Molecular Genetics and Metabolism Reports 8 (2016) 4–7

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Successful pregnancy and delivery in a woman with propionic acidemia from the Amish community☆

Jessica Scott Schwoerer [a,*], Sandra van Calcar [b], Gregory M. Rice [a], James Deline [c]

[a] Department of Pediatrics, University of Wisconsin, Madison, WI, USA
[b] Department of Molecular and Medical Genetics, Oregon Health and Science University, Portland, OR, USA
[c] LaFarge Medical Clinic, LaFarge, WI, USA

ARTICLE INFO

Article history:
Received 12 May 2016
Accepted 12 May 2016
Available online 2 June 2016

Keywords:
Propionic acidemia
Inborn errors in metabolism
Cardiomyopathy
Pregnancy
Organic acidemias

ABSTRACT

Propionic acidemia (PA) is an inborn error of protein metabolism with a variable clinical presentation ranging from neonatal encephalopathy to seemingly asymptomatic individuals who present with cardiomyopathy or sudden death. PA is recognized in the Amish population, often with an early asymptomatic course and eventual cardiac complications. Thus, Amish women with PA may reach reproductive age without clinical sequelae, but are at increased risk for metabolic decompensation during pregnancy, delivery and postpartum period. We describe the care of an Amish woman with PA during her first pregnancy and delivery.

Introduction

Propionic acidemia (PA, OMIM #606054) is an inborn error of metabolism (IEM) caused by a deficiency in propionyl-CoA-carboxylase (PCC), an enzyme with two subunits, A and B, encoded by genes PCCA and PCCB [1]. This enzyme is important in the metabolism of the amino acids isoleucine, valine, threonine and methionine as well as odd chain fatty acids. Reduced enzyme activity leads to an accumulation of organic acids including propionic acid and methylcitrate which are toxic to tissue including the brain and myocardium.

PA can present at any age throughout the lifespan. The severe neonatal form presents with encephalopathy and profound acidosis and hyperammonemia within the first few days of life. Milder forms of PA can present in infancy or early childhood with metabolic decompensation in the setting of a stressor, often an intercurrent illness. During decompensations, individuals with PA are prone to brain injury resulting in developmental delay, seizures and movement disorders caused by injury to the basal ganglia [1]. Recently, a later onset cardiac phenotype has been associated with PA. These patients have few, if any, symptoms during infancy, but can present with dilated cardiomyopathy, arrhythmia and/or sudden death in older children and adults [2–9].

PA is a rare disorder with an incidence in the general population of 1/50,000–1/100,000 births [10]. In the Old Order Amish and Mennonite communities (also referred to as Plain communities), its incidence is higher with a common mutation in the beta subunit of propionyl-CoA-carboxylase, PCCB c.1606 A > G [11]. Although the incidence remains unclear, over 75 individuals in Amish and Mennonite communities throughout the United States have been described with PA over the last 20 years (personal communication – Dr. Holmes Morton 12/18/15). The clinical phenotype most commonly seen in the Amish and Mennonite variant includes seizures (febrile and afebrile), cognitive impairment, hyperactivity-attention deficit disorder, keto-acidemia with coma and risk of basal ganglia necrosis, and most strikingly cardiomyopathy, long QTc and arrhythmias [12,13]. In the plain communities, there are clinically healthy individuals who are not recognized to have PA until death of a family member prompts testing (personal experience).

As with other metabolic disorders, optimal intrapartum management for PA is unclear, even in asymptomatic women who may or may not be on treatment for their disorder. Except for phenylketonuria (PKU), literature on pregnancy care in women with IEM and infant outcomes is scarce. Concerns during pregnancy include maintaining metabolic control throughout pregnancy and, in particular, during the perinatal and postpartum period – a time of significant stress and protein turnover [14]. This is the first case report to describe a pregnancy and intrapartum management for a woman with PA from the Amish community.

Case report

A 21 year old woman from the Old Order Amish community presented for initial prenatal assessment at approximately 27 weeks gestation. She was diagnosed with PA at the age of 18 months after an older

Abbreviations: PA, Propionic acidemia; IEM, Inborn error in metabolism.

☆ Financial support and disclosure: There are no financial disclosures by any author.

* Corresponding author at: 1500 Highland Ave. Rm 341, Madison, WI 53705.
E-mail address: jscottschwoerer@pediatrics.wisc.edu (J. Scott Schwoerer).

http://dx.doi.org/10.1016/j.ymgmr.2016.05.003

brother presented in metabolic crisis. She was asymptomatic. Diagnosis was based on urine organic acid analysis with the characteristic pattern of elevations in methylcitric acid, propionylglycine, tiglylglycine and 3-hydroxypropionic acid. She was also carnitine deficient. She was hospitalized at age 3 with lethargy but improved rapidly with treatment. She had three seizures in early childhood associated with acute illness, but none as an adult. She did not require additional hospitalizations or surgery. She reported no learning difficulties. The patient self-restricted her protein intake. She did not take a medical formula for PA or any dietary supplements. She had not been seen in a metabolic clinic since age 5 due to distance from the metabolic clinic and financial concerns. Family history included two affected siblings. One has learning difficulties and seizures and the other developed a cardiomyopathy at age 20. The patient's husband was tested and did not carry the common Amish mutation for PA.

The patient was evaluated during her pregnancy at 27 weeks, 33 weeks, and 37 weeks gestation. She did not have early prenatal care or an obstetrical ultrasound. An echocardiogram was performed at her first visit and showed a normal ejection fraction at 60–65%. EKG showed normal QT interval of 0.36 s and T wave inversion in the inferior and lateral leads. Fundal height was 23 cm at 27 weeks, felt to be normal given her petite body habitus. By 37 weeks gestation, the fundal height was 36 to 37 cm, consistent with normal fetal growth. She was evaluated by the metabolic team at 33 weeks. Recommendations included supplementation with biotin (10 mg/d) and L-carnitine (50 mg/kg/d) in addition to continuing a multivitamin and iron supplement. Diet history suggested low protein intake and plasma amino acid profile showed levels of some essential amino acids at the low end of concentrations expected for women without an IEM at >30 weeks gestation [15]. Thus, a 10% increase in protein intake was recommended.

The patient presented to the birthing center in early labor at 37 3/7 weeks gestation. Membranes had ruptured spontaneously 4 h prior to arrival (onset of labor). An IV line was placed 6 h after rupture of membranes and 10% dextrose in normal saline (D10NS) was started at 150 ml/h (1.5× maintenance for patient) and continued throughout labor. Patient was also encouraged to drink glucose containing fluids. The glucose infusion rate from intravenous fluids was ~3.8 mg/kg/min. The urine initially showed a small amount of ketones, however after initiation of IV fluids, urine ketones became negative and remained so. Blood samples for electrolytes and serum ammonia were drawn at 6 h after onset of labor and every 4 to 6 h through the course of labor to evaluate for any sign of acidosis or hyperammonemia indicating metabolic decompensation. These labs were normal initially and remained so. L-carnitine was given intravenously at 50 mg/kg of pre-pregnancy weight, followed by an additional 10 mg/kg every 4 h throughout labor. A total of 80 to 90 mg/kg was given through the course of labor. At 14 h of labor, Pitocin was initiated to augment labor. Ampicillin was given at a dose of 2 g intravenously at 18 h after spontaneous rupture of membranes. Delivery occurred at 19 h and 45 min after onset of labor and was uncomplicated. The infant was generous in size at 3930 g with moderate molding of the fetal head. Newborn exam was normal. The infant appeared to be approximately 38 weeks gestation. APGARs were 9 and 10 at 1 and 5 min respectively. There was no neonatal hypoglycemia. There were no maternal obstetric complications such as perineal lacerations or postpartum hemorrhage. Mother and infant did well postpartum and were discharged about 4 h after birth. Complications suggesting compromised metabolic control were not reported after discharge.

For the post-partum period, the patient was instructed to reduce dietary protein intake, but consume adequate calories from carbohydrate sources to reduce protein catabolism. An extra 500 kcal/day was recommended. She reported no concerns. At 1 year of age, the infant has normal growth and development.

Discussion

Cardiac complications are commonly reported in propionic acidemia; one survey of 54 patients, (age range 3 months to 33 years) found 19% with cardiomyopathy and 30% with arrhythmia, although a distinction between the subunit and mutation was not evaluated [16]. In the Amish community, propionic acidemia is commonly associated with a cardiac phenotype, although neurological injuries such as metabolic strokes and associated neurologic sequelae, particularly during periods of catabolism, are also reported [12,13]. Given the often late presentation of the cardiac phenotype, affected individuals may remain healthy into adulthood and wish to start families. There is little in the medical literature providing guidance to clinicians for pregnancy and intrapartum management of women with propionic acidemia. Recent guidelines from Europe recommend close monitoring of protein and carnitine needs as pregnancy progresses and providing supplemental calories using IV glucose during labor and delivery to minimize possible decompensation during labor and delivery [17].

In the literature, only five pregnancies are described in 3 women with PA [18–20] (Table 1). Significant complications included development of preeclampsia in both pregnancies from one woman with mutations in PCCB subunit requiring delivery at 31 and 32 weeks gestation.

Table 1
Prior pregnancies in women with propionic acidemia in the literature[a].

	This report	Lagendonk et al. 2012	Van Calcar et al. 1992	Van Calcar 2015/clinic experience	Van Calcar 2015/clinic experience	Van Calcar 2015/clinic experience
Maternal age at delivery (years)	21	26	22	26	28	30
Diagnosis	Diagnosed at 18 months due to presentation of a sibling		Diagnosis at 6.5 years with hypotonia, growth failure, slow motor development and h/o 3 metabolic decompensations	(Same patient as Van Calcar et al. 1992)	Diagnosis at age 4 with metabolic decompensation	Same patient
Treatment during pregnancy	Biotin, carnitine, protein self-restriction	Biotin, carnitine	Whole protein restriction, medical formula, carnitine	Whole protein restriction, medical formula, carnitine	Whole protein restriction, medical formula, carnitine, biotin	Whole protein restriction, medical formula, carnitine, biotin
Complications during pregnancy	None	None	None	None	Slowed fetal growth, Preeclampsia	Preeclampsia
Gestational age at delivery (weeks)	37	40	37	36.5	31	32
Delivery interventions	IV glucose	IV glucose	No glucose (short labor)	IV glucose	IV glucose	IV glucose
Delivery/postpartum complications	None	Placenta previa	None	None	Preeclampsia	Preeclampsia
Infant outcomes	Normal	Normal	Normal	Normal	Normal	Normal

[a] Table summarizing case reports from references [18,19,20].

Placenta previa was reported in one other woman. Experience in pregnancy, delivery and postpartum care for women with PA in the Amish population is also limited. Three women were diagnosed with PA after each had had multiple pregnancies and deliveries ((personal communication – Dr. Holmes Morton 12/18/15). These women were identified following recognition of PA in a child or sibling who developed cardiomyopathy. All three of these women had mild to moderate dilated cardiomyopathy with low left ventricle ejection fraction, increased end-diastolic volumes, and EKG abnormalities including sinus bradycardia with inverted T-waves and long QTc at the time of diagnosis. One of the three, who had had 5 children, required pacemaker insertion.

More literature exists for experience with pregnancy in women with methylmalonic acidemia (MMA), a metabolic disorder in the same pathway as PA caused by either a deficiency of methylmalonyl CoA mutase or a defect in cobalamin synthesis required for this enzyme's function. Case reports and a review of 17 pregnancies in women with various forms of MMA was recently reported [21–26]. Sixteen of 17 cases resulted in a live birth; complications during the pregnancy included two episodes of hyperammonemia in one pregnancy, pre-eclampsia in 3 pregnancies necessitating preterm delivery in 2 of these pregnancies and intrauterine growth restriction (IUGR) of the fetus was reported in 1 pregnancy [21]. Overall, reported infant outcome was good without growth or development concerns at follow-up ranging for neonatal period to 14 year of age. Complications of microcephaly, congenital heart defects and delayed development reported in maternal PKU were not found in this small cohort of maternal MMA cases, despite significant elevations in methylmalonic acid and other metabolic disturbances throughout many of these pregnancies [27] .

The very limited experience of pregnancy in women with PA suggests that there does not appear to be adverse effects on fetal development except for possible growth retardation noted in one of five known pregnancies [17]. Over-restriction of protein from both whole protein sources and PA/MMA medical formula may have played a role in this complication. For our patient, dietary history and diet record analysis suggested that she did self-restrict protein intake throughout pregnancy and was consuming an average of 1.0 g protein/kg (current weight) at 33 weeks gestation. Her plasma amino acids collected at that time showed low normal concentrations of many essential amino acids, indicating mild protein restriction. There was no evidence of fetal growth retardation in spite of restricted protein intake during pregnancy.

Cardiac output increases throughout pregnancy, especially during labor and delivery Cardiac decompensation during pregnancy is a concern in patients with occult cardiomyopathy, particularly in those with moderate to severe left ventricular systolic dysfunction [28]. Fortunately, an echocardiogram completed in our patient at 28 weeks gestation showed normal cardiac function. In the future, continued monitoring of cardiac status for cardiomyopathy and/or arrhythmia will be important to the patient's health and will impact her care particularly during pregnancy.

During delivery and post-partum, there is risk for metabolic decompensation due to stress and protein turnover, as reported in other inborn errors of protein metabolism. There are several case reports of significant complications in women with various urea cycle disorders, including maternal death from hyperammonemia in women who remained undiagnosed until after delivery [29–34]. Pregnancies in women with maple syrup urine disease are also described, including one maternal death related to cerebral edema from accumulation of leucine [18,35–38]. To help prevent labor and post-partum catabolism in our patient, a protocol was developed that included IV administration of dextrose containing fluids and L-carnitine to help maintain an anabolic state and decrease the production of organic acids. Lab monitoring included bedside urine ketones to demonstrate the patient remained in an anabolic state. The protocol appeared to be well tolerated and helped prevent catabolism during a prolonged labor and delivery.

In the Amish culture, labor and delivery most often occurs at home with minimal medical intervention. The patient, her spouse, and grandmother felt that the interventions during labor and delivery were excessive. Given this patient's uneventful medical history after early childhood, her self-perception was not of a person with an illness. However, given the length of labor, the interventions were reasonable and likely helped prevent excessive catabolism. For any future pregnancies, less medical intervention during labor could be considered by providing oral intake of high carbohydrate drinks with plans to initiate IV dextrose only if urine ketones increase suggesting a catabolic state. This change in protocol may be important to assure that this patient will seek medical care for her next pregnancy and labor.

In summary, this case describes the complexity of care for a woman with propionic acidemia in the Amish community, outlining an approach that successfully prevented catabolism in the setting of a long nulliparous labor.

Acknowledgments

Kate Chandry, CPM at LaFarge Medical Center; Nicoletta Drilias, RD at the University of Wisconsin Waisman Center; Dr. D. Holmes Morton, MD at the Clinic for Special Children, Strasburg PA; Dr. Shawn Sedgwick, MD at LaFarge Medical Center.

References

[1] U. Wendel, O. de Baulny, Branched-chain organic acidurina/acidemias, in: J. Saudubray, v. den Berghe G, W. JH (Eds.), Inborn Metabolic Diseases: Diagnosis and Treatment, fifth ed.Springer, New York, NY 2012, pp. 278–289.
[2] W.J. Rhead, A. White, D. Matern, J. Kraus, M. Ugarte, Cardiomyopathy as the presenting feature in a 15-year-old boy with propionic acidemia, J. Inherit. Metab. Dis. 30 (Suppl. 1) (2007) 35.
[3] A. Bhan, C. Brody, Propionic acidemia: a rare cause of cardiomyopathy, CHF 7 (4) (2001) 218–219.
[4] E. Jameson, J. Walter, Cardiac arrest secondary to Long QTc in a child with propionic acidemia, Pediatr. Cardiol. 29 (2008) 969–970.
[5] B. Kakavand, V.A. Schroeder, T.G. Di Sessa, Coincidence of Long QT syndrome and propionic acidemia, Pediatr. Cardiol. 27 (2006) 160–161.
[6] A. Laemmle, C. Balmer, C. Doell, et al., Propionic acidemia in a previously healthy adolescent with acute onset of dilated cardiomyopathy, Eur. J. Pediatr. 173 (7) (2014) 971–974.
[7] T.M. Lee, L.J. Addonizio, B.A. Barshop, et al., Unusual presentation of propionic acidaemia as isolated cardiomyopathy, J. Inherit. Metab. Dis. 32 (Suppl. 1) (2009) S97–101.
[8] T. Lucke, C. Perez-Cerda, M. Baumgartner, et al., Propionic acidemia: unusual course with late onset and fatal outcome, Metabolism 6 (2003) 809–810.
[9] R. Mardach, M.A. Verity, S.D. Cederbaum, Clinical, pathological, and biochemical studies in a patient with propionic acidemia and fatal cardiomyopathy, Mol. Genet. Metab. 85 (2005) 286–290.
[10] Carrillo-Carrasco N, Venditti C. Propionic Acidemia. In: GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK92946. (Accessed Feb 9, 2015)
[11] E.G. Puffenberger, Genetic heritage of older order Mennonites of Southeastern Pennsylvania, Am. J. Med. Genet. 121C (2003) 18–31.
[12] D.H. Morton, N. Muenke, C. Hendrickson, et al., Propionogenesis in brain: implications for management disorders of propionate metabolism, J. Inherit. Metab. Dis. 38 (Suppl. 1) (2015) S35–S378.
[13] D.H. Morton, P. Donnelly, A. Duffy, et al., Cardiomyopathy & sudden cardiac death are common in patients with the Amish-Mennonite-European variant of propionic acidemia PCCBc.1606A > G heart failure can be prevented & reversed by metabolic therapy, Mol. Genet. Metab. 111 (3) (2014) 409–413.
[14] P.L. Lee, Pregnancy issues in inherited metabolic disorders, J. Inherit. Metab. Dis. 29 (2006) 311–316.
[15] K. Matalon, P.B. Acosta, L. Castiglioni, et al., Protocol for nutrition support of maternal PKU, Maternal PKU Collaborative Study, National Institute of Child Health and Human Development 1998, p. 40.
[16] L. Pena, B.K. Burton, Survey of health status and complications among propionic acidemia patients, Am. J. Med. Genet. 158A (7) (2012) 1641–1646.
[17] M.R. Baumgartner, F. Hörster, C. Dionisi-Vici, et al., Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia, Orphanet J. Rare Dis. 9 (2014) 130.
[18] S.C. Van Calcar, Nutrition management during pregnancy: maple syrup urine disease, propionic acidemia, methylmalonic acidemia and urea cycle disorders, in: L.E. Bernstein, F. Rohr, J.R. Helm (Eds.), Nutrition Management of Inherited Metabolic Disease: Lessons from Metabolic University, Springer International, Switzerland 2015, pp. 229–240.
[19] S.C. Van Calcar, C.O. Harding, S.R. Davidson, et al., Case reports of successful pregnancy in women with maple syrup urine disease and propionic acidemia, Am. J. Med. Genet. 44 (5) (1992) 641–646.

[20] J.G. Langendonk, J.C. Roos, L. Angus, et al., A series of pregnancies in women with inherited metabolic disease, J. Inherit. Metab. Dis. 35 (3) (2012) 419–424.
[21] D.B. Raval, M. Merideth, J.L. Sloan, et al., Methylmalonic acidemia (MMA) in pregnancy: a case series and literature review, J. Inherit. Metab. Dis. 38 (5) (2015) 839–846.
[22] F. Deodato, C. Rizzo, S. Boenzi, et al., Successful pregnancy in a woman with mut_ methylmalonic acidaemia, J. Inherit. Metab. Dis. 25 (2002) 133–134.
[23] R. Lubrano, E. Bellelli, I. Gentile, et al., Pregnancy in a methylmalonic acidemia patient with kidney transplantation: a case report, Am. J. Transplant. 13 (2013) 1918–1922.
[24] E. Diss, J. Iams, N. Reed, D.S. Roe, C. Roe, Methylmalonic aciduria in pregnancy: a case report, Am. J. Obstet. Gynecol. 172 (3) (1995) 1057–1059.
[25] Jacquemyn Y, Den Hartog M, Eyskens F. Methylmalonic acidaemia in pregnancy. *BMJ* Case Rep. doi:http://dx.doi.org/10.1136/bcr-2014-203723 (12/18/15).
[26] A. Boneh, R.F. Greaves, G. Garra, et al., Metabolic treatment of pregnancy and post delivery period in a patient with cobalamin a disease, Am. J. Obstet. Gynecol. 187 (2002) 225–226.
[27] R. Koch, H. Levy, R. Matalon, et al., The north American collaborative study of maternal phenylketonuria, *AMA Am. J. Dis. Child.* 147 (1993) 1224–1230.
[28] J. Lewey, J. Haythe, Cardiomyopathy in pregnancy, Semin. Perinatol. 38 (2014) 309–317.
[29] H. Mendez-Figueroa, K. Lamance, V.R. Sutton, et al., Management of ornithine transcarbamylase deficiency in pregnancy, Am. J. Perinatol. 27 (10) (2010) 775–783.
[30] K. Tihtonen, J. Uotila, J. Lähde, et al., Risk of hyperammonemic coma in the puerperium: two cases of women with diagnosed and undiagnosed deficiency of urea cycle enzymes, Acta Obstet. Gynecol. 89 (2010) 404–406.
[31] D.E. Peterson, Acute postpartum mental status change and coma caused by previously undiagnosed ornithine transcarbamylase deficiency, Obstet. Gynecol. 102 (5Pt 2) (2003) 1212–1215.
[32] D.C. Crosbie, H. Sugumar, M.A. Simpson, et al., Late-onset ornithine transcarbamylase deficiency: a potentially fatal yet treatable cause of coma, Crit. Care Resusc. 11 (3) (2009) 222–227.
[33] U. Schimanski, D. Krieger, M. Horn, et al., A novel two-nucleotide deletion in the ornithine transcarbamylase gene causing fatal hyperammonia in early pregnancy, Hepatology 24 (1996) 1413–1415.
[34] P.H. Arn, E.R. Auser, G.H. Thomas, et al., Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus, N. Engl. J. Med. 322 (23) (1990) 1652–1655.
[35] S. Yoshida, T. Tanaka, Postpartum death with maple syrup urine disease, Int. J. Gynaecol. Obstet. 81 (1) (2003) 57–58.
[36] M. Tchan, M. Westbrook, Wilcox, et al., The management of pregnancy in maple syrup urine disease: experience with two patients, JIMD Rep. 10 (2013) 113–117.
[37] A.E. Wessel, K.M. Mogensen, F. Rohr, et al., Management of a woman with maple syrup urine disease during pregnancy, delivery and lactation, J. Parenter. Enter. Nutr. 39 (7) (2015) 875–879.
[38] S. Grunewald, F. Hinrichs, U. Wendel, (1998) pregnancy in a woman with maple syrup urine disease, J. Inherit. Metab. Dis. 21 (2) (1998) 89–94.