









# BREAST MILK IN ALL ASPECTS

## HER YÖNÜYLE ANNE SÜTÜ

Emine Gülbin GÖKÇAY<sup>1</sup> , Zeynep İNCE<sup>2</sup> , Gonca KESKİNDEMİRÇİ<sup>3</sup> , Asuman GEDİKBAŞI<sup>4</sup> , Yeliz GÜVEN<sup>5</sup> , Şerif Emre GÖKÇAY<sup>6</sup> , F. İlkey ALP YILDIRIM<sup>7</sup> , Sema BAYRAKTAR<sup>8</sup> 

<sup>1</sup>Istanbul University, Institute of Child Health, Department of Social Pediatrics, İstanbul, Türkiye

<sup>2</sup>Istanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İstanbul, Türkiye

<sup>3</sup>Istanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Social Pediatrics, İstanbul, Türkiye

<sup>4</sup>Istanbul University, Institute of Child Health, Department of Pediatric Basic Sciences, İstanbul, Türkiye

<sup>5</sup>Istanbul University, Faculty of Dentistry, Department of Pedodontics, İstanbul, Türkiye

<sup>6</sup>Istanbul University, Faculty of Economics, Department of Public Finance, Division of Fiscal Law, İstanbul, Türkiye

<sup>7</sup>Istanbul University, Faculty of Pharmacy, Department of Pharmacology, İstanbul, Türkiye

<sup>8</sup>Istanbul University, Faculty of Nursing, İstanbul, Türkiye

**ORCID IDs of the authors:** E.G.G. 0000-0003-1042-0407; Z.İ. 0000-0002-7304-099X; G.K. 0000-0003-1797-2802; A.G. 0000-0001-7121-6077; Y.G. 0000-0002-4637-6025; Ş.E.G. 0000-0002-1361-6598; F.İ.A.Y. 0000-0001-5695-5269; S.B. 0000-0002-4509-6275

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### ABSTRACT

Exclusive breastfeeding for the first six months and continuing to breastfeed until at least 2 years of age is recommended by the Ministries of Health of countries worldwide. Breastfeeding contributes to health not only through its nutritional but also immunological properties. Breast milk has unique ingredients that ensure healthy growth. It is rich in bioactive substances such as growth factors; cytokines, microRNAs, human milk oligosaccharides, and cells. Epigenetic studies have identified differences in gene expression between breastfed and formula-fed infants. DNA methylation (DNAm) has been suggested as a mechanism underlying the long-term health effects of breastfeeding. Breastfeeding promotes proper maxillofacial growth and development by stimulating intense oral muscular activity, promoting correct lip closure, mandibular function, and tongue positioning on the palate. In economics, merit good is generally accepted as good (product) that societies should consume regardless of individuals' wishes or demands. The most typical examples of merit products are education and health. From an economic perspective, it can be concluded that breast milk is an economically merit product, and the states should allocate resources by using their public power to increase breastfeeding. Pharmacists and nurses play important and crucial roles in supporting and assisting mothers during the breastfeeding period. Nurses should always play an active role in initiating and maintaining breastfeeding at every stage of life. In this review, breast milk is discussed in every aspect.

**Keywords:** Breastfeeding, health, economics, immunology, epigenetic

### ÖZET

İlk altı ay sadece anne sütü ile beslenmeyi ve en az iki yaşına kadar emzirmeye devam etmeyi dünya çapında ülkelerin sağlık bakanlıkları önermektedir. Emzirme sadece besleyici değil aynı zamanda immünojen özellikleriyle de sağlığa katkıda bulunur. Anne sütü, sağlıklı büyümeyi sağlayan benzersiz bileşenlere sahiptir. Büyüme faktörleri, sitokinler, mikroRNA'lar, anne sütü oligosakkaritleri ve hücreler gibi biyoaktif maddeler açısından zengindir. Epigenetik çalışmalar, anne sütü ile beslenen ve mama ile beslenen bebekler arasında gen ifadesinde farklılıklar tespit etmiştir. DNA metilasyonu (DNAm), emzirmenin uzun vadeli sağlık etkilerinin altında yatan bir mekanizma olarak öne sürülmüştür. Emzirme, yoğun oral kas aktivitesini uyarak, doğru dudak kapanmasını, mandibular fonksiyonu ve dilin damak üzerinde konumlanmasını teşvik ederek uygun maksillofasial büyüme ve gelişmeyi destekler. Ekonomide "erdemli mal" genellikle bireylerin istek ve taleplerinden bağımsız olarak toplumların tüketmesi gereken mal (ürün) olarak kabul edilir. Erdemli ürünlerin en tipik örnekleri eğitim ve sağlıktır. Belirtilen iktisadi bakış açısı ile anne sütünün ekonomik olarak erdemli bir ürün olduğu ve devletlerin emzirmeyi artırmak için kamu gücünü kullanarak kaynak ayırması gerektiği sonucuna varılabilir. Eczacılar ve hemşireler, emzirme döneminde annelere destek ve yardımcı olma konusunda önemli ve hayati bir role sahiptir. Hemşireler emzirmenin başlatılması ve sürdürülmesinde yaşamın her aşamasında aktif rol oynamalıdır. Bu derlemede anne sütü her yönü ile ele alınarak tartışılmıştır.

**Anahtar Kelimeler:** Emzirme, sağlık, ekonomi, immünoloji, epigenetik

**Corresponding author/İletişim kurulacak yazar:** Emine Gülbin GÖKÇAY – drgulbin@gmail.com

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## INTRODUCTION

Academicians from six different institutions of Istanbul University (Faculty of Dentistry, Faculty of Economics, Faculty of Medicine, Faculty of Nursing, Faculty of Pharmacy, and Institute of Child Health) came together as speakers for the symposium "Breast Milk with All Aspects" on December 27, 2023 at the Doctorate Conference Saloon of the historical main building of Istanbul University. The aim of the symposium held under the theme of Child Care, Health and Development from Tradition to Future in the 100<sup>th</sup> Anniversary of our Republic was to discuss different aspects of breast milk from the perspective of different disciplines; to share the accumulated knowledge created by the institutions of Istanbul University in this field, to carry out joint studies, to carry out multidisciplinary projects, to conduct researches, to examine the results of researches that have been carried out or are being carried out in order to bring breastfeeding to the levels targeted in the United Nations sustainable development goals together with different disciplines. This article aims to convey the main themes of the symposium with the multidisciplinary approach and to explain the importance of breast milk in all aspects.

### Role of breast milk in strengthening immunity

Exclusive breastfeeding for the first six months and continuing to breastfeed until at least 2 years of age is recommended by the Ministries of Health of countries worldwide. It has been reported that with this proposal, over 800,000 child deaths and at least 20,000 maternal deaths will be prevented, and an economic gain of 300 million dollars will be achieved (1). The 2025 target of the Global Nutrition Goal is to increase the rate of exclusive breastfeeding within the first six months to at least 50%. The central part of the Sustainable Development Goals (SDG) for 2030 is breastfeeding. Breastfeeding is at the centre of the first, eighth, and tenth goals of the SDGs, which aim to end poverty and economic growth worldwide; the twelfth goal aims to have the least ecological footprint; the fourth goal aims to achieve global learning goals; and the second and third goals aim to prevent hunger and ensure healthy individuals (2).

Breast milk has unique ingredients that ensure healthy growth. Breastfeeding contributes to health not only through its nutritional but also immunological properties. This contribution begins with the mother's first milk after birth. The first milk, called colostrum, is a source of nutrients and has a high immunoglobulin (Ig) content (3). Although all Ig subtypes are present in colostrum, the largest component is secretory IgA (sIgA). sIgA, which is found in breast milk, particularly in colostrum, has a protective effect against infections. In a study conducted by Juncker et al. in the Netherlands, IgA antibodies specific to SARS-CoV-2 were detected in breast milk, and it was

reported that this high antibody level caused passive immunity in many breastfed babies and protected them against COVID-19 infection (4). Studies have shown that breast milk protects against infections not only because of its sIgA content but also because of its IgG and IgM antibody contents (5-7). Because of these ingredients, promoting and protecting breastfeeding in extraordinary situations such as pandemics is of great importance for the health of the child, mother, and society (8).

The lysozyme content of breast milk is another factor that contributes to the immunological and immunomodulatory effects of breastfeeding. In addition to causing bacterial lysis, lysozyme provides a synergistic effect with Ig and lactoferrin. Lactoferrin in breast milk also has a broad antimicrobial spectrum and has been considered to prevent excessive immune response by blocking inflammatory cytokines (3, 7, 9). Mothers infected with the Hepatitis B virus will not pose a risk of virus transmission to their babies through breastfeeding because of the lactoferrin content of their breast milk, according to the findings of an *in vitro* study (10).

Another immunomodulator found in breast milk is human alpha-lactalbumin, which is lethal to tumour cells (HAMLET). HAMLET is a protein-lipid complex consisting of alpha-lactalbumin and oleic acid that is lethal to tumour cells. In a meta-analysis examining the relationship between breastfeeding and childhood cancers, breastfeeding was found to reduce the risk of leukaemia by 0.77 for both breastfeeding at any time and for long breastfeeding durations, emphasising the protective effect of milk (11).

Breast milk is rich in bioactive substances such as growth factors, which are important in organogenesis; cytokines with immunomodulatory effects; microRNAs effective in epigenetic regulation; human milk oligosaccharides with antipathogenic, immunomodulatory, anti-inflammatory, and prebiotic effects; and cells such as stem cells, lymphocytes, natural killer cells, and neutrophils. Factor content is another component of breast milk that contributes to immunity (12, 13).

### Epigenetic perspective on breast milk

The term 'epigenetics' is used to describe the changes in the expression of genetic information encoded in DNA without any change in the structure or sequence of DNA, with the suffix 'epi' meaning 'above' in Latin, meaning 'genetics above genes'. Epigenetics are natural control mechanisms that affect gene expression (14). Considering that the genome is like a computer; Genetics (Genome) is the hardware (functional activity) of the computer. Epigenetics (Epigenome) is a software that tells the computer when to work, how to work, and how long to work. Epigenetics is like an on/off switch that regulates the operation of genes. Epigenetic switches and labels

turn off or on the expression of certain genes. The main epigenetic mechanisms include DNA methylation, histone modification, noncoding RNAs, such as microRNAs, and RNA-associated silencing. Recent epigenetic studies have identified differences in gene expression between breastfed and formula-fed infants. DNA methylation (DNAm) has been suggested as a mechanism underlying the long-term health effects of breastfeeding (15).

DNA methylation (DNAm), the most extensively studied epigenetic mechanism associated with early life nutrition, involving the addition or removal of a methyl group to cytosine-guanine dinucleotides (CpGs), has been suggested as a key factor in the long-term health effects of breastfeeding. In the study examining the relationship between breastfeeding and DNA methylation in the peripheral blood cells of 37 children aged 9 months to 4 years, the Epigenome-Wide Association Study (EWAS) method was used (16). As a result, significant differences between breastfeeding duration and methylation level were detected for 2635 genes. According to the functional analysis, these genes were predominantly involved in the control of cell signaling systems and, most importantly, in the development and function of the immune and central nervous systems (CNS). In a case-control study of asthma in 200 children, the duration of breastfeeding (none, less than 3 months, more than 3 months) was associated with different patterns of whole-genome methylation (17). Leptin (LEP) is a hormone important in growth, insulin sensitivity, and appetite control. LEP promoter methylation was examined in relation to breastfeeding duration in toddlers, and LEP promoter methylation in white blood cells was lower and serum leptin levels were higher in children who were breastfed for at least 1 to 3 months than in children who were never breastfed (18). Recent studies have shown that breastfeeding is negatively associated with the promoter methylation of LEP, CDKN2A (gene involved in tumour suppression), and SLC2A4 (gene encoding an insulin-related glucose transporter) and positively correlated with Nyp (gene encoding an orexigenic neuropeptide). In addition, breastfeeding duration modulates the epigenetic effects of global methylation patterns and genetic variants (19).

In breast milk, some noncoding RNAs that play a role in epigenetic mechanisms have been identified, but their function is less well known. MicroRNAs (miRNAs) surrounded by membranous microvesicles called exosomes play a crucial role in horizontal miRNA transfer. Long non-coding RNAs and miRNAs in milk exosomes, along with breast milk stem cells, survive digestion, enter the bloodstream, and cross the blood-brain barrier. Some of these non-coding RNAs may regulate genes involved in brain development and function, whereas nestin-positive stem cells can differentiate into neural cells and potentially serve as epigenetic regulators in the brain (20). A

study conducted on 18 pregnant women found a strikingly different miRNA composition in breast milk obtained during colostrum and mid-lactation. Seven miRNAs (miR-148a-3p, 22-3p, 26a-5p, 21-5p, 7b-5p, 7g-5p, and 24-3p) were found to be common in breast milk, nipple aspirate, serum, plasma, and breast tissue (21). The study involving breast milk and colostrum reported different miRNA compositions and, interestingly, no common miRNAs were identified. This finding supports the production of milk specific to infants' needs (22).

The epigenetic effects of breastfeeding are still in their early stages. When the study results are considered in terms of clinical significance, variations in laboratory analyses are high, and their reproducibility is low. Therefore, more trials are needed to provide evidence-based information.

### Effect of breastfeeding on oral health

The numerous benefits of breastfeeding for general health are well documented in the literature (23). Research in the field of oral health has specifically investigated the long-term effects of breastfeeding on both jaw development and the occurrence of dental caries (24). Breastfeeding promotes proper maxillofacial growth and development by stimulating intense oral muscular activity, promoting correct lip closure, mandibular function, and tongue positioning on the palate. This dynamic process encourages a more intensive squeeze action for milk extraction, in contrast to the more passive feeding motion associated with bottle feeding. Thus, breastfeeding potentially facilitates better occlusal development and is associated with a lower risk of malocclusion (25). According to the results of a recent systematic review, children who are breastfed for at least six months are less likely to have class II malocclusion and posterior crossbite (26).

The relationship between breastfeeding and dental caries is controversial in dentistry. A meta-analysis showed that breastfeeding during the first year of life has a potential protective effect against dental caries in children. This was attributed to the possibility that breastfeeding delays the introduction of free sugar-containing foods and the initiation of bottle feeding (27). Another factor is related to breast milk's composition, which is rich in immunomodulatory factors, thus supporting the establishment of a healthy oral microbiome in infants, potentially offering initial protection against dental caries. (27-29). However, the risk of dental caries may change as the child's oral microbiome evolves with the eruption of new teeth.

The same meta-analysis demonstrated that prolonged breastfeeding (beyond 12 months), particularly during nighttime and more frequently, was a contributing factor for an increased risk of dental caries. However, the authors indicated that it was not the act of breastfeeding

itself but rather other confounding factors, such as maternal oral health status, poor oral hygiene practices, and the introduction of other sugary foods and drinks that contribute to dental caries in breastfed children (27). Mutans streptococci, such as *Streptococcus mutans*, can be transmitted from mother to child via direct contact with the mother's saliva. Kissing, sharing utensils, or cleaning a pacifier with the mother's mouth can all transfer bacteria to the child's oral cavity. However, the cariogenicity and levels of these bacteria can vary between individuals. Several factors influence this variation, including maternal bacterial levels, caries prevalence, and oral hygiene practices. For instance, mothers with higher levels of mutans streptococci or poor oral hygiene practices are more likely to transmit these bacteria to their children, increasing the child's risk of developing dental caries (30, 31). Similarly, if a child is exposed to sugary foods and drinks frequently, it can further promote the growth and activity of cariogenic bacteria in their oral cavity, contributing to the development of dental caries. Importantly, the cariogenicity of different milks and formulas, related to their carbohydrate content, could also contribute to the observed differences in caries risk before and after 12 months of age (27).

Various studies, ranging from meta-analyses to in vitro investigations, have investigated the relationship between breastfeeding and dental caries. However, despite this extensive research, there is no clear consensus regarding the possible cariogenic potential of breastfeeding. The lack of a definitive cause-effect relationship in these studies can be attributed to various factors, including the development of diverse feeding patterns unique to each child with the introduction of solid foods after 6 months, differences in oral hygiene habits, and the socioeconomic status of the parents. Furthermore, it is not possible to consider all these confounding factors when designing a study (32, 33). Therefore, further research is necessary to elucidate the complex interaction between breastfeeding practices and the risk of dental caries comprehensively. Given the many benefits of breastfeeding for overall health, the potential association with dental caries should prompt an emphasis on improving oral hygiene practices rather than advocating the cessation of breastfeeding.

### **Breastfeeding in the context of economics: The public nature of breast milk as a merit product**

In economics, merit goods are generally accepted as goods (products) that societies should consume regardless of individuals' wishes or demands. The most typical examples of merit goods (products) are education and health (34). In this study, the term 'product' will be used, as it was suggested and decided to be a more appropriate expression at the Symposium "Breast Milk with All Aspects.

The acceptance that merit products should be consumed without considering the wishes or demands of individuals is a result of the characteristics of these products. These products have the following characteristics:

- Merit products have positive externalities. Social costs and benefits extend beyond the private costs and benefits of consumers (individuals) and are therefore outside the prices realised through the market mechanism. With such externalities, the market mechanism fails and leads to inefficient decisions regarding resource allocation (35). For example, if more education increases productivity not only of an individual worker but also of co-workers, the individual chooses the level of education and ignores this production externality. In this context, if people demand too little education, the provision of education to society should be encouraged (34).
- Another characteristic of merit products is that people have insufficient information about their benefits. If consumers have insufficient information and consequently consume products below their optimal consumption levels, the market mechanism fails to increase social welfare (35).

These two fundamental characteristics of merit products imply that individuals may not be able to act in their own and public interests and therefore require decisions to be made on their behalf. In this context, the function of state intervention, which has more information or is in a more favourable position to make a decision, is to enable people to access and consume merit products rather than telling them what is beneficial or not beneficial (34).

Accepting the postulate that societies should consume merit products regardless of the wishes or demands of individuals makes it necessary for governments to provide these products (although they can be consumed and purchased individually through the market mechanism) and intervene to achieve the level of consumption required for society. This is because if the task of providing merit products is left to the market mechanism alone, such products will be under-consumed in society (34). In this context, for example, individual preferences regarding breastfeeding should be guided by public interventions, and the production and consumption levels of merit products should be increased.

When we evaluate the benefits of breast milk and breastfeeding as an economic product based on consumption data, the following conclusions are reached (36):

- Breast milk is a unique source of nutrients for the growth and development of children. Breast milk has benefits that extend from infancy to childhood and adulthood.

- The World Health Organisation (WHO) considers the exclusive breastfeeding of infants for the first 6 months and the continuation of breastfeeding for at least 2 years as natural nutrition. Breastfeeding also provides maternal health benefits in addition to child health.
- Breast milk has a species-specific and dynamic structure. Its content changes during breastfeeding and varies according to the age of the baby.
- Babies who cannot be fed breast milk are more likely to be hospitalised, especially due to infectious diseases, resulting in treatment and high health costs.
- Babies fed with breast milk become healthier and more successful adults. With these features, breastfeeding benefits the future of society in a sense.
- According to the results of the 2018 Demographics and Health Survey (37), breastfeeding of infants and children in Turkey is not at the desired level.

The aforementioned qualities of breast milk require it to be accepted as an economically merit product. Because: It provides benefits to the baby and mother; it has external benefits to society depending on its production and consumption; and it is consumed below the optimum level.

The acceptance of breast milk as a merit product requires the state to make public interventions to increase its consumption. These interventions are outlined as follows:

- Use of legal power: Dissemination and continuity of baby-friendly hospital practice.
- Improving information: Making it clear to people, especially mothers, the risks they face if they do not breastfeed.
- Incentive: Provide the necessary conditions to achieve optimal breastfeeding rates using various incentive mechanisms to address the difficulties faced by families (especially mothers).

In this context, it can be concluded that breast milk is an economically merit product, and the state should allocate resources by using its public power to increase breastfeeding. Otherwise, societies and individuals may make choices that they regret in the future. Furthermore, this will reduce social welfare.

### **Proactive role of pharmacists in breastfeeding**

Pharmacists play an important role as primary healthcare providers in many healthcare settings, including community pharmacies, hospitals, and clinics. They are often the first point of contact for patients and work with physicians

and other healthcare professionals to ensure optimal patient care. Pharmacists also play a crucial role in supporting and assisting mothers during the breastfeeding period (38, 39).

The key roles and responsibilities of a pharmacist during the breastfeeding period include (40, 41).

1. Help to increase breastfeeding rates in their country, in line with the WHO guidelines, based on the principle that every child has the right to the best start in life, thus helping society achieve a healthier and sustainable future.
2. Provide information and education on the importance of breastfeeding, correct positioning, proper nutrition, and/or supplementation, as appropriate.
3. Educate mothers about medication safety: During breastfeeding, interrupting treatment because of concerns about drug use can cause undesirable and permanent damage to the health of the mother and baby. In cases where the mother should take medication while breastfeeding, the ability of the mother to continue to breastfeed should be assessed on an evidence-based risk-benefit basis. Pharmacists can provide information about the transfer of medicines into breast milk, potential adverse effects, and alternative treatments, if necessary.

Approaches to reducing infant exposure to medicines include (42, 43):

- As most drugs are excreted in breast milk, the main question regarding the use of drugs during lactation is not whether the medicine is excreted in breast milk; it is whether the amount of the drug excreted in breast milk is likely to cause a serious or severe adverse effect in the infant.
- Drug selection during lactation is a multifactorial process that should be evaluated on an individual basis. Therefore, pharmacists can relieve the concerns of mothers and direct them to physicians for safer drug alternatives.
- Drugs reach peak concentration 1-2 hours after oral administration. Breastfeeding at the end of the dosing interval, expressing milk 1-2 hours after taking the medication, and excreting the milk can be used. This method may be effective in drugs with short half-lives and infrequent breastfeeding.
- Selection of drugs with known pharmacokinetic properties and toxic effects, less excretion into breast milk, and a low relative infant dose. For example, sertraline may be preferred over fluoxetine as an antidepressant in postpartum depression because it is less excreted in breast milk.

- Generally, drugs without oral absorption do not have any systemic effects in infants, even if they are passed into milk. For example, aminoglycosides, vancomycin,
- If possible, use local or generic drugs instead of systemic.
- As drugs with a long half-life may cause accumulation in infants; therefore, it is appropriate to administer a single dose just before the infant's longest sleep period.
- Drugs with active ingredients that are widely used in children and whose effects are well known should be preferred for treating mothers.
- Drugs with a high protein-binding rate, such as warfarin, should be preferred because they are less likely to pass into milk.
- Temporarily interrupt breastfeeding when medications are used temporarily: If the mother is undergoing short-term treatment after dental or surgical intervention, she can pump extra milk before the procedure.
- Breastfeeding should be stopped when taking medication known to be harmful

In conclusion, pharmacists play a crucial role in empowering and motivating mothers during lactation by providing education, guidance, medication safety, and breastfeeding support, thus contributing to the UN Sustainable Development Goals on women's and children's health. Therefore, it is crucial that pharmacists properly learn how to use evidence-based scientific sources that provide the greatest quantity of safe-rated drugs among all lactation resources while making maternal medication decisions for women in the lactation period. To enhance the contribution of community pharmacists, the primary most accessible health care provider, to preventive health practices that are more visible and effective, the cooperation between healthcare teams (physician, nurse and pharmacist) and recognition by the health authority is very critical; thus, future focus should be placed on implementing this issue through undergraduate pharmacy education and continuous vocational training.

### **Role of nurses in lactation counselling**

All health authorities recommend that children receive exclusive breast milk for the first 6 months of life and that breastfeeding should continue at least until 2 years of age (44). However, promotion, protection, and support for breastfeeding, such as breastfeeding counselling, are needed to achieve this recommendation (45).

Breastfeeding counselling is an integral part of professional practice. Nurses play a key role in promoting breastfeeding and supporting breastfeeding mothers.

One of the important roles of nurses is to implement the Baby Friendly Hospital Initiative (BFHI) in hospitals. Nurses are the first health care professionals to be consulted when there is a problem with the mother or baby during the breastfeeding process after birth (46). Nurses are effective in helping mothers have positive views about breastfeeding (47). Breastfeeding counselling given to mothers plays a great role in the continuation of breastfeeding and prevention of problems that may occur (45, 46). Nurses should adopt a broad social approach that includes both mothers and fathers to maintain breastfeeding (47).

Breastfeeding counselling should cover all stages of life for children and their mothers. Breastfeeding counselling should anticipate and address important challenges related to breastfeeding, and nurses should be involved at every stage of breastfeeding counselling. For example, every step of the hand expression technique should be explained by nurses (48). The mothers should be informed by nurses how to feed their babies. Nurses should provide breastfeeding support in their routine nursing care and recommend that mothers use community resources to provide breastfeeding support. Nurses should work with many communities to improve breastfeeding support services in the society (44, 46, 49). Therefore, during the education and training of nurses on breastfeeding counselling, attention should be paid not only to the theoretical explanation but also to the clinical practical part. For this reason, it would be useful to add the applied Breastfeeding Consultancy as an elective course to the program. To address graduate nurses' lack of knowledge about breastfeeding through post-graduation in-service training programs will support breastfeeding (50).

For successful breastfeeding, the health status of the infant and mother should be monitored (44). In some cases, breastfeeding should be stopped temporarily or permanently because of maternal and infant diseases. In such cases, a decision should be made in consultation with the treating paediatrician.

While providing support, the nurse should help the mother gain self-confidence. Starting from birth, during breastfeeding counselling, the nurse should identify the difficulties experienced and provide counselling again when necessary (44, 47).

Regardless of the reasons for applying to health institutions, mothers should be encouraged to continue to breastfeed. Within the scope of public health practices, families should be reached through home visits or telephone calls if necessary (50).

In conclusion, nurses play an important role as breastfeeding counsellors. In line with these duties, nurses should play an active role in initiating and maintaining

breastfeeding and ensure that mothers have positive views about breastfeeding.

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