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Breastfeeding practices for infants with inherited metabolic disorders: A survey of registered dietitians in the United States and Canada

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ABSTRACT

Background: Breast milk is considered the optimal first food for infants. Breastfeeding infants with inherited metabolic disorders (IMDs) is complex due to the critical need to manage intake of specific macronutrients depending on the type of IMD.
Objective: To describe current practices of registered dietitians (RD) who treat patients with IMDs regarding the incorporation of breastmilk into disease management.
Design: Cross-sectional survey.
Participants/setting:
online survey conducted in December 2020 of 66 RDs who treat patients with IMDs in the United States and Canada.
Main outcome measures:
the survey focused on personal demographics, clinic characteristics, institutional feeding protocols for infants with IMDs, confidence in working with breastfeeding parents of infants with IMDs, and knowledge about breastfeeding with questions derived from the Iowa Infant Feeding Attitudes Scale.
Statistical analysis performed:.
Fisher's exact test was used for comparisons.
Results: Most RDs were confident or very confident in their ability to provide nutritional guidance for breastfeeding infants with IMDs. Half of the participants reported that they had received training on breastfeeding of infants of IMDs. For infants with phenylketonuria (PKU), most RDs include breastfeeding as part of nutritional management. Breastfeeding is less likely to be used in the management of infants with other aminoacidopathies and fatty acid oxidation disorders. Use of measured expressed breastmilk was preferred, including for aminoacidopathies other than PKU, organic acidemias, and fatty acid oxidation disorders. Knowledge about breastfeeding varied. Less than half of RDs referred mothers to a lactation specialist somewhat regularly or frequently.
Conclusions: Our survey found variation in experience, training, and use of breastfeeding-related nutritional management protocols in IMDs. A lack of formal training programs for the nutritional management of IMDs may account for some of this variation. Future research, including the collection of more detailed disorder-specific data, could help contribute to the development of clinical practice guidelines.

1. Introduction

Inherited Metabolic Disorders (IMDs) comprise more than 750 diseases caused by genetic mutations that lead to enzymatic deficiencies within specific metabolic pathways [1,2,3]. This reduction of enzymatic activity can result in the toxic accumulation of compounds in the blood or brain, or a deficiency of necessary substances, depending on the type of IMD [4]. Although each individual disorder is relatively rare, collectively the incidence has an estimated range of 1 in 784 to 1 in 2555 live births [5,6]. The recommended uniform screening panel (RUSP) for newborn screening is maintained by the United States (US) Department of Health and Human Services and includes 20 IMDs in the primary disorders and 22 IMDs in the secondary disorders [7,8]. In the US, more than 98% of newborns are screened, and early identification and

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treatment of these disorders subsequently reduces the morbidity and mortality [9]. IMDs require lifelong management and treatment, often focused on the restriction of the substrate that cannot be metabolized from the diet, replacement of other nutrients with supplements (medical foods), and medications [10,11].

Breastmilk is considered to be the optimal first food for infants, and confers short and long-term health benefits to both infants and mothers [12–14]. Exclusive breastfeeding from birth through 6 months of age is recommended by the World Health Organization (WHO) and the American Academy of Pediatrics, with the WHO recommending breastfeeding continue through age two years [15,16]. Breastfeeding offers important immunological benefits, including protection against certain types of infectious diseases in infancy, such as gastrointestinal and respiratory illnesses, and is associated with a reduced risk of childhood leukemia [17,18]. Breast milk also has beneficial effect in the gastrointestinal tract due to a reduction in propionate [19,20]. Additionally, breastfeeding has been linked to higher levels of parental attachment, improved cognitive development and higher educational attainment [21,22,23]. In mothers, breastfeeding is associated with a reduced risk of both invasive breast cancer and ovarian cancer [16].

Nutritionally, breastmilk is a complex, dynamic fluid that changes and adapts to meet the needs of the rapidly growing infant [24]. The composition of human milk is generally thought to be approximately 87% water, 3.8% fat, 1.0% protein, and 7% lactose; additionally, it contains vitamins, minerals, digestive enzymes, hormones, immune cells and other bioactive molecules [25]. Lipids provide the major source of energy in breastmilk, comprising 44% of the total energy content [24]. In some instances, the nutrient content of breastmilk is impacted by maternal nutritional status, such as lipids and iodine, but other nutrients, such as calcium, do not appear to be impacted by maternal dietary intake [26].

Breastfeeding may safely be incorporated into the management of infants with certain IMDs such as some aminopacidopathies and urea cycle disorders due to the lower protein and amino acid content of breastmilk relative to infant formula. Breastfeeding at the breast or from expressed breastmilk is included in management guidelines for some IMDs, including glutaric aciduria type I [27], maple syrup urine disease [28], phenylketonuria (PKU) [29, 30]; propionic acidemia [31], urea cycle disorders [32], and very long chain acyl-CoA dehydrogenase deficiency [33], although measuring and careful monitoring may be warranted. However, there is no universal approach to breastfeeding in IMD; practices and recommendations for breastfeeding infants with IMD vary widely depending on the type and severity of the metabolic disorder.

Our primary aim with this survey was to collect the practices and recommendations related to breastfeeding for infants with IMDs that metabolic dietitians in US and Canada commonly relay to their patients. Additionally, we examined the type of IMD-specific training and amount of clinical experience of RDs, their level of confidence in supporting breastfeeding mothers of infants with IMD, and specific questions from the Iowa Infant Feeding Attitude Scale (IIFAS) [34].

2. Methods

This was a cross-sectional study that surveyed RDs in the US and Canada who work with patients with IMDs. All study procedures were reviewed and approved by the Teachers College, Columbia University Institutional Review Board. All participants provided written informed consent.

Eligibility criteria included the following: 18 years of age or older, credentialed as an RD, and working in the US or Canada with patients with IMDs. Potential participants were recruited through the Emory University GNO Metab listserv, which includes all Genetic Metabolic Dietitians International group members as well as other practitioners who treat patients with IMDs or who have an interest in the nutrition management of IMDs globally. The listserv included 453 members at the time of the request to participate; however, all members did not meet the eligibility criteria, as the listserv includes other practitioners (e.g., MDs, diet technicians), RDs who are not involved in direct patient care (e.g., those involved in solely in research), and members from other countries. The eligibility criteria were outlined in the recruitment email. In December 2020, members of the GNO Metab Listserv were invited to participate in the study via email with the subject line "Survey of Breastfeeding Practices in IMD". The survey was active for 14 days, and a second recruitment email was sent to the listserv 7 days prior to the closing of the survey to increase participation.

Respondents accessed the self-administered 39-question survey through Qualtrics. The average duration of the survey was 27 min and 17 s. The survey was comprised of open-ended questions and questions with 4 and 5-point likert scales. Questions were derived from a previous study [35] and from questions developed by the authors. The survey focused on personal demographics, clinic characteristics, institutional feeding practices for infants with IMDs, confidence in working with breastfeeding parents of infants with IMDs, and knowledge about breastfeeding with questions derived from the Iowa Infant Feeding Attitude Scale (IIFAS) (De la Mora & Russell 1999). The IIFAS questionnaire measures attitudes toward infant feeding [34].

Fisher's exact test was used to compare the confidence in working with breastfed patients with IMDs and frequency of referrals to a lactation specialist among RDs who had or had not received training related to breastfeeding in the management of infants with IMDs. Statistical significance was defined as *P*-value less than 0.05, and no corrections were made for multiple comparisons.

3. Results

Characteristics of 66 participants are described in Table 1. Participants included 62 females and 1 male, and 3 individuals who did not specify gender. Mean age of the participants was 38.7 years (range: 24–70 years). Median number of years of experience working with patients with IMDs was 5 years (range: <1–34 years). Half of the participants ($n = 33$) had received training related to the breastfeeding of babies with IMDs, including from on-the-job training ($n = 10$), conferences and lectures ($n = 9$), Metabolic University ($n = 6$), Genetics Metabolic Dietitians International (GMDI) ($n = 4$), and genetic metabolic fellowships ($n = 2$).

The majority of newborns with IMDs identified through newborn

Table 1
Participant characteristics ($N = 66$).

	n (%)
Race	
White	59 (89.4%)
Black or African-American	1 (1.5%)
Native Hawaiian or Pacific Islander	2 (3.0)
Asian	4 (6.1%)
Ethnicity	
Hispanic or Latino	5 (7.57%)
Not Hispanic or Latino	61 (92.42%)
Gender	
Female	62 (98.4%)
Male	1 (1.6%)
How many newborns with IMD are treated in your center each year?	
<50	45 (91.8%)
50–100	1 (2.0%)
>100	3 (6.1%)
Have you received training in breastfeeding of babies with IMD?	
Yes	33 (50.0%)
No	33 (50.0%)
If Yes, Where?	
Genetic Metabolic Fellowship	2 (6.4%)
Genetics Metabolic Dietitians International (GMDI)	4 (12.9%)
Metabolic University	6 (19.4%)
Conferences and lectures	9 (29.0%)
On the job training	10 (32.2%)

screening programs began dietary treatment before the age of 2 weeks (Table 2). Practices related to the management of breastfed infants with IMDs are described in Tables 2 and 3. For infants with PKU, most RDs reported that biochemical monitoring occurs weekly (63.3%). A minority (16.3%) of RDs indicated that routine biochemical monitoring is recommended to occur more frequently for infants with IMDs who are breastfed. Most RDs (81.2%) reported other changes made to the management of babies with IMDs who are breastfed, including more frequent monitoring of growth, and consideration of providing breastmilk by bottle.

Table 2
Breastfeeding practices for infants with IMDs (N = 66).

	n (%)
For newborns with IMDs identified through newborn screening, what is the average age of the baby when dietary treatment is started in your clinic?	
<1 week	16 (43.2%)
1 week	8 (21.6%)
1–2 weeks	11 (29.7%)
2–3 weeks	1 (2.7%)
Other	1 (2.7%)
In PKU, how often does your clinic measure metabolic biochemical levels in the first 12 months of life following stabilization of condition?	
Twice weekly	3 (6.1%)
Once weekly	31 (63.3%)
Every two weeks	2 (4.1%)
Every month	1 (2.0%)
Other	12 (24.5%)
Is the frequency of biochemical monitoring affected by breastfeeding versus formula feeding?	
Yes, more frequently if breastfed	8 (16.3%)
No, it remains the same	41 (83.7%)
Are there any other changes are made to the infant monitoring protocol for the breastfed infant versus the formula fed infants?	
Yes	39 (81.2%)
No	9 (18.8%)
Approximately what percentage of your newborn patients are breastfed at the time of diagnosis of IMD through newborn screening?	
Unsure	7 (15.2%)
0–25%	4 (8.7%)
26–50%	5 (10.9%)
51–75%	18 (39.1%)
76–100%	12 (26.1%)
On average, how many months do mothers of babies with IMDs continue to breast feed in your clinic?	
<1 month	6 (11.8%)
1–3 months	4 (7.8%)
3–6 months	10 (19.6%)
>6 months	31 (60.8%)
How do you advise medical food is given to breast-fed infants?	
Alternate feeds of breast milk and medical food	21 (42.8%)
A measured amount of medical food before breast feed to satiety (i.e. no time limits on breast)	16 (32.6%)
Other	12 (24.5%)
How frequently do you refer breastfeeding mothers of infants with IMD to a lactation specialist, i.e. an Internationally Board Certified Lactation Counselor (IBCLC) or a Certified Lactation Counselor (CLC)?	
Frequently	11 (22.4%)
Somewhat regularly	10 (20.4%)
Occasionally	20 (40.8%)
Never	8 (8.2%)

Table 3
Breastfeeding practices by type of IMD (n = 66).

	PKU	Other aminoacid-opathies	Organic acidemias	Fatty acid oxidation disorders
Do you include breastfeeding as part of nutritional management of your patients? n (%)				
Yes	46 (93.9%)	38 (77.6%)	28 (58.3%)	35 (72.9%)
No	0 (0%)	2 (4.1%)	4 (8.3%)	2 (4.2%)
Other	3 (6.1%)	9 (18.4%)	16 (33.3%)	11 (22.9%)
Approximately what percentage of your newborn patients with IMDs continue to breastfeed after diagnosis?n (%)				
<50%	3 (7.3%)	12 (36.4%)	22 (66.7%)	7 (20.0%)
50–100%	38 (92.7%)	21 (63.6%)	11 (33.3%)	28 (80.0%)

Medical food is recommended to be given to breastfed infants by alternate feeds of breastmilk and medical food (42.8%), or by giving a measured amount of medical food before breastfeeding to satiety (32.6%) or by other recommendations (24.5%). The "other" recommendations included a mixture of these two methods based on disorder or mother's preference ($n = 8$), adding a measured amount of pumped breastmilk to medical formula ($n = 1$), and medical food before breastfeeding with a time limit (n = 1). Less than half of RDs (44.8%) referred mothers of patients to a lactation specialist somewhat regularly or frequently. Referral practices were not related to whether or not the RD had received training related to breastfeeding of infants with IMDs.

More than half of the RDs indicated that at least half of the babies with IMDs are breastfed at the time of diagnosis and that, on average, mothers continue to breastfeed for at least six months following diagnosis. (Table 2) This is consistent with the national breastfeeding rates in the United States, with 56.7% of women breastfeeding at 6 months [36].

Table 3 describes questions related to practices and experiences with breastfeeding of infants with IMDs by type of disorder. For PKU, most RDs (93.9%) include breastfeeding of as part of nutritional management of affected infants, and an additional three RDs indicated that it depends on the severity of the disorder ($n = 1$) and mother's preference ($n = 2$). Most RDs (92.7%) indicated that at least half of the mothers continue to breastfeed after diagnosis of PKU. Breastfeeding is less likely to be used in the management of babies with other aminoacidopathies, and in fatty acid oxidation disorders. For fatty acid oxidation disorders, nine RDs indicated that it depends on the severity of the disorder, with RDs stating that they recommend breastfeeding in the nutritional management of their patients in some cases of Medium chain acyl-CoA dehydrogenase deficiency (MCAD) ($n = 2$) and Very Long Chain Acyl-CoA Dehydrogenase deficiency (VLCAD) (n = 2), but not in cases of Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) ($n = 3$). RDs reported that measured expressed breastmilk was preferred, including for aminoacidopathies other than PKU ($n = 5$), organic acidemias ($n = 10$), and fatty acid oxidation disorders (n = 1).

About three-quarters of RDs indicated that they were confident or very confident in their ability to provide nutritional guidance for IMDs for a breastfed infant (Fig. 1). RDs were slightly less confident in their ability to support breastfeeding mothers or to address a mother's basic questions or concerns related to breastfeeding and IMDs. Confidence in

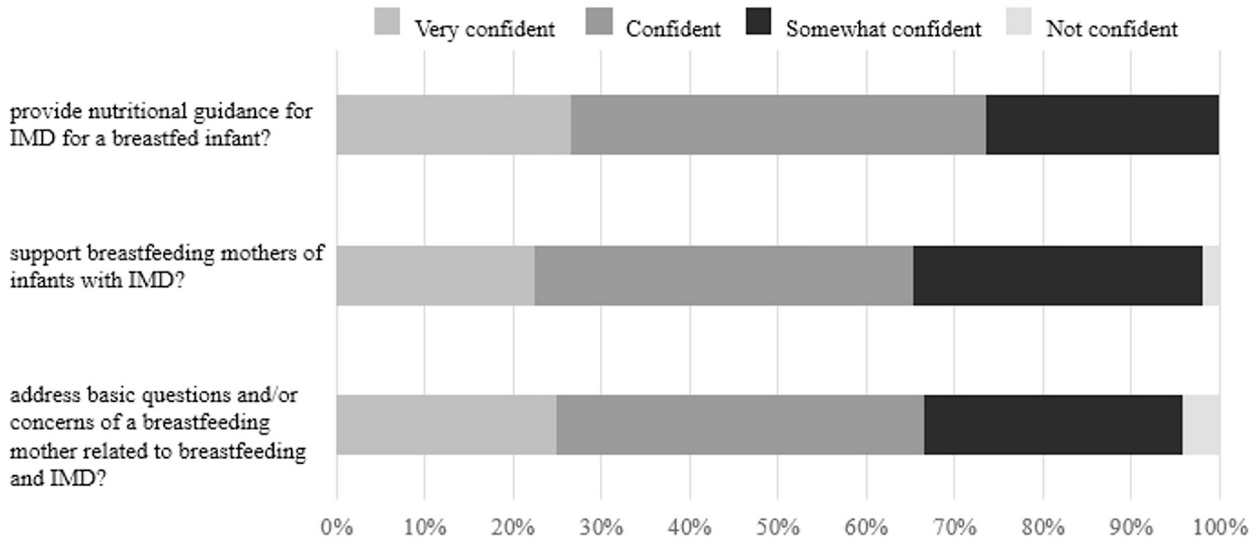

Fig. 1. Participants' confidence in their ability to manage breastfed infants with IMDs.

the third area (addressing a mother's questions of concerns) was related to whether or not the RD had received training. Among RDs with training, 80% reported that they were confident or very confident in this area, but only 50% of RDs without training reported the same level of confidence ($p = 0.03$).

Finally, we asked several knowledge-based questions from the IIFAS (Table 4). Most participants believed that the benefits of breastfeeding last beyond the time of breastfeeding (93.9%) and that breastmilk is more easily digested than formula (83.3%). About one quarter of RDs (26.2%) believed that breastmilk is lacking in iron. There was no consensus among respondents as to whether or not formula fed infants are more likely to be overfed than breastfed infants.

4. Discussion

Our survey found that less than half of respondents received any formal training related to breastfeeding of babies with IMDs, with the greatest number of respondents indicating that their training was on-the-job. The descriptions of on-the-job training varied and include primarily colleague-to-colleague training and mentorship by experienced metabolic RDs. This lack of formalized training may account for some of the variation in management protocols that we found across clinics.

Breastfeeding was widely supported for babies with PKU, and slightly less for babies with other aminoacidopathies. This may be because clinicians have been supporting breastfeeding in PKU for decades, through giving infants a measured amount of low phenylalanine formula prior to breastfeeding to limit phenylalanine intake [20]. Breastfeeding was least likely to be recommended for babies with organic acidemias, although many RDs reported that they recommend measured expressed breastmilk. In fatty acid disorders, respondents indicate that it depends on the severity of the disorder.

Less than half of the RDs refer to a lactation specialist at least somewhat regularly. This may be because nearly three-quarters of respondents felt confident or very confident in their ability to provide nutritional guidance for IMD in breastfed infants. Nevertheless, referral to an IBCLC can improve breastfeeding outcomes in both hospital and outpatient settings, and patients may benefit from this being a more frequent consideration, as milk insufficiency is an often-cited issue in breastfeeding with IMD [20,37].

Finally, we asked several knowledge-based questions from the IIFAS, with varying results. Most participants (93.9%) agreed that the benefits of breastfeeding last beyond the time of breastfeeding. Breastfeeding has been associated with multiple health-related outcomes post-infancy, with some evidence indicating a protective effect against obesity, diabetes and asthma [38, 39, 40];. Additionally, breastfeeding is associated with a reduced risk of leukemia when compared to infants who were never breastfed [18]. Most respondents (83.3%) also agreed that breastmilk is more easily digested than formula (83.3%). It has been established that some of the components of breastmilk, including lipids, are more easily digested than those found in infant formula. Fat in human milk is digested more efficiently than fat found in infant formula, possibly owing to the larger diameter of human milk fat globules [41].

Fewer participants correctly responded to the remaining two questions. Approximately one-quarter of RDs (26.2%) believed that breastmilk is lacking in iron. While breastmilk is relatively low in iron, the lactoferrin iron found in breastmilk is highly bioavailable, with average absorption of 49%, due to lactoferrin iron specific receptors in the infant gut [42,43]. Infants born at term with sufficient birth weight levels generally have iron stores sufficient for the first 4 to 6 months of life [44]. A randomized controlled trial in Honduras found that no exclusively breastfed infants with a birth weight of >3000 g had low ferritin

Table 4
Knowledge of breastfeeding (N = 66).

	n (%)
The benefits of breastfeeding last only as long as the baby is breastfed	
Strongly disagree	20 (40.8)
Disagree	26 (53.1)
Neutral	1 (2.0)
Agree	1 (2.0)
Strongly Agree	1 (2.0)
Breastmilk is lacking in iron.	
Strongly disagree	2 (4.1)
Disagree	17 (34.7)
Neutral	17 (34.7)
Agree	9 (18.4)
Strongly Agree	4 (8.2)
Formula fed babies are more likely to be overfed than breastfed babies.	
Strongly disagree	0 (0)
Disagree	12 (24.5)
Neutral	17 (34.7)
Agree	18 (36.7)
Strongly Agree	2 (4.1)
Breastmilk is more easily digested than formula.	
Strongly disagree	0 (0)
Disagree	0 (0)
Neutral	8 (16.7)
Agree	13 (27.1)
Strongly Agree	27 (56.2)

status at 6 months, and concluded that the risk of iron deficiency in these infants was low [45].

Less than half of the respondents (40.8%) agreed that formula fed infants are more likely to be overfed than breastfed infants. Formula fed infants are more likely to have excessive or rapid weight gain than their breastfed counterparts. This is likely due to several factors, including overfeeding of formula, which can occur during bottle feeding when caregivers are unfamiliar with or unresponsive to infant satiety signals [46]. Given the responses to these four knowledge questions, it appears that RDs who treat patients with IMDs would benefit from educational strategies to increase their knowledge about breastfeeding.

The results of this study provide important information about the use of breastfeeding for infants with IMDs. However, there are some limitations to this study that should be noted. In our questions about breastfeeding practices, we did not distinguish between breastfeeding at the breast and the use of expressed breast milk, although many participants clarified which they recommended in the comments sections of questions. In addition, there is no validated instrument for the assessment of breastfeeding knowledge and attitudes designed specifically for health care providers who treat infants with medical conditions that may impact the use of the breastfeeding, Therefore, we used selected questions from the IIFAS to capture some information about the knowledge of RDs related to breastfeeding in general. While we asked whether or not RDs referred patients to lactation consultants, we did not ask whether or not RDs were lactation consultants or had received any lactation consultant training themselves. It is possible that such training may impact their knowledge and practices, but we are unable to assess this. This was an anonymous survey, so we were unable to compare answers among RDs who may work at the same clinic. We did not ask about interactions between RDs and IBCLCs when referrals were made; relations between practitioners could influence referral practices. We do not know if infants were admitted to the hospital at the time of diagnosis; breastfeeding practices may be different for babies who are ill or in a metabolic crisis. Additionally, we did not ask about how breastmilk was given to the infant, beyond at the breast or expressed milk. Finally, given the large number of IMDs, we were only able to capture information about categories of disorders. We recognize that due to the diversity of disorders within each category, a variety of approaches tailored to the specific disorder and individual patient's needs will be necessary.

Future research should include the collection of data on disorder-specific practices, which would be helpful in the development of clinical practice guidelines. Evidence-based recommendations with specific guidelines on how to best incorporate breastfeeding in the nutrition management of IMDs may help standardize practices across clinics. Formal training programs for RDs who provide nutrition management for patients with IMDs may also help standardize practices, as well as improve the confidence of RDs in the incorporation of breastfeeding recommendations for patients. Finally, development of an instrument for the measurement of health care providers' knowledge and attitudes toward breastfeeding of infants with medical conditions such as IMDs would be an important contribution to the field, and would be useful in the study of the impact of guidelines and training programs.

5. Conclusions

This study provides a snapshot of current practices of RDs in the US and Canada regarding the use of breastfeeding for infants with IMDs. Although there appears to be widespread support for breastfeeding in this population, there are variations across clinics in implementation. Efforts toward the standardization of approaches, with tailoring for specific patients based on severity of disorder and individual needs, should include development of specific evidence-based guidelines and formal training programs for RDs who treat patients with IMDs. Given the well-known benefits of breastfeeding, it is important to continue efforts to safely include breastfeeding in the nutritional management of infants with IMDs.

CRediT authorship contribution statement

Allison Buckingham: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Project administration, Visualization. **Aileen Kenneson:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Project administration, Visualization. **Rani H. Singh:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

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