Use of Gastrostomy Tube to Prevent Maternal PKU Syndrome

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Abstract Maternal Phenylketonuria Syndrome (MPKU) can occur in infants born to mothers with PKU with poor metabolic control during pregnancy. Elevated phenylala-

nine (phe) acts as a teratogen to the developing fetus with consequences including intellectual disability, microcephaly, facial dysmorphism, growth retardation, and congenital heart disease. MPKU can be prevented if metabolic control is achieved by 8–10 weeks gestation. If control is not achieved, there is a significant risk for MPKU. Therefore, in women with poor metabolic control at time of pregnancy, establishing metabolic control quickly is important.

Clinically, establishing metabolic control in women with PKU can present challenges. Social issues, psychological issues, and insufficient education about PKU play an important role in a patient's inability to reinstitute this challenging diet. Maintaining phe levels within a range to allow for infant growth, while preventing toxicity, is challenging, particularly for those women who no longer follow the PKU diet. Gastrostomy tube placement is an option to deliver medical formula to women who are unable to restart diet due to severe nausea or palatability issues.

Here we discuss two pregnancies in which a gastrostomy tube was placed to achieve metabolic control after other measures failed to reduce phe concentrations into the recommended range. For these two pregnancies, placement of the gastrostomy tube led to improvement in phe levels with normal infant outcomes including normal growth, head circumference, and heart structure.

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Abbreviations

CHD	Congenital heart disease
Gm	Grams
Kcals	Kilocalories
MPKU	Maternal phenylketonuria syndrome
phe	Phenylalanine
PKU	Phenylketonuria

U.S United States
Kg Kilogram
cm centimeter

Introduction

Maternal phenylketonuria (PKU; MIM #261600) syndrome (MPKU) is well described in infants born to women with PKU in poor metabolic control (Koch et al. 1993, 2000; Lee et al. 2003; Levy 2003; Levy and Ghavami 1996; Levy et al. 2001; Lenke and Levy 1980; Matalon et al. 2003; Rouse et al. 2000). Its sequelae include intellectual disability, microcephaly, facial dysmorphism, growth retardation, and congenital heart disease.

Current U.S. recommendations to prevent MPKU include achieving blood phenylalanine (phe) concentrations of 120–360 $\mu\text{mol/L}$ three months prior to conception and maintaining this control throughout pregnancy (National Institutes of Health Consensus Development Panel 2001). The United Kingdom recommends lower levels of 60–240 $\mu\text{mol/L}$ prior to conception and throughout the pregnancy (Medical Advisory Panel of the National Society for Phenylketonuria 2004).

Unfortunately, there are many barriers for women to achieve these recommendations. Many pregnancies are unplanned and therefore phe concentrations are often elevated at conception. Reinitiating diet can be difficult prior to pregnancy, especially for women who have discontinued a phe-restricted diet (Brown et al. 2002).

New treatment options to prevent maternal PKU syndrome include sapropterin dihydrochloride (Kuvan[®], Biomarin Pharmaceuticals, Novato, CA), which is effective in women who respond to this medication (Koch et al. 2005; Koch 2008; Lee et al. 2008; Trefz and Blau 2003; Pridjian et al. 2008). However, diet management remains the only treatment for the majority of women and new options are needed to improve diet success.

Use of feeding tubes, both percutaneous gastrostomy and jejunostomy tubes, have been reported for nutritional support during pregnancy, especially for the treatment of severe hyperemesis gravidarum (Godil and Chen 1998; Irving et al. 2004; Koh and Lipkin 1993; Pendlebury et al. 1997; Saha et al. 2009; Serrano et al. 1998; Shaheen et al. 1997). In these case reports and series, placement of the tubes to provide nutrition proved to be safe and effective and led to improved nutritional status during pregnancy and normal fetal outcomes. Complications included superficial infection (Irving et al. 2004; Serrano et al. 1998) and dislodgment of the tube (Saha et al. 2009). Use of a feeding tube in a pregnant woman with PKU to improve metabolic control has not been previously reported in the literature.

In this case series, we discuss use of a gastrostomy tube to help establish metabolic control in pregnant women with PKU who failed to establish phe concentrations within the recommended range of 120–360 $\mu\text{mol/L}$ despite multiple interventions to reinitiate diet including education, antiemetics, and intravenous hydration.

Methods

For each pregnancy, phe and tyrosine concentrations were monitored weekly on filter paper by tandem mass spectroscopy and plasma amino acid profile was evaluated each trimester (Rashad et al. 1995; Slocum and Cummings 1991). Other prenatal laboratory tests were ordered at the discretion of the patient's obstetrician. Changes in diet were recommended based on laboratory data and maternal weight gain.

A fetal echocardiogram and anatomic fetal ultrasound was obtained at approximately 20 weeks gestational age. Serial ultrasound evaluations monitored fetal growth. Neonatal echocardiogram was obtained. Growth parameters and physical exam were assessed at birth and 8 weeks of age.

Case Reports

Patient A

Patient A was a 26-year-old woman with classical PKU diagnosed by newborn screening and was on a phe-restricted diet until age 9. After that time, clinic follow-up was sporadic and infrequent phe levels averaged 1,200 $\mu\text{mol/L}$. She had a history of frequent vomiting during adolescence.

She presented to our clinic at 5 weeks gestation with an unplanned pregnancy. Her initial phe level was 647 $\mu\text{mol/L}$ (Table 1). She was admitted for dietary education and management. Phe levels decreased quickly to 85 $\mu\text{mol/L}$. Over the next month, the patient had persistent nausea despite treatment with intravenous fluids and ondansetron

Table 1 Phe concentrations pre- and post-gastrostomy tube placement

	Patient A	Patient B
Gestational age at placement of gastrostomy tube	13 3/7 weeks	13 weeks
Phe concentration at presentation	647 $\mu\text{mol/L}$	538 $\mu\text{mol/L}$
Mean phe concentration ($\pm$ st dev) before gastrostomy tube	469 $\mu\text{mol/L}$ ($\pm$ 306)	382 $\mu\text{mol/L}$ ($\pm$ 157)
Mean phe concentration ($\pm$ st dev) after gastrostomy tube	282 $\mu\text{mol/L}$ ($\pm$ 135)	168 $\mu\text{mol/L}$ ($\pm$ 92)

administration. She tried multiple medical formulas, including prepackaged liquid and capsules, with poor tolerance. At 13 3/7 weeks gestation, the patient was readmitted with increasing phe levels and poor weight gain. A gastrostomy tube was placed without complication.

Even with a gastrostomy tube, nausea and vomiting continued during the day, and thus continuous feeding of medical formula was initiated overnight. Medical formula provided 60-gm protein equivalents (1.1 gm/kg pre-pregnancy weight) and 372 kcals per day. All other calorie sources were taken orally. The patient was prescribed 300 mg phe per day; however, even with education, she failed to formally count phe intake, which likely caused several elevated phe levels after gastrostomy tube placement. Since her formula was provided overnight, her phe levels were likely lower in the morning when bloods were collected (MacDonald et al. 1996). Thus, phe concentrations were obtained on 1 day in the morning and evening and showed similar results. With this regimen, the patient gained weight and maintained blood phe concentrations near or within the control range of 120–360 $\mu\text{mol/L}$ (Fig. 1).

Ultrasounds showed appropriate fetal growth with normal head circumference. Initial fetal echocardiogram at 20 weeks gestation was within normal limits. A subsequent echocardiogram 2 days prior to delivery showed a normal four chambered heart, but a mildly dilated pulmonary artery was noted. An infant girl was born at 40 6/7 weeks via Cesarean section due to failure to progress and unsuccessful attempt at forceps-assisted delivery. Infant growth parameters were within normal limits (Table 2). Echocardiogram on day 2 of life showed a moderate patent ductus arteriosus, which was considered normal for a newborn. Repeat study at 8 weeks of life showed normal heart anatomy. Normal

development and neurologic exam were found at 19 days and 8.5 weeks of age.

Patient B

At presentation, Patient B was a 26-year-old woman with classical PKU diagnosed on newborn screening and remained on a phe-restricted diet with good metabolic control until age 12. She was followed regularly in clinic until age 18 with a mean phe concentration of 1,000 $\mu\text{mol/L}$. She attended a camp for adolescent females with PKU during several summers. The patient reinitiated care when planning to start a family and completed a trial of sapropterin (Kuvan®). She responded with a 21% decrease in the levels, but she elected to not continue this medication.

The patient informed our clinic of her pregnancy at approximately 4 weeks gestation, and her initial phe concentration was elevated at 538 $\mu\text{mol/L}$ (Table 1). Her compliance with diet and formula improved, and her phe level initially decreased to the recommended range; however, nausea and vomiting became significant issues and she was unable to consume the recommended formula volume. She tried multiple medical formulas and capsules, with poor tolerance. Regular ondansetron administration was initiated, but she continued to be unable to consume all of her formula. At 10 weeks gestation, the risks and benefits of sapropterin use during pregnancy were discussed with the patient and treatment initiated. Despite sapropterin treatment, phe levels remained above 360 $\mu\text{mol/L}$. Thus, at 13 weeks gestation, a gastrostomy tube was placed without complication.

Fig. 1 Blood phe concentrations during pregnancy. Both patients A and B had an elevated blood phe concentration at presentation. Gastrostomy tubes were placed at 13 weeks gestation. Blood phe

concentrations remained in recommended range for the majority of the remainder of both pregnancies. Circle symbol designates patient A and triangle symbol designates patient B

Table 2 Infant outcome for patients with gastrostomy tubes placed during pregnancy

	Infant A	Infant B
Gestational age at delivery	40 6/7 weeks	38 6/7 weeks
Sex	Female	Male
Head circumference at delivery (% ^a)	34 cm (25%)	34 cm (18%)
Weight at delivery (% ^a)	3,236 gm (25%)	3,218 gm (25%)
Length at delivery (% ^a)	51 cm (40%)	50.8 cm (50%)
Echocardiogram results	Normal	Normal
Newborn screen	Normal	Normal
Neurologic exam ^b	Normal	Normal
Developmental assessment ^b	Normal	Normal

^a Percentiles from CDC growth chart^b In the neonatal period and 8 weeks of age

Shortly after gastrostomy tube placement, the patient discontinued sapropterin. With four daily bolus medical formula feedings via gastrostomy tube, the patient gained weight and maintained phe levels near or within the control range of 120–360 $\mu\text{mol/L}$ (Fig. 1). Her medical formula provided 80 gm protein equivalents (1.2 gm/kg pre-pregnancy weight) and 496 kcals per day. Additional kcals sources were taken orally. Prior to gastrostomy tube placement, she consumed less than 225 mg phe per day. After gastrostomy tube placement, phe tolerance immediately improved and intake increased to 300 mg phe per day. Phe tolerance increased further during the second half of pregnancy, and 1,500 mg phe per day was tolerated at the time of delivery.

Ultrasounds showed appropriate fetal growth. A 20-week anatomic survey ultrasound showed a four chambered heart and outflow tracts. An infant boy was born at 38 6/7 weeks via vaginal delivery after induction of labor due to severe preeclampsia. Growth parameters were within normal limits (Table 2). Echocardiogram on day 0 of life showed a structurally normal heart and patent ductus arteriosus. Normal development and neurologic exam were noted at 11 days and 8 weeks of age.

Results

For both patients A and B, phe concentrations in early pregnancy were above the recommended range of 120–360 $\mu\text{mol/L}$, but improved following gastrostomy tube placement (Table 1 and Fig. 1). Maternal weight gain also improved after gastrostomy tube placement (Fig. 2). Ultrasound findings for infants A and B showed good weight gain and

Fig. 2 Maternal weight gain during pregnancy. Improved maternal weight gain was noted for both patients after placement of a gastrostomy tube. Circle symbol designates patient A and triangle symbol designates patient B

expected head circumference growth. After delivery, both infants showed normal growth, heart structure, and neurologic evaluation (Table 2). For both patients, the gastrostomy tube was removed in the postpartum period.

Discussion

Maternal PKU syndrome is a known risk to infants born to mothers with PKU. Good outcomes for these infants can be achieved with strict control of maternal blood phe concentrations prior to conception and throughout pregnancy. Achieving metabolic control in patients can be challenging due to nausea and vomiting that accompanies pregnancy and poor palatability of formula, particularly for women who discontinued diet treatment during adolescence or adulthood.

One option to ensure optimal intake of medical formula is placement of a gastrostomy tube. Placement of a gastrostomy tube is a surgical procedure with risk of complications, particularly from infection. However, both gastrostomy and jejunostomy tubes have been used on a limited basis in pregnant women with hyperemesis gravidarum (Godil and Chen 1998; Irving et al. 2004; Koh and Lipkin 1993; Pendlebury et al. 1997; Saha et al. 2009; Serrano et al. 1998; Shaheen et al. 1997). In these reports, the women showed improved nutritional status and normal infant outcome with minimal complications and risk to the pregnancy. Surgery is relatively common during pregnancy and occurs in 0.5–2% of pregnancies (Allaert et al. 2007; Kuczkowski 2004). Surgery and anesthesia do pose a small risk, particularly for spontaneous abortion and lower birth weight, although this risk may be related to the woman's underlying medical condition (Allaert et al. 2007; Cheek and Baird 2009).

For women with PKU, these risks need to be weighed against the risk of maternal PKU symptoms for the infants.

For our patients, attempts at diet control with adequate intake of medical formula failed due to significant nausea and issues with palatability. This issue was particularly evident in patient A who required continuous nocturnal feeds to prevent emesis. Gastrostomy tube placement allowed for achievement of metabolic control with a normal infant outcome, including growth and heart structure. However, feeding tubes are only beneficial if compliance with medical formula and a low phe diet is maintained. Thus, a woman's motivation to use the tube and comply with clinic recommendations needs to be assessed prior to gastrostomy tube placement.

In conclusion, early placement of the gastrostomy tube is an option to improve blood phe concentrations when other options to improve diet compliance have failed. Placement of a gastrostomy tube should be considered if phe concentration remains elevated despite maximizing other therapies including nutrition, treatment of nausea and vomiting, psychosocial support, and possibly use of sapropterin. Patient compliance is key for success of gastrostomy tube feedings to improve metabolic control and prevent MPKU syndrome.

Synopsis Statement

Gastrostomy tube placement in pregnant women with phenylketonuria is another option to control phenylalanine levels and prevent *maternal PKU syndrome*.

Jessica Scott Schwoerer

Conflict of Interest Questions

1. Have you in the past 5 years accepted the following from an organization that may in any way gain or lose financially from the result of your study or the conclusion of your review, editorial, or letter:
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3. Have you acted as an expert witness on the subject of your study, review, editorial, or letter? No
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Gregory Rice

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 - a. Reimbursement for attending a symposium? – Yes, BioMarin Pharmaceuticals, Kuvan Advisory Meeting 2009. I do not believe that this publication will have any financial effect on the above but I am disclosing the relationship for completeness.
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3. Have you acted as an expert witness on the subject of your study, review, editorial, or letter? No
4. Do you have any other competing financial interests? No

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