BACKGROUND

For pregnant women with Phenylketonuria (PKU), it is critical to maintain blood phenylalanine (phe) levels in treatment range of 2-6 mg/dL (120-360 µmol/L) due to the harmful effects of elevated phe to the developing fetus. These teratogenic effects can include growth retardation, microcephaly, developmental delays, dysmorphic features, congenital heart defects and seizures known as maternal PKU syndrome. Dietary treatment and/or use of pharmaceuticals to control phe levels have been shown to maintain phe levels within treatment range. Amino acids have traditionally been used as the main source of phe in a PKU diet. Glycomacropeptide (GMP), an intact protein low in phe, is a recent product that has been used as an option for a protein source. In 2007, sapropterin dihydropyridine (Kuvan), a synthetic form of the naturally occurring co-factor tetrahydrobiopterin, was approved as the only pharmacologic agent used to lower blood phe levels.

There is limited data regarding use of sapropterin and GMP formula during pregnancy; however, both sapropterin and GMP are both viable options in PKU treatment. During pregnancy, individual treatment methods are tailored specifically for each woman.

METHODS

A retrospective chart review of maternal PKU pregnancies from the past fifteen years was performed at Ann and Robert H. Lurie Children’s Hospital of Chicago. Treatment methods and birth outcomes were assessed. Dietary treatment methods included phenylalanine (phe) restricted diet, amino acid (AA) based medical formula and glycomacropeptide (GMP) based medical formula. Pharmaceutical treatment included use of sapropterin (S) in combination with diet therapy except for two pregnancies where sapropterin was used as the sole treatment method. Sapropterin was dosed and maintained at approximately 20 mg/kg using the pre-pregnancy weight for all but one pregnancy. Treatment outcomes reviewed were blood phe levels, phe intake, protein intake, nutritional labs and birth outcomes. Anthropometric measurements were assessed using the WHO 0-24 months and 2013 Fenton growth charts, specifically z-scores for head circumference (HC) and weight (wt). Z-scores of >2 were considered to be within normal limits. Microcephaly is defined as a head circumference z-score of <−2 SD from the mean. Low birth weight (LBW) is defined as <2.5 kg.

RESULTS

Sixteen PKU women with nineteen live births were included in the review. Median infant age at follow up visit and assessment of anthropometric measurements was 8 weeks old.

Four women with four births were treated with phe restriction, GMP formula and sapropterin. Three out of the four women were on full treatment prior to pregnancy. One patient started treatment at 6 weeks of pregnancy. The average phe level in these women during pregnancy was 2.61 mg/dL (n = 161). Average percentage of protein intake was 59.7% from GMP and 40.3% from food derived protein. Average HC z-score was −0.48 and average wt z-score was −0.08. Infant of mother who started treatment after pregnancy was found to have LBW, yet average phe levels were within treatment range throughout pregnancy. This patient discontinued sapropterin use for 10 days in the first trimester. Based on phe levels assessed during these 10 days, sapropterin was restarted at 10 mg/kg. All other birth outcomes in this group were normal.

One woman with two births was treated with sapropterin exclusively. Patient was on full treatment prior to both pregnancies. The average phe level during pregnancy was 3.67 mg/dL (n = 88). 100% of protein intake was from food derived protein. Average HC z-score was 0.75 and average wt z-score was 0.51. Both birth outcomes were normal.

One woman with a single birth was treated with phe restriction, AA formula and sapropterin. Treatment was started at 5 weeks of pregnancy. The average phe level during this pregnancy was 3.6 mg/dL (n = 24). Average percentage of protein intake was 84% from AA and 16% from food derived protein. Average HC z-score was 1.1 and average wt z-score was 2.21. Birth outcomes were normal.

Two women with three births were treated with phe restriction, GMP and AA formula. One woman with two births was on full treatment prior to both pregnancies. One patient started treatment at 6 weeks of pregnancy. The average phe level during pregnancy was 3.02 mg/dL (n = 179). Average percentage of protein intake was 13.4% from GMP, 78.8% from AA and 7.8% from food derived protein. Average HC z-score was −0.76 and average wt z-score was −0.47. One patient who started treatment after pregnancy had an average phe level of 6.4 mg/dL in the 1st trimester. All birth outcomes in this group were normal.

Eight women with nine births were treated with phe restriction and AA formula. In four of the nine pregnancies, the women were on full treatment prior to pregnancy. One patient started treatment at 3.5 weeks of pregnancy. One patient started treatment at 10 weeks of pregnancy and one patient started treatment at 6 weeks of pregnancy but never achieved phe control throughout the pregnancy. The average phe level in this treatment group during pregnancy was 3.88 mg/dL (n = 471). Average percentage of protein intake was 91.6% from AA and 8.4% from food derived protein. Average HC z-score was −0.77 and average wt z-score was −0.32. One pregnancy where treatment was started at 6 weeks of pregnancy resulted in premature birth, microcephaly, minor dysmorphic facial features and LBW consistent with maternal PKU syndrome. The mother was admitted to the hospital twice within the 1st trimester for hyperemesis and poor phe control. Average phe level per trimester was 11 mg/dL in the 1st, 15 mg/dL in the 2nd and 15.8 mg/dL in the 3rd trimester. She was again admitted in the 3rd trimester for steroid injections for poor fetal growth. There was no weight gain throughout pregnancy. The child was later diagnosed with seizures at four years of age. Another pregnancy where treatment was not started until 10 weeks of pregnancy also resulted in microcephaly, minor dysmorphic facial features and low birth weight consistent with maternal PKU syndrome. The mother was admitted after a 2 week failed attempt to attain phe control at home. Average phe level per trimester was 9.7 mg/dL in the 1st, 1.8 mg/dL in the 2nd and 1.6 mg/dL in the 3rd trimester. Patient lost 5.45 kilograms during the pregnancy and was induced at 37 weeks due to poor fetal growth. A third infant where mother was on full treatment prior to conception was noted to have LBW. During this pregnancy, average phe levels in the 2nd and 3rd trimesters were 6.2 mg/dL and 6.4 mg/dL. Patient was induced at 38 weeks due to high phe levels. All other birth outcomes for this treatment group were normal. One infant was diagnosed with PKU; treatment was initiated with sapropterin at one year of age.

SUMMARY

All average phe levels were within treatment range across treatment groups. All treatment groups had average z-scores for HC and wt that fell within normal limits. Two infants in the phe restricted and AA formula treatment group had LBW and findings consistent with maternal PKU syndrome. These birth outcomes were likely due to delayed treatment or poor phe control. One other pregnancy in the phe restricted and AA formula group resulted in LBW, which was possibly related to poor phe control. A fourth infant in the phe restriction, GMP and sapropterin treatment group whose mother started treatment at six weeks of pregnancy was found to have LBW, yet average phe levels were within treatment range throughout pregnancy. Although there is limited data regarding use of sapropterin and GMP formula during pregnancy, this chart review shows positive treatment outcomes including average phe levels within treatment range and average z-scores for HC and wt within normal limits for pregnancies treated with GMP and sapropterin.

REFERENCES