arch Med Sci* 2019; 18: 388-394.
4. Respondek-Liberska M, Sylwestrzak O. Fetal foramen ovale flap tracings, as determined by M-mode echocardiography between weeks 24 and 39 of gestation. *Kardiologia Polska* 2022; 80: 598-600.
5. van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis* 2017; 12: 162.
6. Tan R, Li J, Liu F, Liao P, Ruiz M, Dupuis J, et al. Phenylalanine induces pulmonary hypertension through calcium-sensing receptor activation. *Am J Physiol Lung Cell Mol Physiol* 2020; 319: L1010-L1020.
7. Kaluarachchi DC, Smith CJ, Klein JM, Murray JC, Dagle JM, Ryckman KK. Polymorphisms in urea cycle enzyme genes are associated with persistent pulmonary hypertension of the newborn. *Pediatr Res* 2018; 83: 142-147.
8. Steurer MA, Oltman S, Baer RJ, Feuer S, Liang L, Paynter RA, et al. Altered metabolites in newborns with persistent pulmonary hypertension. *Pediatr Res* 2018; 84: 272-278.
9. Murlewska J, Sylwestrzak O, Respondek-Liberska M. Unfavorable postnatal outcome with significant dilation of the fetal main pulmonary artery near term. *Birth Defects Res* 2021; 113: 55-62.
10. Sylwestrzak O, Strzelecka I, Słodki M, Respondek-Liberska M. Fetal echocardiography is not only used to detect congenital heart disease but also to monitor fetuses, especially those with different pathologies. *Kardiologia Polska* 2022; 80: 966-967.

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