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Breastfeeding Success Among Infants with Phenylketonuria

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Breast milk is the nutrition of choice for human infants (American Academy of Pediatrics, 2005; American Association of Family Physicians, 2008; Association of Women's Health Obstetric and Neonatal Nurses, 2005; Canadian Paediatric Society, 2005; U.S. Preventive Services Task Force, 2008; World Health Organization, 2009). The literature on the benefits of breast milk and breastfeeding for infants and mothers has established multiple positive outcomes for infants (Hoddinott, Tappin, & Wright, 2008; Horta, Bahl, Martines, & Victora, 2007; Ip et al., 2007). Breast milk has advantages for infants that distinguish it from standard commercial infant formulas. These advantages include growth factors, hormones, immunological factors, and long-chain polyunsaturated fatty acids. For infants with phenylketonuria (PKU), breast milk has additional advantages over any standard commercial infant formula, such as a lower concentration of protein and a lower content of the amino acid, phenylalanine. Despite these benefits, some clinics encourage mothers of infants with PKU to breastfeed whereas others present breastfeeding as an unacceptable option. Although the possible risks and benefits of breastfeeding infants with PKU have been discussed, there is limited research and practice describing breastfeeding infants with PKU. As a result, breastfeeding infants with PKU is based more upon limited clinical experiences rather than upon evidence based practice that aims to apply the best scientific evidence gained from research to clinical decision making.

Review of the Literature

Phenylketonuria is an autosomal recessive genetic disorder that, although most common in people of Northern European heritage, is found in all ethnic groups (Donlon, Levy, &

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Scriver, 2007; Kaye, & Committee of Genetics, 2006; Meyers, 2002). In classic PKU, there is a metabolic block that prevents the conversion of phenylalanine (Phe) to tyrosine (Tyr) in the normal metabolism of protein within the liver (Jervis, 1953) (See Figure 1). Excessive Phe accumulates in the blood and tissues as a toxic metabolite that damages central nervous system cells resulting in progressive and irreversible cognitive deficits (Huttenlocher, 2000; Malamud, 1966; Scriver, Levy, & Donlon, 2008).

Prior to newborn screening for PKU, the disorder was diagnosed from classical clinical manifestations that became apparent over time. These manifestations included: normal development at birth but failure to attain early developmental milestones; excessively fair hair, skin, and eyes; and a "musty" odor of skin, hair, perspiration, and urine. By the time the infant was diagnosed, impairment of cerebral function had already occurred (Huttenlocher, 2000; Malamud, 1966; Scriver et al., 2008). Today, PKU diagnosis is made soon after birth from results of newborn screening tests and treatment begins immediately (Dhondt, 2007; Guthrie, & Susi, 1963; Therrell, & Adams, 2007). The treatment of PKU involves a lifelong diet low in Phe, frequent monitoring of blood Phe values and regular consultation with the pediatric metabolic team of physicians, nurses, and dieticians. Normal cognitive development is expected when Phe blood levels are managed and remain within acceptable levels (120–360µmol/L) (Cummings, 2008; de Baulny, Abadie, Feillet, & de Parscau, 2007).

In the early years of PKU treatment, the standard of care for infants diagnosed with PKU was to be immediately weaned from breastfeeding. To maintain appropriate Phe levels (120–360µmol/L), the infant was then placed on a diet of Phe-free or low-Phe formula combined with standard commercial infant formula (Ernest, McCabe, Neifert, & O'Flynn, 1980; Huner, & Demirkol, 1996; McCabe et al., 1989; Motzfeldt, Lilje, & Nylander, 1999). This combination was believed to be the only effective way to monitor the infant's intake and allow for precise titration and measurement of the intake of Phe in order to protect the infant's neurological and cognitive development (Blau, Duran, & Gibson, 2008). Mothers of infants with PKU titrated Phe-free formula with standard commercial formula based on Phe levels obtained from infant heel sticks. This management strategy thus precluded breastfeeding infants with PKU (Ernest et al., 1980; Huner, & Demirkol, 1996; McCabe et al., 1989; Motzfeldt et al., 1999).

In the late 1970's, researchers determined that breast milk was lower in Phe than standard commercial formula (Janas, Picciano, & Hatch, 1985; Lonnerdal, Forsum, Gebre-Medhin, & Hambraeus, 1976; Nayman, Thomson, Scriver, & Clow, 1979). Thus, a larger volume of breast milk than standard commercial infant formula could be fed to infants with PKU. In 1980, the first publication appeared describing breastfeeding infants with PKU (Ernest et al., 1980). Subsequent research on bottle-fed infants with PKU compared to breast-fed infants with PKU during the first six months, showed that those infants with PKU who had been breast-fed and supplemented with Phe-free formula had lower protein and Phe levels (van Rijn et al., 2003). In addition, combining breast milk and Phe-free formula in managing the diet of infants with PKU did not adversely affect Phe control (Greve, Wheeler, Green-Burgeson, & Zorn, 1994; McCabe et al., 1989). In more recent studies, breast-fed infants with PKU had no significant differences in weight gain, daily Phe intake, and the mean plasma Phe concentrations compared to formula-fed infants with PKU (Cornejo et al., 2003; Demirkol et al., 2001; Huner, Baykal, Demir, & Demirkol, 2005; Kanufre et al., 2007; McCabe et al., 1989; Motzfeldt et al., 1999; van Rijn et al., 2003). Although based on relatively small samples (usually < 50 participants) reflecting the rarity of PKU in the population, the results from these studies consistently supported the conclusion that breast milk supplemented with Phe-free formula is an acceptable dietary treatment for infants with PKU.

Despite evidence that breast milk is compatible with effective dietary management of PKU, the majority of breastfeeding studies in PKU are studies of the incidence of breastfeeding in infants with PKU and consistently showed that few mothers of infants with this condition persist in breastfeeding. For example, an Italian study identified one-year breastfeeding rates were significantly lower in infants with PKU than in the general population (Agonstoni, Verduci, Fiori, Riva, & Giovannini, 2000). Most recently, only 19 of 35 Brazilian mothers were found to be breastfeeding at 6 months and only 11 of these mothers continued to breastfeed at 12 months (Kanufre et al., 2007).

The duration of breastfeeding is also shorter for infants diagnosed with PKU. In Norway, where breastfeeding is the norm with 92% of mothers exclusively breastfeeding during the first three months and 40% continuing to breastfeed to infant age of 15 months (World Health Organization, 2007), mothers breast-fed their infants with PKU (n = 74) for a mean duration of 7 months (Motzfeldt, Lilje, & Naylander, 1999). In another study, breast-fed infants with PKU (n = 39) were identified to have a shorter mean duration of 4 months (Segev, Abraham, Anikster, & Schwartz, 2004) as did a Dutch study at 2.5 months (van Rijn et al., 2003) and the Italian study with a median of 1 month (Agostoni, Verduci, Fiori, Riva, & Giovannini, 2000). In two Turkish studies, the mean duration of breastfeeding by mothers of infants with PKU was higher with one group breastfeeding for a mean of 9.6 months (n = 13; Hunter & Demirkol, 1996), overall, mothers with infants with PKU tend to breastfeed for a shorter period of time than mothers of infants with PKU.

Notably, there are no published studies of the incidence or duration of breastfeeding infants with PKU conducted in the United States. Therefore, the purpose of this study was to compare the incidence and duration of breastfeeding and corresponding Phe levels of breastfeed and formula-fed infants with PKU in the caseload of a pediatric metabolic clinic at an urban tertiary-care medical center in the United States. Our first objectives were to determine the incidence of breastfeeding at the time of diagnosis, determine the duration of breastfeeding after infants were diagnosed, determine Phe control during the period of breastfeeding, and compare Phe values between breast-fed and formula-fed infants with PKU.

Methods

The study design was a retrospective chart review performed at an urban, tertiary-health care center with two hospitals, an adult hospital and a children's hospital. Serving Oregon and Southwest Washington, the two hospitals had combined inpatient beds of 560. The children's hospital is dedicated to the care of children and their families, and includes a 20 bed pediatric intensive care unit and a 46 bed neonatal intensive care unit. In addition, the children's hospital has the only pediatric metabolic clinic program in the state, to which all infants diagnosed with PKU are referred.

The retrospective chart review took place from 2006 through 2008 following institutional review board approval. Medical records for infants diagnosed with PKU were reviewed beginning with 2005 and ending with 1980, the year when no further breastfeeding cases in the PKU population were identified. Specifically, infants' medical, dietary, and clinical records that provided assessments of the infant from both dietitian and medical perspectives, as well as serial information on the Phe levels over time, provided the data.

The data were collected using a medical record abstraction tool for recording data and recording data were limited to those variables needed to address the study objectives (i.e., dates of serial Phe levels and mode of feeding). In addition, demographic data were

collected on the infant. Phe results that had been reported from newborn screening and follow up serial Phe results in the past were documented. No newborn screen bloodspots were accessed or retested. The frequency of measuring plasma Phe levels with Guthrie cards, specific filter paper onto which blood from a heel-prick is saturated, is depended on the infant's age and Phe tolerance. Generally, the frequency that Phe levels were assessed ranged from every other day to twice a week when levels were stable within the therapeutically aimed range (120–360 μ mol/1). Between 1980 and 2002, plasma Phe levels were determined using an amino acid analyzer. During 2002, the laboratory transitioned to tandem mass spectrometry to determine Phe analytes, and this method was used through 2005. The use of tandem mass spectrometry has improved the detection of inborn errors of metabolism with improved sensitivity and specificity of newborn screening for amino acid disorders, such as PKU.

Infants were categorized as breast-fed or bottle-fed from the medical record, in which the type of feeding was noted with the serial Phe levels. Breastfeeding/breast-fed was defined as an infant with PKU who received breast milk either directly from the breast or as expressed breast milk delivered from a bottle, and received Phe-free formula from a bottle to maintain appropriate Phe levels. Bottle-feeding/bottle-fed was defined as an infant with PKU who received all sources of nourishment, including standard commercial infant formula and Phe-free formula, from a bottle. The date breastfeeding was terminated was determined in two ways. The date that the last breastfeeding was recorded was taken as the end date of breastfeeding or, alternatively, the date that breastfeeding was terminated was located in the dietitian's record. If this latter date was the most precise, it was accepted over the first. Statistical analyses were conducted using SPSS 16 (SPSS Corporation, Chicago, IL). Data were analyzed using descriptive statistics, chi square and ANOVAs as appropriate.

Sample

Charts were reviewed for all newborns who were screened positive for PKU, confirmed by laboratory analysis, and began medical and dietary management of PKU at the pediatric metabolic clinic between 1980 and 2005. Of the 102 infants diagnosed with PKU during these 25 years, the data for 97 infants were retained for analysis. Five were eliminated due to fewer than five Phe levels during the first year, transfer of care to another metabolic clinic, or transfer from another metabolic clinic prior to one year of age. Of the 97 infants with complete data managed by the Pediatric Metabolic Clinic during the study period, 75 infants were breast-fed for varying lengths of time after their diagnosis and 22 infants were bottlefed. The proportion of males (n = 48; 50%) and females (n = 49; 51%) was comparable to that of other autosomal recessive disorders. Most of the infants had normal birth weights. Gestational age was not systematically recorded, but the birth weights suggested that these infants were born at term as birth weights were of normal range and indicative of full term births. The infant characteristics of both groups are presented in Table 1; there were no significant differences between the breast-fed and bottle-fed infants with PKU.

Results

Incidence of Breastfeeding at Time of Diagnosis

The overall initiation rate for breastfeeding of infants (n = 75) with PKU was 77%. The incidence of breastfeeding at the time of diagnosis by decade for infants diagnosed with PKU consistently exceeded the *Healthy People 2000* and *2010* breastfeeding objective for initiation of breastfeeding (Tables 2 and 3). During the 1980's, the incidence of breastfeeding at the time of diagnosis was 72%. This slightly decreased during the 1990's to 70%. However from 2000 to 2005, the incidence of breastfeeding at the time of diagnosis increased to 87%. These levels of breastfeeding not only consistently exceeded the

breastfeeding initiation rates established by *Healthy People* objectives, but the national and state initiation rates at those times.

Duration of Breastfeeding for Infants with PKU

The mean duration for breastfeeding infants with PKU from 1980 to 2005 was 6.8 months. Every decade, there were mothers who initiated breastfeeding, but stopped within one month (n = 16, 21%). The maximum breastfeeding duration for breastfeeding infants with PKU between 1980 and 1989 was 24 months with a mean of approximately 9 months. For breastfeeding infants with PKU between 1990 and 1999, the maximum duration decreased to 16 months with a mean of 5 ½ months. Between 2000 and 2005, breastfeeding duration increased from the previous decade for breast-fed infants with PKU to a maximum of 23 months with a mean of 6 months.

Breast-fed infants with PKU in this study successfully met the *Healthy People 2000* six month objective from 1980 to 1989 (Tables 2 and 3). Mothers breastfeeding infants with PKU from 1990 to 2005 did not met the *Healthy People 2000* or *2010* breastfeeding objective for six months. In addition, the mothers from 1980 to 1989 almost met the *Healthy People 2000* breastfeeding objective at twelve months (15% vs goal of 16%) while mothers breastfeeding infants with PKU from 1990 to 2005 did not meet the *Healthy People 2000* or *2010* twelve months breastfeeding objective.

Comparison of Phe Values

To calculate the mean Phe level while breastfeeding and formula-feeding, each infant was required to have at least five Phe levels; typically, these were in addition to the two newborn screen results and confirmatory test which were elevated and skewed the data. These diagnostic elevated Phe levels were eliminated from the analysis. The mean Phe levels while breastfeeding and formula feeding are presented in Figure 2. Eighty percent (n = 59) of the breast-fed infants with PKU and 77% (n = 22) of the bottle-fed infants with PKU had mean Phe values within the desired treatment range (120–360µmol/l). The mean Phe levels were then categorized into low, normal and high mean Phe levels. As shown in Figure 3, there was a significant association between type of feeding and category of mean Phe level, χ^2 (2, N = 3,260) = 205, p < .001. Specifically, breastfed babies were more likely to have a normal mean Phe level and therefore successful management of PKU. Bottle-fed babies were more likely to have a normal mean Phe level and the two groups were comparable in their distribution in the high mean Phe level category. Both low (< 120µmol/l) and high (> 360µmol/l) Phe levels reflect poor management of PKU.

Given that the pediatric metabolic clinic was the only clinic in the state for the management of PKU, a posthoc analysis was conducted to ascertain whether management of the Phe level differed by proximity to the clinic or region of the state. Breast-fed and bottle-fed infants with PKU were categorized as living within the metropolitan area where the clinic was located or living outside the metropolitan area. There was a significant association between type of feeding and location within or outside the metropolitan area and for attaining a normal mean Phe level (120–360µmol/l), $\chi^2(1, N=1,685) = 18.56, p < .001$. Breast-fed infants living in the metropolitan area, bottle-fed infants outside the metropolitan area were more likely to be in the normal mean Phe level category; and outside the metropolitan area, bottle-fed infants outside the metropolitan area were more likely to be in the normal mean Phe level category (Figure 4). When assessed in relation to the low mean Phe level and in relation to the high mean Phe category, type of feeding and location were not significantly associated.

Further post-hoc analysis of regional data shown in Figure 5 revealed regional differences in the mean Phe values; regions are listed in order of approximate progressive distance from

the metropolitan area where the pediatric metabolic clinic is located. The Central High Mountain Desert and the Coastal regions had significantly higher mean Phe levels than the metropolitan and other regions, R(6, 2251) = 5.2, p < .001. As the metropolitan area has a lower percent of uninsured families compared to the rest of the state, an analysis was performed to evaluate if there was any difference between Phe control and form of family medical insurance. Medical insurance was categorized as private, state Health Plan, adjacent state health plan, and self-pay. The 95% confidence intervals (CIs) for each independent variable were derived through regression analysis and were not significant.

Discussion

These results were remarkable considering that mothers of infants with PKU who were breastfeeding were also managing the disorder of PKU. These mothers were not only meeting the *Healthy People* breastfeeding objectives, but at times surpassing them for breastfeeding initiation and continuation rates at six months. Oregon has one of the nation's highest breastfeeding rates and was the first state to meet the *Healthy People 2010* breastfeeding objectives. The State of Oregon actively encourages breastfeeding within the Office of Family Health with the program, Breastfeeding Promotion. Oregon law requires employers to offer lactation consultation and support to breastfeeding mothers and has legislation to protect mothers' right to breastfeed in public. In Oregon, breastfeeding is the norm and this norm has been clearly extended to mothers of infants with PKU even in the face of challenges to maintain therapeutic Phe levels.

Mothers' breastfeeding infants with PKU consistently surpassed initiation of breastfeeding objectives for *Healthy People 2000* and *2010*. Not only did these mothers surpass the initiation rates from 1980 to 1999, but they also exceeded the rate at six months for the nation. However, over time, mothers of breast-fed infants with PKU varied in meeting the breastfeeding objective for six months duration from 38% (1980's) to 24% (1990's) to 30% (2000's). Except for the 1980's, there was a decline of fifty percent or more of breastfeeding at six months. In addition, there was another steep decline in breastfeeding at twelve months from 15% (1980's) to 4% (1990's) to 5% (2000's). Although there has been progress in Oregon for breastfeeding infants with PKU, these data may not reflect the breastfeeding rate in the rest of the nation. In addition, little is known about how mothers manage breastfeeding infants with PKU and what contributes to the decline that begins at six months and accelerates at twelve months.

During the first year of life, the majority of infants, whether breast-fed or bottle-fed, had similar mean Phe levels. Overall, more breast-fed infants with PKU had Phe levels within the normal range (120–360 μ mol/L) and were less likely to have a low Phe levels (<120 μ mol/L) especially in the metropolitan area. This finding supports previous research that breast-fed infants with PKU can have Phe levels within the desired therapeutic range (Cornejo et al., 2003; Huner, & Demirkol, 1996; Kanufre et al., 2007; McCabe et al., 1989; van Rijn et al., 2003). These mothers were effectively managing their infant's Phe levels, successfully managing the disorder of PKU, and breastfeeding their infants with PKU. Further research is needed to understand how mothers manage breastfeeding in the context of PKU. If breastfeeding management for mothers of infants with PKU is understood, it can be taught and breastfeeding could be encouraged in other parts of the country where breastfeeding is not the norm.

We can only hypothesize why infants with PKU living in the Central and Coastal regions of Oregon have significantly higher mean Phe levels. One possible cause might be due to difficulty of access to the tertiary clinic as there are no direct roads over both the Cascade and Coastal Mountain Ranges along with the termination of train and bus services to these

rather remote areas of the state. Other possibilities could be due to a lack of professional support with lactation knowledge about breastfeeding infants with PKU within those two regions or parental understanding of the management of PKU and the need to maintain normal mean Phe level (120–360 μ mol/l). Clearly more research is needed to clarify why infants with PKU living in these areas have consistently higher Phe levels and how to change this trend so that Phe levels are in the normal therapeutic range.

Limitations

This research has the limitations that are inherent to retrospective studies with small unique populations. In this study, the population was cared for in one clinical metabolic program. In addition, descriptive data to further evaluate breastfeeding and Phe levels were not systematically documented in the medical records over the 25 years covered in the study. For example, there was incomplete documentation of maternal characteristics such as race, age, marital status, and level of education, variables typically positively linked to breastfeeding initiation rates and duration rates. Other variables negatively associated with breastfeeding, such as smoking and returning to employment, were also not systematically documented. In addition, there was insufficient documentation to determine which mothers qualified for the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) that encourages breastfeeding among its participants.

Future Research

The results of this study clearly provide evidence that mothers are capable of breastfeeding infants with PKU and maintaining normal therapeutic Phe levels. It is possible mothers who were able to persist with the challenges of simultaneously managing breastfeeding and PKU were more motivated to continue breastfeeding. Further research is needed to explore the variables that are associated with successfully breastfeeding infants with PKU as it is unknown if these variables are the same characteristics that have been associated with successful breastfeeding in other populations, such as healthy term infants and premature infants (Forster, McLachlan, & Lumley, 2006; Thulier, & Mercer, 2009; Zachariassen et al., 2010). In addition, it is unknown what factors predict a more successful duration of breastfeeding infants with PKU. There also are no studies that retrospectively or prospectively examine specific reasons for early cessation of breastfeeding infants with PKU. Moreover, it is unknown what resources help mothers' to successfully breastfeed infants with PKU. Mothers of infants with PKU could need more intensive, individualized support during the early weeks after diagnosis of PKU and later as low-Phe table foods are introduced. Further research into these aspects will provide knowledge that is needed to develop interventions that will help mothers continue to breastfeed infants with PKU, to support their breastfeeding goals, and to increase breastfeeding durations recommended by Healthy People objectives.

Clinical Implications

Breastfeeding can be successful provided in the management of infants with PKU while maintaining normal therapeutic Phe levels. The infants' success reflects the success of their mothers' efforts to manage breastfeeding in this unique and challenging context. Mothers with breastfeeding infants who have PKU and who had planned to breastfeed should be supported and encouraged to continue breastfeeding. Nurses need to determine mothers' breastfeeding goals, and identify mothers' available supports when planning and providing metabolic guidance in managing their infant's Phe levels. Lastly, it is imperative that nurses who provide metabolic care to mothers of infants with PKU reinforce mothers' breast milk remains the optimal base feeding for their infants with PKU.

Summary

Data gleaned from this study serve to document that breastfeeding success is possible for mothers with infants who have PKU and Phe levels can optimally be managed when breastfeeding. Further research is needed to explore how these mothers successfully maintain breastfeeding in the context of managing the disorder of PKU for their infants. Such research will contribute to the identification of effective strategies for the clinical management of breastfeeding and PKU.

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References

- Agonstoni C, Verduci E, Fiori L, Riva E, Giovannini M. Breastfeeding rates among hyperphenylalaninemic infants. ACTA Paediatrica Scandinavica. 2000; 89:366–367.
- American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. [Policy Statement]. Pediatrics. 2005; 115(2):496–506. [PubMed: 15687461]
- American Association of Family Physicians. Breastfeeding, Family Physicians Supporting. 2008. Retrieved September 7, 2009, from

http://www.aafp.org/online/en/home/policy/policies/b/breastfeedingpositionpaper.html

- Association of Women's Health Obstetric and Neonatal Nurses. 2007 Role of the Nurse in the Promotion of Breastfeeding. 52005 Dec 1. Retrieved September 7, 2009, from http://www.awhonn.org/awhonn/content.do?name=05_HealthPolicyLegislation/5H_PositionStatements.htm
- Blau, N.; Duran, M.; Gibson, KM. Laboratory Guide to the Methods in Biochemical Genetics. Berlin, Germany: Springer-Verlag; 2008.
- Canadian Paediatric Society. Exclusive breastfeeding should continue to six months. Paediatric Child Health. 2005; 10(3):148.
- Cornejo V, Manriquez V, Colombo M, Mabe P, Jimenez M, De la Parra A, et al. [Phenylketonuria diagnosed during the neonatal period and breast feeding]. Revist Medica de Chile. 2003; 131(11): 1280–1287.
- Cummings, M. Human heredity:Principles and issues. Florence, Kentucky: Brooks/Cole Publishing Co; 2008. From proteins to phenotypes; p. 231-257.
- de Baulny HO, Abadie V, Feillet F, de Parscau L. Management of phenylketonuria and hyperphenylalaninemia. J Nutr. 2007; 137(6 Suppl 1):1561S–1563S. discussion 1573S–1575S. [PubMed: 17513425]
- Demirkol M, Huner G, Kuru N, Donmez S, Baykal T, Seckin Y. Feasibility of breastfeeding in inborn errors of metabolism: Experience in phenylketonuria. Ann Nutr Metab. 2001; 45(supplement 1): 497–498.
- Dhondt JL. Neonatal screening: from the 'Guthrie age' to the 'genetic age'. Journal of Inherited Metabolic Disease. 2007; 30(4):418–422. [PubMed: 17505914]
- Donlon, F.; Levy, H.; Scriver, CR. The hyperphenylalaninemias. In: Valle, D.; Beaudet, AL.; Vogelstein, B.; Kinzler, KW.; Antonarakis, SE.; Ballabio, A., editors. The Metabolic and Molecular Bases of Inherited Disease. 8. New York: McGraw-Hill; 2007.
- Ernest, AE.; McCabe, ERB.; Neifert, NR.; O'Flynn, ME. Guide to Breast Feeding the Infant with PKU (DHHS Publication #79-5110). 1. Washington, D.C: U.S. Government Printing Office; 1980.
- Forster DA, McLachlan HL, Lumley J. Factors associated with breastfeeding at six months postpartum in a group of Australian women. International Breastfeeding Journal. 2006; 1:1–18. [PubMed: 16722586]

- Greve LC, Wheeler MD, Green-Burgeson DK, Zorn EM. Breast-feeding in the management of the newborn with phenylketonuria: a practical approach to dietary therapy. Journal of the American Dietetic Association. 1994; 94(3):305–309. [PubMed: 8120296]
- Guthrie R, Susi A. A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants. Pediatrics. 1963; 32:338–343. [PubMed: 14063511]
- Hoddinott P, Tappin D, Wright C. Breast feeding. British Medical Journal. 2008; 336(7649):881–887. [PubMed: 18420694]
- Horta, BL.; Bahl, R.; Martines, JC.; Victora, CG. Evidence on the long-term effects of breastfeeding. Geneva: World Health Organization; 2007.
- Huner G, Baykal T, Demir F, Demirkol M. Breastfeeding experience in inborn errors of metabolism other than phenylketonuria. Journal of Inherited Metabolic Disease. 2005; 28(4):457–465. [PubMed: 15902548]
- Huner, G.; Demirkol, M., editors. Breast-feeding the Phenylketonuria. Istanbul, Turkey: Turkish Society for PKU; 1996.
- Huttenlocher PR. The neuropathology of phenylketonuria: human and animal studies. European Journal of Pediatrics. 2000; 159(Suppl 2):S102–106. [PubMed: 11043154]
- Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep). 2007; 153:1–186. [PubMed: 17764214]
- Janas LM, Picciano MF, Hatch TF. Indices of protein metabolism in term infants fed human milk, whey-predominant formula, or cow's milk formula. Pediatrics. 1985; 75(4):775–784. [PubMed: 3872443]
- Jervis GA. Phenylpyruvic oligophrenia deficiency of phenylalanine-oxidizing system. Proceedings of the Society for Experimental Biology and Medicine. 1953; 82(3):514–515. [PubMed: 13047448]
- Kanufre VC, Starling AL, Leao E, Aguiar MJ, Santos JS, Soares RD, et al. Breastfeeding in the treatment of children with phenylketonuria. Jornal de Pediatria. 2007; 83(5):447–452. [PubMed: 17676249]
- Kaye CI. Committee of Genetics. Newborn screening fact sheets. Pediatrics. 2006; 118(3):934–963.
- Lonnerdal B, Forsum E, Gebre-Medhin M, Hambraeus L. Breast milk composition in Ethiopian and Swedish mothers. II. Lactose, nitrogen, and protein contents. American Journal of Clinical Nutrition. 1976; 29(10):1134–1141. [PubMed: 973602]
- Malamud N. Neuropathology of phenylketonuria. Journal of Neuropathology & Experimental Neurology. 1966; 25(2):254–268. [PubMed: 5949175]
- McCabe L, Ernest AE, Neifert MR, Yannicelli S, Nord AM, Garry PJ, et al. The management of breast feeding among infants with phenylketonuria. Journal of Inherited Metabolic Disease. 1989; 12(4): 467–474. [PubMed: 2516178]
- Meyers, C. Incidence of hyperphenylalaninemia in Louisana from 1985–1999. Paper presented at the Newborn Screening and Genetic Testing Symposium; 2002.
- Motzfeldt K, Lilje R, Nylander G. Breastfeeding in phenylketonuria. Acta Paediatrica Supplement. 1999; 88(432):25–27. [PubMed: 10626572]
- Nayman R, Thomson ME, Scriver CR, Clow CL. Observations on the composition of milk-substitute products for treatment of inborn errors of amino acid metabolism. Comparisons with human milk. A proposal to rationalize nutrient content of treatment products. Am J Clin Nutr. 1979; 32(6): 1279–1289. [PubMed: 375713]
- Scriver, CR.; Levy, H.; Donlon, J. Hyperpenylalaninemias: Phenylalanine hydroxylase deficiency. In: Valle, D.; Beaudet, AL.; Vogelstein, B.; Kinzler, KW.; Antonarakis, SE.; Ballabio, A., editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2008.
- Segev, R.; Abraham, S.; Anikster, U.; Schwartz, G. The incidence and duration of breastfeeding in the PKU clinic. Paper presented at the Dietary Management of Inborn Errors of Metabolism; 2004.
- Therrell BL, Adams J. Newborn screening in North America. Journal of Inherited Metabolic Disease. 2007; 30(4):447–465. [PubMed: 17643194]
- Thulier D, Mercer J. Variables associated with breastfeeding duration. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2009; 38(3):259–268.

- U.S. Preventive Services Task Force. Primary Care Interventions to Promote Breastfeeding. 2008. Retrieved from http://www.ahrq.gov/clinic/uspstf08/breastfeeding/brfeedrs.htm#rationale
- van Rijn M, Bekhof J, Dijkstra T, Smit PG, Moddermam P, van Spronsen FJ. A different approach to breastfeeding of the infants with phenylketonuria. European Journal of Pediatrics. 2003; 163:323– 326. [PubMed: 12692713]
- World Health Organization. The WHO Global Data Bank on Breastfeeding and Complementary Feeding. Geneva: World Health Organization; 2007.
- World Health Organization. Breastfeeding: A vital emergency response. Are you ready?. 2009. Retrieved September 7, 2009, from

 $http://www.who.int/mediacentre/news/statements/2009/world_breastfeeding_week_20090731/en/index.html$

Zachariassen G, Faerk J, Grytter C, Esberg B, Juvonen P, Halken S. Factors associated with successful establishment of breastfeeding in very preterm infants. Acta Paediatrica. 2010; 99(7):1000–1004. [PubMed: 20151950]



Figure 1. Simplified phenylalanine pathway in PKU © Banta-Wright 2011

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Figure 2. Mean Phe level for each infant by birth year

The shaded area between 120 μ mol/l and 360 μ mol/l represents the normative range for Phe levels for infants with PKU, and therefore, successful management of PKU.

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Figure 3. Frequency Differences between Breast-fed and Bottle-fed Infants with PKU and the Probability of having a Normal (120–360 μ mol/l), Low (<120 μ mol/l) or High (>360 μ mol/l) Phe Levels

* = χ^2 (df = 2, N= 3,260) = 205, p < .001



Figure 4. Comparison between Breast-fed and Bottle-fed Infants with PKU living in the metropolitan area vs non-metropolitan area and the Probability of having a Normal Phe Level Metropolitan area includes the three counties of Clackamas, Multnomah, and Washington which designates the Portland metropolitan area. The non-metropolitan area included the following regions: Willamette valley, central high mountain desert, mountainous southern, coastal, rural eastern, and adjacent southern region of the state of Washington. The shaded area between 120 μ mol/l and 360 μ mol/l represents the normative range for Phe levels for infants with PKU, and therefore, successful management of PKU. * = χ^2 (df = 1, N = 1,685) = 18.56, p < .001



Figure 5. Regional Difference in the mean Phe Levels

The shaded area between 120 μ mol/l and 360 μ mol/l represents the normative range for Phe levels for infants with PKU, and therefore, successful management of PKU. * = significant, R(6, 2251) = 5.2, p < .001

Table 1

Baseline infant characteristics

	Breast-fed (n = 75)	Formula-fed (n = 22)
Age in days at diagnosis	15 (5–65) ^a	17 (6–44) ^a
Plasma Phe level at diagnosis (µmol/l)	1,126.8 (240–3,534) ^{<i>a</i>}	1,339.8(480–2,802) ^a
Birth weight (kg)	3.46 (2.05–5.3) ^a	3.66 (1.5–5.2) ^a
Gender (M/F)	39M:36F	9M:13F

 $^{a}\mathrm{Numbers}$ represent means with ranges min/max are given in parentheses.

Table 2

Incidence and Duration of Breastfeeding Infants with PKU, 1980-1999

Duration of Breastfeeding	Healthy People 2000 Objectives ^a	Breastfeeding PKU Infants, 1980– 1989 $(n = 27)$	National US Breastfeeding b 1980	Breastfeeding PKU Infants, 1990– 1999 ($n = 28$)	National US Breastfeeding ^b 1990
Initial postpartum	64%	79% ($n = 27$)	55%	74% $(n = 28)$	51.5%
6 months	29%	38% (n = 13)	23%	25% (n = 7)	17.6%
12 months	16%	15% $(n = 4)$	VN	4% (n = 1)	NA

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^aU.S. Department of Health and Human Services. (2000). Healthy People 2000: National Health Promotion and Disease Prevention Objectives. Retrieved from http://healthypeople.gov/.

 $b_{
m Ross}$ Laboratories Mother Survey, Ross Laboratories, Columbus, OH.

Table 3

Incidence and Duration of Breastfeeding Infants with PKU, 2000-2005

Duration of Breastfeeding	Healthy People 2010 Objectives ^a	Breastfeeding PKU Infants, 2000–2005 (n=20)	National US Breastfeeding 2005 ^b	Oregon Breastfeeding 2005 ^b
Initial postpartum	75%	87% (n = 20)	74%	86%
6 months	50%	30% (n = 6)	43%	60%
12 months	25%	5% (n = 1)	21.5%	37%

^aU.S. Department of Health and Human Services. (2000). *Healthy People 2010: National Health Promotion and Disease Prevention Objectives.* Retrieved from http://healthypeople.gov/.

^bCenter for Disease Control. (2005). *Final geographic-specific breastfeeding rates among children born in 2005*. Retrieved from http://www.cdc.gov/breastfeeding/data/NIS_data/2005/state_any.htm