

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/382460784>

Biological clock and circadian rhythm of breast milk composition

Article in *Chronobiology International* · July 2024

DOI: 10.1080/07420528.2024.2381599

CITATIONS

3

READS

269

2 authors:



Ceren Akanalçi
Ege University

5 PUBLICATIONS 14 CITATIONS

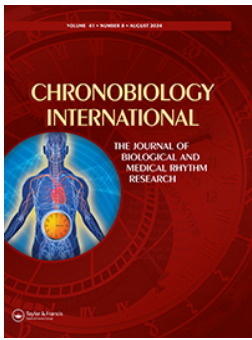
[SEE PROFILE](#)



Saniye Bilici
Gazi University

65 PUBLICATIONS 966 CITATIONS

[SEE PROFILE](#)



Chronobiology International

The Journal of Biological and Medical Rhythm Research

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icbi20

Biological clock and circadian rhythm of breast milk composition

Ceren Akanalçı & Saniye Bilici

To cite this article: Ceren Akanalçı & Saniye Bilici (2024) Biological clock and circadian rhythm of breast milk composition, Chronobiology International, 41:8, 1226-1236, DOI: [10.1080/07420528.2024.2381599](https://doi.org/10.1080/07420528.2024.2381599)

To link to this article: <https://doi.org/10.1080/07420528.2024.2381599>



Published online: 22 Jul 2024.



Submit your article to this journal [↗](#)



Article views: 266



View related articles [↗](#)



View Crossmark data [↗](#)

REVIEW ARTICLE



Biological clock and circadian rhythm of breast milk composition

Ceren Akanalçı ^a and Saniye Bilici ^b

^aDepartment of Nutrition and Dietetics, Faculty of Health Sciences, Ege University, Izmir, Turkey; ^bDepartment of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Turkey

ABSTRACT

Breast milk provides numerous benefits for both the baby and the mother, making it a unique and valuable food. The World Health Organization and the United Nations International Children's Emergency Fund (UNICEF) state that exclusive breastfeeding in the first six months of life is an important strategy for reducing mortality and morbidity in infants. The circadian rhythm formation, which starts in the mother's womb, continues after the baby is born. Breast milk plays an active role in regulating the baby's circadian rhythm through the hormones, basic immune factors and bioactive components it contains, as well as meeting almost all nutritional elements for babies. Since the neural control mechanisms in the newborn are not yet fully developed, breast milk undertakes the task of helping the biological rhythms in the regulation of the infant's sleep-wake cycles, thanks to the circadian rhythm of some elements in its composition. There are studies showing that breast milk contains high levels of cortisol and amino acids that promote activity during the day, while night milk has high levels of melatonin and tryptophan, and micronutrients vary throughout the day. A better understanding of the circadian rhythm displayed by the elements in the composition of breast milk is important for improving maternal and infant health. Since there are many factors affecting the composition of breast milk, it is recommended that breast milk studies should be done on a country or regional basis, and breastfeeding policies can be developed as a result of the results to be obtained.

ARTICLE HISTORY

Received 16 January 2024
Revised 18 June 2024
Accepted 13 July 2024

KEYWORDS

Breast milk; breast milk composition; biological clock; circadian rhythm; circadian variation

Introduction

Breast milk is the basis of newborn nutrition. Breastfeeding has short- and long-term beneficial health effects for both mother and baby. Breastfeeding mothers are less likely to suffer from postpartum depression, cancer (breast, ovarian, endometrial), diabetes, cardiovascular disease, hypertension, hyperlipidemia and osteoporosis (Ciampo and Ciampo 2018; Granger et al. 2021). Breast milk protects infants from morbidity and mortality due to infectious diseases, shortens the course of diseases and is the baby's first vaccine. It provides almost all the nutrients necessary for the growth and development of the baby in the first 6 months (Victoria et al. 2016). However, breast milk is much more than a food that meets the nutritional needs of the infant, it is a biological system with components that determine the interactions with both mother and infant. Breast milk is responsible for the transfer of macro- and micronutrients, hormones, immune factors, microbiota and numerous bioactive factors from mother to child. It plays an important role in laying the foundations for the formation of a healthy intestinal flora that will affect the baby's whole life. In addition, it is reported that

breast milk contributes to the baby's circadian rhythm of rest-activity (Agostoni et al. 2009; Temizsoy 2022). For all these reasons, the World Health Organization (WHO) recommends starting breastfeeding within the first hour after birth, feeding babies exclusively with breast milk for the first 6 months, and then continuing breastfeeding with complementary foods until they are 2 years old (Guideline: counselling of women to improve breastfeeding practices 2018).

Breast milk is a dynamic nutrient. Although it is known that the composition of breast milk varies in conditions such as gestational week, lactation stage, duration and frequency of breastfeeding, it has also been reported that some elements in its composition show a circadian rhythm (Jackson Dorothy A et al. 1988; Cubero et al. 2009; Italianer et al. 2020; Pham et al. 2020; Pundir et al. 2017). Information about the time of day is transferred from the mother to the newborn through the change in breast milk during the day. Therefore, mothers are influential in the circadian rhythm of their infants through mother-infant interaction and environmental stimuli including light. Therefore, breastfeeding during infancy is considered

to be an important factor in the formation of circadian rhythm (Kikuchi et al. 2020). This situation reveals that breast milk should be evaluated from a chronobiological perspective since it is a biological system (Hahn-Holbrook et al. 2019).

This review examines how the biological clock is formed in infants and discusses the role of breast milk in this process, including the daily rhythms of macronutrients and hormones it contains.

Circadian rhythm, mother and baby biological clock

The circadian rhythm is driven by an endogenous oscillator with a cycle lasting approximately (circa) one day (diem); it regulates and optimizes biochemical, physiological and behavioral events of the organism (Hastings et al. 2003; Mazri et al. 2020; Mohawk et al. 2012). In humans, the central circadian system regulated by the suprachiasmatic nucleus (SCN) in the anterior hypothalamus is responsible for various functions that can affect different tissues and organs of the body such as sleep-wake cycle, glucose metabolism (gluconeogenesis, glucose transport, insulin/glucagon secretion, etc.), gastric emptying, repair and maintenance of the mucosal barrier, absorption of nutrients, adipose tissue differentiation, and leptin secretion. The other controlling structure in the circadian system other than the SCN is the peripheral clocks. Peripheral clocks are 24-hour rhythms in which clock genes are expressed in many tissues such as liver, pancreas, lungs, kidneys, skeletal muscle and adipose tissue (Stenvers et al. 2019).

Light is the most important zeitgeber (rhythm transmitter) for the SCN and plays an important role as a central clock in the transmission of photic entrainment and light-dark signals to peripheral organ clocks (Finger and Kramer 2021). Light is sensed by photoreceptors in the retina and transmitted to the SCN via the retinohypothalamic tract (RHT) (Korf and von Gall 2022). The rhythmic information generated in the SCN is transmitted to cells in other parts of the brain and peripheral organs via neural, endocrine and behavioral signals. Peripheral clocks generally operate in response to messages from the SCN, but most do not receive direct light information and are sensitive to other zeitgebers such as nutrition, sleep, exercise, temperature, etc (Bass and Takahashi 2010; Dibner et al. 2010; Stenvers et al. 2019).

During pregnancy, the mother's hormonal profile adapts to the changes that occur to meet the needs of the fetus (Bates and Herzog 2020). The placenta is the only organ formed by the interaction of both maternal and fetal/embryonic tissues and forms an interface

between the circulatory systems of the baby and the mother. The circadian clock, which is strongly involved in the regulation of functions such as hormone synthesis and immunity in adults, is then involved in the diurnal regulation of these functions through the placenta.

The fetal circadian system develops under the influence of endogenous and exogenous entrainment signals passing through the placenta (Wharfe et al. 2011). Maternal melatonin easily crosses the placenta and the fetal blood-brain barrier, allowing circadian information to be transmitted to the fetus (Serón-Ferré et al. 2012). Melatonin acts at all levels of the maternal-placental-fetal system and plays a critical role in circadian rhythm entrainment in the fetus. Melatonin is also important for its scavenging effect on free radicals and its effects on cell proliferation and fetal growth (Hassell et al. 2013). In humans, melatonin receptors appear in the fetal SCN as early as 18 weeks of gestation, suggesting that melatonin is the primary communicator of circadian information for the fetus (Reppert et al. 1988). Glucocorticoids (cortisol), like melatonin, can cross the placenta. The driving signals of melatonin and glucocorticoids play an important role in establishing, modulating or assisting the development of circadian rhythms in the fetus, both directly, as they can cross the placenta, and indirectly, as they affect the maternal peripheral clock. Maternal body temperature, nutrition and hormone secretion also play a role in the development of fetal rhythms (Logan and McClung 2019).

Circadian rhythm formation, which starts in the womb, continues after birth and takes shape in the first months of life. During pregnancy, the embryonal clock is directly synchronized by the mother's SCN, but this direct communication is lost after birth. Therefore, immediately after birth, the baby begins to develop its own independent central clock. Temperature rhythms appear immediately in term babies, while other rhythms such as sleep-wake and hormonal cycles are regulated between 3–6 months (Olejniczak et al. 2023). Babies, who do not have a fully functioning circadian rhythm at birth because their neural control mechanisms have not yet matured, use their own biological rhythms and circadian signals in breast milk to regulate their circadian rhythms (Thomas et al. 2014). Light plays a role in regulating diurnal fluctuations directly in the fetus through the placenta and indirectly in the newborn through breast milk (Wong et al. 2022). Studies show that daily fluctuations in breast milk components have evolved to convey time-of-day information and promote the development of a built-in circadian clock in the infant (Cubero et al. 2007). The varying concentrations of breast milk hormones at different times of

the day contribute to the formation of a circadian rhythm in breastfed infants. The earlier occurrence of circadian rhythmicity in body temperature in breastfed infants compared to bottle-fed infants suggests that breast milk may facilitate the maturation of the circadian clock. If bottle-fed infants are fed according to the timing of expressed breast milk, they may benefit from the same advantages (Lodmore et al. 1992; Wong et al. 2022).

Physiological developments

During the first week after birth, the neuronal and glial networks in the infant brain undergo changes. Although the baby's SCN already releases basic elements of the circadian system, such as the *Per*, *Cry*, *Bmal1* and *Clock* genes, there is a marked increase shortly after birth. This is an important step for the immature central clock (Greiner et al. 2022; Perez-Catalan et al. 2021). Another component that mediates the development of the circadian system in the newborn is the RHT. Light travels to the infant's SCN via the RHT, which continues to develop after birth. Light as an environmental input plays an important role in the infant's circadian rhythm. The role of light in infant circadian rhythm was examined in newborns kept in continuous darkness or under a 24-hour light-dark cycle (12/12 light/dark) in the first few days after birth. Accordingly, higher levels of melatonin were found in the plasma of infants kept in continuous darkness compared to those kept under light-dark cycle conditions. This proves that the newborn is sensitive to light immediately after birth (Olejniczak et al. 2023; Wong et al. 2022).

Breast milk

Breast milk has various components that can regulate the baby's circadian system. Studies have shown that breast milk contains higher concentrations of different components during the day and night, which plays an important role in regulating the baby's circadian system.

The circadian rhythm, which is not yet developed in the newborn, is regulated by the significant contributions of the hormones cortisol and melatonin in breast milk. These hormones mark the time of day and regulate the sleep-wake cycle. When these hormones enter the infant's circulation through breast milk, they provide clock information to the organs. Previous studies have examined the variation of these hormones. Melatonin levels in breast milk are higher at night than during the day, while cortisol levels are higher during the day than at night. This variation helps to establish the infant's sleep-wake rhythm (Figure 1) (Carissimi et al. 2016; Italianer et al. 2020; Olejniczak et al. 2023; Sorensen et al. 2020).

It has been reported that breastfed babies develop a circadian rhythm after about 2–3 weeks, while this period can reach 12 weeks in mixed-fed babies (Kikuchi et al. 2020). Another study found that the formation of circadian rhythm peaks at week 4 in breastfed infants (Oda et al. 2008). Additionally, sleep parameters, indicators of circadian rhythm, were found to be better in exclusively breastfed infants compared to formula-fed infants (Jafar et al. 2021). In contrast to formula-fed infants, breastfed 2-month-old infants experienced significantly fewer colic attacks and less severe irritability, which was associated with melatonin consumption through breast milk at night (Cohen Engler et al. 2012). It is believed that the shorter time for the circadian rhythm to develop in exclusively breastfed babies is due to the fact that breastfeeding mothers serve as a stronger zeitgeber compared to mothers who use mixed feeding. This can be attributed to multiple factors: different contact times between mothers and their babies, feeding schedules, variations in mothers' circadian rhythms, differences in the composition of breast milk and formula milk, varying light conditions, and more (Kikuchi et al. 2020). Maternal contact is important; one study reported that the duration of breastfeeding was longer than the duration of mixed feeding (Lucas and St James–Roberts 1998). Kikuchi et al. also found that the frequency of daily

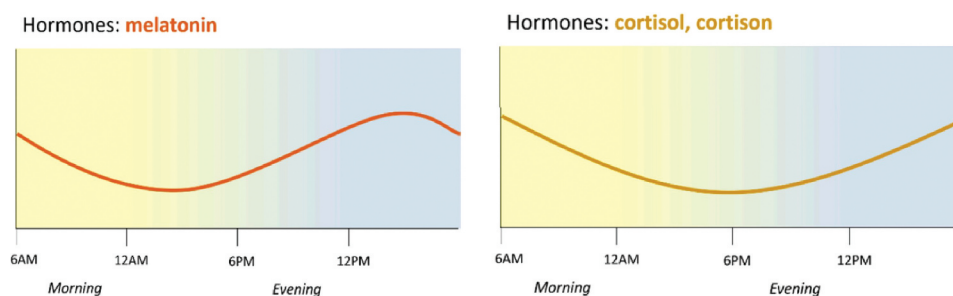


Figure 1. Circadian variation of melatonin, cortisol and cortisone in breast milk (reproduced from 7 with permission from [MDPI]. © 2020). (Italianer et al. 2020).

breastfeeding was higher than that of mixed feeding, as mothers can breastfeed quickly whenever the baby demands it. Considering all factors, breastfeeding mothers are in closer contact with their babies than mixed-feeding mothers, making them a stronger stimulant for establishing the baby's circadian rhythm. Ultradian rhythms in breastfed babies were also found to be more pronounced at 6 and 12 weeks compared to mixed-fed babies. Breastfeeding mothers can more easily adjust their timing to their babies' demands than mixed-feeding mothers (Kikuchi et al. 2020). Circadian fluctuations in the composition of breast milk help transfer information about the time of day from mother to newborn, making breast milk a unique form of "chrono-nutrition" and plays an important role in the newborn's adaptation to the outside world (Hahn-Holbrook et al. 2019). Accordingly, it has been reported that the mismatch between milking time and feeding time may have negative consequences for the development of circadian clock and sleep homeostasis in infants fed with donor milk (Italianer et al. 2020). Maternal, fetal and neonatal circadian rhythm development is summarized in Figure 2.

Circadian disruption during pregnancy has adverse effects on fetal health in infancy and adulthood, demonstrating the important role of the mother in influencing fetal circadian rhythms. Studies in rodents have shown that circadian disruption in the womb is associated with cardiovascular disease, reduced bone mass and strength, glucose intolerance, insulin resistance and behavioral disorders in adulthood (Chaves et al. 2019; Wong et al. 2022). Human studies have shown that when the mother's sleep and diet are disrupted and her

working hours are irregular, the likelihood of both low birth weight and premature babies and miscarriage increases (Logan and McClung 2019). It has been reported that maternal chronosis may lead to memory and learning deficits, increased anxiety and depressive behaviors, adiposity and impaired glucose tolerance in the long term (Mendez et al. 2016; Vilches et al. 2014; Voiculescu et al. 2016).

Circadian rhythms of breast milk components

Breast milk is a unique nutrient for both full-term and preterm babies. In fact, the composition of breast milk varies to meet the physiologically changing needs of the infant. It is well known how the composition of breast milk changes at different stages of lactation, or the differences in macro- and micro-components between foremilk and hindmilk during breastfeeding. What is less well known is how the composition of breast milk shows a circadian rhythm over a 24-hour period (White 2017). In previous studies, macronutrients, some vitamins and minerals, some hormones and energy have been studied to examine the diurnal rhythm of breast milk components. A summary of the literature review on the circadian rhythms of some elements in breast milk is presented in Table 1.

For some nutrients (especially melatonin, cortisol, cortisone, cortisone and fat), circadian rhythms have been determined, while for others, the results are mixed.

Circadian rhythm exhibited by hormones

Studies have particularly focused on melatonin and cortisone/cortisol due to their key roles in metabolism

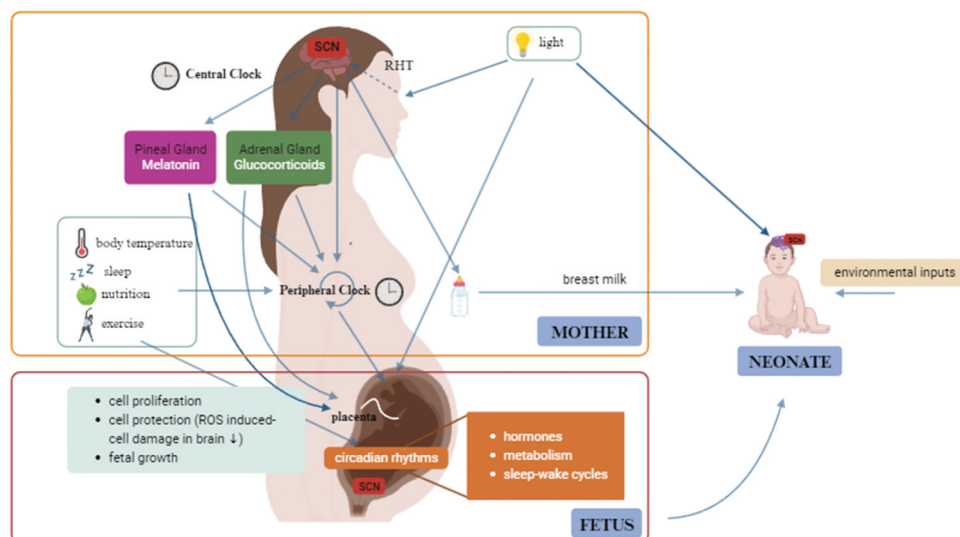


Figure 2. Maternal, fetal and neonatal circadian rhythm development.

Table 1. Summary of studies on the circadian rhythms displayed by breast milk components.

Year	Participants	Lactation Stage	Breast Milk (BM) Sample	Parameter Analyzed	Storage	Analysis Method	Results	References
2023	10 mothers	–	For 24 hours before and after each breastfeeding	Leptin, adiponectin, insulin, fat and glucose	–	–	–Leptin, adiponectin, insulin and fat concentrations are different before and after feeding –Circadian changes were detected in adiponectin concentration, fat content, glucose (both amount and concentration) and insulin (both amount and concentration) over a 24-hour period	Suwaydi et al. (2023a)
2023	22 mothers (all term babies)	Mature milk	For 24 hours before and after each breastfeeding	Leptin, adiponectin, insulin, fat and glucose	BM samples were frozen at –20 °C	Human Leptin ELISA DuoSet (leptin) Human Adiponectin ELISA (adiponectin) Human Insulin ELISA BioVendor (insulin) Chromatocrit (fat) D-Glucose HK Assay Kit (glucose)	–Higher concentrations of adiponectin and glucose were found in the pre-feeding concentration –Lower concentrations of insulin and fat were found in the post-feeding concentration –Leptin, adiponectin, insulin, glucose and fat concentration exhibited circadian	Suwaydi et al. (2023b)
2020	45 mothers (27-premature 18-term)	14–16 days after birth	4 times a day (06:00, 12:00, 18:00, 00:00) Total = 180 samples	Macronutrient, energy	Freezing-thawing process Ø Storage at +4°C for 1 day	Mid-infrared spectrophotometry (MIRIS)	–Protein, carbohydrate, fat and energy content is highest in daytime expressions (12:00–18:00) and lowest in nighttime expressions (00:00–06:00) –The least fluctuation is in carbohydrates –Daily variations are more pronounced in premature milk samples	Paulaviciene et al. (2020)
2019	98 mothers (32-premature 66-term)	Colostrum, transitional milk and mature milk (days 0–30 after birth)	4 times a day (03:00, 09:00, 15:00, 21:00) Total: 392 samples	Melatonin	BM samples were frozen at –20 °C Then stored at –80°C in the laboratory until analysis	IBL Melatonin ELISA	–There is a circadian rhythm for melatonin levels in milk from mothers of both premature and term infants (this rhythm is observed in colostrum, transitional milk and mature milk) –Compared to term infant milk, premature milk has a higher concentration of melatonin, especially in colostrum –Melatonin levels peaked at 03:00 in the milk of both premature and term infants. Melatonin levels in the milk of premature infants (both in colostrum – meaning colostrum, transitional milk and mature milk) were higher at 03:00 than in the milk of term infants	Qin et al. (2019b)
2019	10 mothers (all term babies)	Mature milk	24 hours after each breastfeeding Total = 45 samples	Cortisol, cortisone, macronutrient	BM samples were frozen at –20 °C	Mid-infrared spectrophotometry (for macronutrients) Liquid chromatography-tandem mass spectrometry (LC-MS/MS) (for cortisol and cortisone) Liquid chromatography-tandem mass spectrometry	–Cortisol and cortisone show a diurnal rhythm –There is no rhythm for macronutrients –Cortisol and cortisone levels were highly correlated –Cortisol and cortisone levels were not correlated with carbohydrate, protein and fat	Hollanders et al. (2019)
2017	23 mothers	–	AS samples taken from each breast before and after each breastfeeding for 24 hours Total = 502samples	Cortisol, cortisone,	BM samples were frozen at –20 °C Then stored at –80°C in the laboratory until analysis	Liquid chromatography-tandem mass spectrometry	–A positive correlation has been found between cortisol and cortisone –Glucocorticoid concentrations exhibited a 24-hour pattern, reaching their highest peak in the early morning –No difference was found between glucocorticoid levels in milk expressed before or immediately after breastfeeding and milk from the left or right breast	Pundir et al. (2017)

(Continued)

Table 1. (Continued).

Year	Participants	Lactation Stage	Breast Milk (BM) Sample	Parameter Analyzed	Storage	Analysis Method	Results	References
2017	52 mothers (30- premature 22-term)	27- transitional milk, 25-mature milk	3 times a day (morning, noon and night) Total = 156 samples	Macro nutrient	Freezing-thawing process Storage at +4°C for 1 day	Mid-infrared spectrophotometry (MIRS)	–Morning, midday and night macronutrient levels are not significantly different –Macronutrient levels of transitional and mature milk are not significantly different –Macronutrient levels of term infant milk and premature milk are not significantly different –Premature bebeği olan annelerin sütlerinde kortizol ve kortizon düzeyleri daha düşüktür	Çetinkaya et al. (2017)
2016	20 mothers (10- premature 10-term)	Colostrum, transitional milk and mature milk (days 0–30 after birth)	Weekly, during the first month after birth, at the same time of day Total = 75 samples	Cortisol, cortisone,	BM samples were frozen at –20 °C	Liquid chromatography – tandem mass spectrometry	–Macronutrient levels of term infant milk and premature milk are not significantly different –Premature bebeği olan annelerin sütlerinde kortizol ve kortizon düzeyleri daha düşüktür	van der Voorn et al. (2016)
2016	10 mothers (all term babies)	Mature milk	24 hours at every feeding Total = 92 samples	Cortisol, cortisone,	BM samples were frozen at –20 °C	Liquid chromatography – tandem mass spectrometry	–Milk cortisol and cortisone concentrations correlated with collection time (peak at 07:00) –Cortisol and cortisone concentrations in breast milk and saliva correlated with each other	van der Voorn et al. (2016)
2016	21 mothers (14- premature 7-term)	Transitional milk, mature milk	5 samples from each mother at 4–6 hour intervals for 24 hours (10:00–22:00, day milk; 22:00–10:00, night milk) Total: 105 samples	Melatonin, superoxide dismutase-SOD, glutathione peroxidase-Gpx3, total antioxidant capacity (TAOC)	BM samples were frozen at –80 °C	IBL Melatonin ELISA (melatonin) IBL Cu/ZnSOD ELISA (SOD) ALPCO ELISA (Gpx3) Sigma-Aldrich assay kit (TAOC)	–Melatonin and Gpx3 concentrations are significantly higher in night milk –Melatonin had a circadian rhythm in both preterm and term milk and its concentration at night was significantly higher –Melatonin, SOD, Gpx3 and TAOC did not differ in milk from premature and term infants –There is no significant relationship between melatonin concentration and SOD, Gpx3 or TAOC concentrations	Katz et al. (2016)
2015	32 mothers (all premature babies)	Transitional milk and mature milk (1–7 weeks after birth)	Total: 133 pairs (266 samples)	Macro nutrient, energy	BM samples were frozen at –20 °C	Mid-infrared spectrophotometry (MIRS)	–Over the whole period, fat and energy contents are significantly higher in the evening samples –No significant difference in carbohydrate and protein content between day and night	Moran-Lev et al. (2015)
2013	15 mothers (all term babies)	Mature milk	AS samples taken from each breast before and after each breastfeeding for 24 hours Total: 165 samples	Fat, lactose, total protein, whey, casein	BM samples were frozen at –20 °C	Chromatocrit Plus device (fat) Enzymatic spectrophotometric method (lactose) Bradford protein assessment (protein)	–Milk fat content changed significantly during 24 hours, while lactose and protein content remained the same –24-hour average total protein, whey and casein intake is inversely related to the number of feedings per day –24-hour mean lactose concentration is positively associated with the number of days of breastfeeding –No association between 24-hour mean fat concentration and number of breastfeedings per day	Khan et al. (2013)
2012	77 mothers	Colostrum, transitional milk, mature milk	Every 3 hours for 24 hours Total: 105 samples	Amino acid	BM samples were frozen at –80 °C	High Performance Liquid Chromatography Electrospray Ionization Mass Spectrometry (HPLC-ESI-MS/MS)	–In colostrum; only tryptophan showed a circadian rhythm (peak at 00:00) –In transitional milk, a circadian rhythm was detected in tryptophan (peak at 03:00) and methionine (peak at 18:00) –In mature milk; tryptophan (peak at 06:00), methionine (peak at 21:00), aspartic acid (peak at 12:00), histidine (peak at 03:00), phenylalanine (peak at 12:00), tyrosine (peak at 06:00) showed circadian rhythm	Sánchez et al. (2013)
2009	7 mothers	Colostrum (1–5 days postpartum)	24 hours before each breastfeeding	Antioxidant capacity	BM samples were frozen at –80 °C	TEAC (Trolox equivalent antioxidant capacity) method	–There was a difference between day and night in breast milk samples. Antioxidant capacity was significantly higher in milk samples taken at 18:00 and 21:00 hours	Cubero et al. (2009)

(Continued)

Table 1. (Continued).

Year	Participants	Lactation Stage	Breast Milk (BM) Sample	Parameter Analyzed	Storage	Analysis Method	Results	References
2006	39 mothers (all premature babies)	Day 7–14 after delivery	Twice a day (06:00–09:00–21:00–00:00) Total: 78 samples	Fat	–	Chromatocrit	– Total fat content of breast milk is significantly higher in evening samples – The difference in total fat content between morning expressed breast milk and evening expressed breast milk is not associated with gestational age and birth weight	Lubetzky et al. (2006)
1990	6 mothers (all term babies)	Mature milk	5 times a day at 06:00, 10:00, 14:00, 18:00, 22:00	Fat, fatty acids, total cholesterol, lactose, glucose, protein, energy, α - and γ -tocopherol	BM samples were frozen at -70°C	Gas-liquid chromatography (fat, fatty acids, total cholesterol) YSI model 27 industrial analyzer (glucose, lactose) Micro-Kjeldahl method (protein nitrogen concentration) South-Durnin equation (energy) High performance liquid chromatography with normal phase (tocopherol) Chromatocrit	– Fat is highly variable during the day. The amount of fat in women's milk varied from 2.1 g/dL to 5.3 g/dL. Variability in the amount of fat in the same woman's milk throughout the day, with a minimum of 1.2 g/dL and a maximum of 2.2 g/dL – Lactose and glucose concentrations did not vary during the day – Protein levels show a circadian rhythm during the day. The highest values were observed at 06:00 and 18:00 – Energy, cholesterol, α- and γ-tocopherol levels did not differ significantly during the day	Lammi-Keefe et al. (1990)
1988	6 mothers (all term babies)	Colostrum, transitional milk and mature milk	24 hours before and after each breastfeeding	Fat	–	Chromatocrit	– Fat concentrations peaked between 16:00–20:00 – Fat concentration at the beginning and end of feeding changed significantly over 24 hours – The most important determinant of fat concentration was found to be the length of time since the previous feeding – The greater the milk intake in a feeding, the greater the increase in fat concentration from the beginning to the end of the feeding – The concentration of nitrogenous substances in milk varies significantly between women but is constant throughout the day – Taurine and glutamine+glutamic acid concentrations vary widely between women – Glutamine+glutamic acid concentration increased as taurine concentration decreased – Levels of other amino acids, especially those in low concentration, fluctuated throughout the day – Bile salt-stimulated lipase does not show variation throughout the day, whereas serum-stimulated lipase has significant day-to-day variability	Jackson et al. (1988)
1987	7 mothers (all term babies)	Mature milk	5 times a day at 06:00, 10:00, 14:00, 18:00, 22:00	Total nitrogen, protein nitrogen, urea nitrogen and free amino acids	BM samples were frozen at -70°C	Micro-Kjeldahl method (total nitrogen and protein nitrogen) Crocker method-calorimetric measurement (urea nitrogen) HPLC (free aminosacids)	– The concentration of nitrogenous substances in milk varies significantly between women but is constant throughout the day – Taurine and glutamine+glutamic acid concentrations vary widely between women – Glutamine+glutamic acid concentration increased as taurine concentration decreased – Levels of other amino acids, especially those in low concentration, fluctuated throughout the day – Bile salt-stimulated lipase does not show variation throughout the day, whereas serum-stimulated lipase has significant day-to-day variability	Clark et al. (1987)
1986	6 mothers (all term babies)	Mature milk	5 times a day at 06:00, 10:00, 14:00, 18:00, 22:00	Bile salt-stimulated lipase and serum-stimulated lipase	BM samples were frozen at -70°C	HPLC (free aminosacids) Harnell and Olivecrona method (bile salt-stimulated lipase) Nilsson-Ehle and Schotz method (serum-stimulated lipase)	– Bile salt-stimulated lipase does not show variation throughout the day, whereas serum-stimulated lipase has significant day-to-day variability	Lavine et al. (1986)
1983	17 mothers (all term babies; 13-German, 4-British)	Colostrum, transitional milk and mature milk	5 samples per day on days 1, 3, 5, 8, 15, 22, 29 and 36 of lactation (for 4 participants only on days 5, 8, 15, 22, 29 and 36 of lactation)	Fat	BM samples were stored below -30°C	Thin-layer chromatography	– In 13 participants, lipid levels peaked in the afternoon (midday to 18:00) – In 4 participants, lipid levels peaked in the evening (between 18:00 and midnight)	Harzer et al. (1983)
1981	60 mothers	Mature milk	For 12 hours both before and after breastfeeding	Fat	BM samples were frozen at -20°C	Chromatocrit	– There is a distinct circadian rhythm during the day. Highest levels were found in the early morning and lowest in the afternoon	Prentice et al. (1981)
1949	8 mothers	Transitional milk	At 4-hour intervals throughout a day	Fat	–	Gerber	– Lipid concentration is highest during the day and at noon and lowest between 20:00–04:00	Gunther and Stanier (1949)

and immune activity. As a result, it is currently possible to discuss a 24-hour circadian rhythm related to these hormones. These hormones directly affect the baby's circadian rhythm regulation, and their rhythm patterns are shown graphically in [Figure 1](#) above, in the section on the regulation of the baby's circadian rhythm (Hahn-Holbrook et al. 2019; Hollanders et al. 2019; Italianer et al. 2020; Katzer et al. 2016; Pundir et al. 2017; Qin et al. 2019a; van der Voorn et al. 2016).

Other than melatonin and cortisol, leptin in breast milk has been the most widely studied appetite hormone. Considering that leptin suppresses hunger and reduces the risk of developing obesity, its importance in breast milk is clear (Cannon et al. 2015). Therefore, leptin is thought to play a key role in appetite regulation and energy balance in breastfed infants (Palou and Picó 2009). One study found that leptin levels increased between 20:00 and 06:00, peaking around 05:00, which is consistent with the nocturnal increase in human circulating leptin (Saad et al. 1998; Suwaydi et al. 2023b). Another study found that leptin concentration in milk was significantly higher between 22:00 and 04:00 compared to 04:00 and 22:00 (Cannon et al. 2015). Although more studies are needed on the circadian rhythm of leptin in breast milk, understanding the role of this hormone's increase during the day and lactation could be very important for future applications (Nozhenko et al. 2015).

Prolactin, which is thought to aid in nutrient absorption from the baby's intestines, tends to be at higher levels in the morning hours (02:00–06:00) (Cregan et al. 2002; Hahn-Holbrook et al. 2019). Although a few studies indicate that adiponectin and insulin levels in breast milk change during lactation, there is not enough research to determine their circadian rhythms (Hahn-Holbrook et al. 2019; Suwaydi et al. 2023b).

Circadian rhythm exhibited by macronutrients

Many studies have been conducted to determine the circadian rhythm of protein, carbohydrate, and fat concentrations in breast milk. Some of these studies are presented in [Table 1](#). While some studies do not detect a circadian rhythm for any macronutrient (Çetinkaya et al. 2017; Hollanders et al. 2019), others indicate a rhythm for only some of them (Khan et al. 2013; Moran-Lev et al. 2015). When methodologically similar studies are evaluated, it is generally not possible to identify a circadian rhythm for carbohydrate and total protein amounts (Italianer et al. 2020; Khan et al. 2013). Studies investigating daily changes in protein have mostly focused on specific amino acids. Notably, activity-promoting amino acids are higher in daytime milk

(tyrosine, methionine, phenylalanine) (Hahn-Holbrook et al. 2019; Sánchez et al. 2013), while tryptophan peaks in the early morning hours (Italianer et al. 2020). The macronutrient whose circadian rhythm is most clearly determined is fat. Although their methodologies differed, most studies reported circadian variation in fat concentration, with acrophase found in the evening hours (Italianer et al. 2020; Jackson et al. 1988; Selvalatchmanan et al. 2021; Suwaydi et al. 2023b).

Conclusions and recommendations

In humans, light is the most important zeitgeber for the circadian rhythm regulated by the SCN in the anterior hypothalamus. However, there are also zeitgebers for the peripheral clock such as feeding, sleep, exercise and temperature. Fetal circadian rhythm regulation occurs both in the infant SCN through light and through hormones and metabolites from the placenta and mother. After the baby is born, its own biological rhythms begin to develop, and components in breast milk play a role in establishing a rhythm for the baby.

Although the presence of circadian rhythm was determined for some nutrients and hormones of the breast milk in the studies reviewed (mainly cortisone/cortisol, melatonin and fat), the results obtained for some of them are not clear. The most important reason for this is thought to be the heterogeneous nature of the studies. Basic characteristics such as the characteristics of the infants included in the studies (term/premature), lactation stage (colostrum/transitional milk/mature milk), milking and storage procedures, and analysis methods used are different from each other. In addition, the sample sizes of the studies are small. This situation may affect the quality of existing studies and make the results different from each other.

A connection has been established between many chronic diseases and nutrition in the fetal and neonatal periods, a concept known as “metabolic programming.” More studies are needed on the epigenetic effects of breast milk. However, the concept of “metabolic programming” indicates that early-life nutrition may influence brain development and body functions, potentially playing a decisive role in health status in adulthood. In this context, it is important to understand the circadian rhythms of the elements in breast milk (Singhal and Lucas 2004). With the increase in methodologically stronger studies, various recommendations can be developed in this field. For example, the knowledge that antioxidant capacity and melatonin hormone are at higher levels at night may help to form a recommendation for prioritizing the administration of milk expressed at night, especially to high-risk

infants, or it may be recommended that breast milk be given to the infant at the same time of the day when it is expressed in order for the infant to obtain more physiological benefits from breast milk and to ensure the synchronization of its systems. Considering that circadian disruption can negatively affect almost every process in the body, it would be a logical approach to give babies circadian compatible milk (Hahn-Holbrook et al. 2019; Sinkiewicz-Darol et al. 2022).

Instead of combining international data, it would be more useful to conduct country- or region-specific studies to assess infant and maternal nutritional needs. The information obtained may be useful in assessing infant and maternal nutritional needs, may provide more information for health workers in promoting and recommending breastfeeding, and may even contribute to policy making in the country or region in question.

Finally, supporting the proper development of the baby's circadian rhythm and investigating the potential effects on baby development if the rhythms of breast milk components are determined are among the desired goals for future studies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Ceren Akanalci  <http://orcid.org/0000-0003-2184-8417>
Saniye Bilici  <http://orcid.org/0000-0002-1235-0329>

References

- Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, et al. 2009. Breast-feeding: a commentary by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr.* 49:112–125.
- Bass J, Takahashi JS. 2010. Circadian integration of metabolism and energetics. *Science.* 330:1349–1354. doi: [10.1126/science.1195027](https://doi.org/10.1126/science.1195027).
- Bates K, Herzog ED. 2020. Maternal-fetal circadian communication during pregnancy. *Front Endocrinol.* 11:198. doi: [10.3389/fendo.2020.00198](https://doi.org/10.3389/fendo.2020.00198).
- Cannon AM, Kakulas F, Hepworth AR, Lai CT, Hartmann PE, Geddes DT. 2015. The effects of leptin on breastfeeding behaviour. *Int J Environ Res Public Health.* 12:12340–12355. doi: [10.3390/ijerph121012340](https://doi.org/10.3390/ijerph121012340).
- Carissimi A, Martins AC, Dresch F, da Silva LC, Zeni CP, Hidalgo MP. 2016. School start time influences melatonin and cortisol levels in children and adolescents—a community-based study. *Chronobiol Int.* 33:1400–1409. doi: [10.1080/07420528.2016.1222537](https://doi.org/10.1080/07420528.2016.1222537).
- Çetinkaya AK, Dizdar EA, Yarcı E, Sari FN, Oguz SS, Uras N, Canpolat FE. 2017. Does circadian variation of mothers affect macronutrients of breast milk? *Amer J Perinatol.* 34:693–696. doi: [10.1055/s-0036-1597327](https://doi.org/10.1055/s-0036-1597327).
- Chaves I, van der Eerden B, Boers R, Boers J, Streng AA, Ridwan Y, Schreuders-Koedam M, Vermeulen M, van der Pluijm I, Essers J. 2019. Gestational jet lag predisposes to later-life skeletal and cardiac disease. *Chronobiol Int.* 36:657–671. doi: [10.1080/07420528.2019.1579734](https://doi.org/10.1080/07420528.2019.1579734).
- Ciampo LAD, Ciampo IRLD. 2018. Breastfeeding and the benefits of lactation for Women's health. *Rev Bras Ginecol Obstet.* 40:354–359. doi: [10.1055/s-0038-1657766](https://doi.org/10.1055/s-0038-1657766).
- Clark RM, Ross SA, Hill DW, Ferris AM. 1987. Within-day variation of taurine and other nitrogen substances in human milk. *J Dairy Sci.* 70:776–780. doi: [10.3168/jds.S0022-0302\(87\)80073-5](https://doi.org/10.3168/jds.S0022-0302(87)80073-5).
- Cohen Engler A, Hadash A, Shehadeh N, Pillar G. 2012. Breastfeeding may improve nocturnal sleep and reduce infantile colic: potential role of breast milk melatonin. *Eur J Pediatr.* 171:729–732. doi: [10.1007/s00431-011-1659-3](https://doi.org/10.1007/s00431-011-1659-3).
- Cregan MD, Mitoulas LR, Hartmann PE. 2002. Milk prolactin, feed volume and duration between feeds in women breastfeeding their full-term infants over a 24 h period. *Exp Physiol.* 87:207–214. doi: [10.1113/eph8702327](https://doi.org/10.1113/eph8702327).
- Cubero J, Narciso D, Terrón P, Rial R, Esteban S, Rivero M, Parvez H, Rodríguez AB, Barriga C. 2007. Chrononutrition applied to formula milks to consolidate infants' sleep/wake cycle. *Neuroendocrinol Lett.* 28:360–366. PMID: 17693960.
- Cubero J, SÁÑCHEZ CL, Bravo R, SÁÑCHEZ J, Rodríguez AB, Rivero M, Barriga C. 2009. Analysis of the antioxidant activity in human milk, day vs. night. *Cell Membranes Free Radical Res.* 1:100–101.
- Dibner C, Schibler U, Albrecht U. 2010. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol.* 72:517–549. doi: [10.1146/annurev-physiol-021909-135821](https://doi.org/10.1146/annurev-physiol-021909-135821).
- Finger AM, Kramer A. 2021. Mammalian circadian systems: organization and modern life challenges. *Acta Physiol (Oxf).* 231:e13548. doi: [10.1111/apha.13548](https://doi.org/10.1111/apha.13548).
- Granger CL, Embleton ND, Palmer JM, Lamb CA, Berrington JE, Stewart CJ. 2021. Maternal breastmilk, infant gut microbiome and the impact on preterm infant health. *Acta Paediatrica.* 110:450–457. doi: [10.1111/apa.15534](https://doi.org/10.1111/apa.15534).
- Greiner P, Houdek P, Sládek M, Sumová A. 2022. Early rhythmicity in the fetal suprachiasmatic nuclei in response to maternal signals detected by omics approach. *PLOS Biol.* 20:e3001637. doi: [10.1371/journal.pbio.3001637](https://doi.org/10.1371/journal.pbio.3001637).
- Guideline: counselling of women to improve breastfeeding practices. 2018. Geneva: World Health Organization; [assessed 2022 Feb 21].
- Gunther M, Stanier J. 1949. Diurnal variation in the fat content of breast-milk. *Lancet.* 254:235–237. <https://www.sciencedirect.com/science/article/pii/S0140673649912428>
- Hahn-Holbrook J, Saxbe D, Bixby C, Steele C, Glynn L. 2019. Human milk as “chrononutrition”: implications for child

- health and development. *Pediatr Res*. 85:936–942. doi: [10.1038/s41390-019-0368-x](https://doi.org/10.1038/s41390-019-0368-x).
- Harzer G, Haug M, Dieterich I, Gentner PR. 1983. Changing patterns of human milk lipids in the course of the lactation and during the day. *Am J Clin Nutr*. 37:612–621. doi: [10.1093/ajcn/37.4.612](https://doi.org/10.1093/ajcn/37.4.612).
- Hassell KJ, Reiter RJ, Robertson NJ. 2013. Melatonin and its role in neurodevelopment during the perinatal period: a review. *Fetal Matern Med Rev*. 24:76–107. doi: [10.1017/S0965539513000089](https://doi.org/10.1017/S0965539513000089).
- Hastings MH, Reddy AB, Maywood ES. 2003. A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci*. 4:649–661. doi: [10.1038/nrn1177](https://doi.org/10.1038/nrn1177).
- Hollanders JJ, Kouwenhoven SM, van der Voorn B, van Goudoever JB, Rotteveel J, Finken MJ. 2019. The association between breastmilk glucocorticoid concentrations and macronutrient contents throughout the day. *Nutrients*. 11:259. doi: [10.3390/nu11020259](https://doi.org/10.3390/nu11020259).
- Italianer MF, Naninck EFG, Roelants JA, van der Horst GTJ, Reiss IKM, Goudoever JBV, Joosten KFM, Chaves I, Vermeulen MJ. 2020. Circadian variation in human milk composition, a systematic review. *Nutrients*. 12:2328. doi: [10.3390/nu12082328](https://doi.org/10.3390/nu12082328).
- Jackson DA, Imong SM, Silprasert A, Ruckphaopunt S, Woolridge M, Baum J, Amatayakul K. 1988. Circadian variation in fat concentration of breast-milk in a rural northern Thai population. *Br J Nutr*. 59:349–363. doi: [10.1079/BJN19880044](https://doi.org/10.1079/BJN19880044).
- Jafar NKA, Tham EK, Pang WW, Fok D, Chua MC, Teoh O-H, Goh DY, Shek LP, Yap F, Tan KH. 2021. Association between breastfeeding and sleep patterns in infants and preschool children. *The Am J Clin Nutr*. 114:1986–1996. doi: [10.1093/ajcn/nqab297](https://doi.org/10.1093/ajcn/nqab297).
- Katzer D, Pauli L, Mueller A, Reutter H, Reinsberg J, Fimmers R, Bartmann P, Bagci S. 2016. Melatonin concentrations and antioxidative capacity of human breast milk according to gestational age and the time of day. *J Hum Lact*. 32:[NP105–NP110 p.]. doi: [10.1177/0890334415625217](https://doi.org/10.1177/0890334415625217).
- Khan S, Hepworth AR, Prime DK, Lai CT, Trengove NJ, Hartmann PE. 2013. Variation in fat, lactose, and protein composition in breast milk over 24 hours: associations with infant feeding patterns. *J Hum Lact*. 29:81–89. doi: [10.1177/0890334412448841](https://doi.org/10.1177/0890334412448841).
- Kikuchi S, Nishihara K, Horiuchi S, Eto H. 2020. The influence of feeding method on a mother's circadian rhythm and on the development of her infant's circadian rest-activity rhythm. *Early Hum Dev*. 145:105046. doi: [10.1016/j.earlhumdev.2020.105046](https://doi.org/10.1016/j.earlhumdev.2020.105046).
- Korf HW, von Gall C. 2022. Circadian Physiology. In: Pfaff D, Volkow N, Rubenstein J, editors. *Neuroscience in the 21st century: From basic to clinical*. Switzerland: Springer. p. 2541–2576.
- Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr*. 11:83–88. doi: [10.1002/j.1536-4801.1990.tb10064.x](https://doi.org/10.1002/j.1536-4801.1990.tb10064.x).
- Lavine ME, Clark RM, Hundrieser KE, Ferris AM. 1986. Within-day variation of lipolytic activity in human milk. *J Dairy Sci*. 69:1784–1786. doi: [10.3168/jds.S0022-0302\(86\)80601-4](https://doi.org/10.3168/jds.S0022-0302(86)80601-4).
- Lodemore MR, Petersen SA, Wailoo MP. 1992. Factors affecting the development of night time temperature rhythms. *Archiv Disease in Child*. 67:1259–1261. doi: [10.1136/ad.67.10.1259](https://doi.org/10.1136/ad.67.10.1259).
- Logan RW, McClung CA. 2019. Rhythms of life: circadian disruption and brain disorders across the lifespan. *Nat Rev Neurosci*. 20:49–65. doi: [10.1038/s41583-018-0088-y](https://doi.org/10.1038/s41583-018-0088-y).
- Lubetzky R, Littner Y, Mimouni FB, Dollberg S, Mandel D. 2006. Circadian variations in fat content of expressed breast milk from mothers of preterm infants. *J Am Coll Of Nutr*. 25:151–154. doi: [10.1080/07315724.2006.10719526](https://doi.org/10.1080/07315724.2006.10719526).
- Lucas A, St James–Roberts I. 1998. Crying, fussing and colic behaviour in breast-and bottle-fed infants. *Early Hum Devel*. 53:9–18. doi: [10.1016/S0378-3782\(98\)00032-2](https://doi.org/10.1016/S0378-3782(98)00032-2).
- Mazri FH, Manaf ZA, Shahar S, Mat Ludin AF. 2020. The association between chronotype and dietary pattern among adults: a scoping review. *Int J Environ Res Public Health*. 17:68. doi: [10.3390/ijerph17010068](https://doi.org/10.3390/ijerph17010068).
- Mendez N, Halabi D, Spichiger C, Salazar ER, Vergara K, Alonso-Vasquez P, Carmona P, Sarmiento JM, Richter HG, Seron-Ferre M. 2016. Gestational chronodisruption impairs circadian physiology in rat male offspring, increasing the risk of chronic disease. *Endocrinology*. 157:4654–4668. doi: [10.1210/en.2016-1282](https://doi.org/10.1210/en.2016-1282).
- Mohawk JA, Green CB, Takahashi JS. 2012. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci*. 35:445–462. doi: [10.1146/annurev-neuro-060909-153128](https://doi.org/10.1146/annurev-neuro-060909-153128).
- Moran-Lev H, Mimouni FB, Ovental A, Mangel L, Mandel D, Lubetzky R. 2015. Circadian macronutrients variations over the first 7 weeks of human milk feeding of preterm infants. *Breastfeed Med*. 10:366–370. doi: [10.1089/bfm.2015.0053](https://doi.org/10.1089/bfm.2015.0053).
- Nozhenko Y, Asnani-Kishnani M, Rodriguez AM, Palou A. 2015. Milk leptin surge and biological rhythms of leptin and other regulatory proteins in breastmilk. *PLOS ONE*. 10:e0145376. doi: [10.1371/journal.pone.0145376](https://doi.org/10.1371/journal.pone.0145376).
- Oda GA, Torres F, Bueno C, Wey D, Duarte L, Menna-Barreto LS. 2008. Breastfeeding, sleep and wake circadian rhythms show distinct temporal emerging patterns. *Biol Rhythm Res*. 39:379–387. doi: [10.1080/09291010701425397](https://doi.org/10.1080/09291010701425397).
- Olejniczak I, Pilorz V, Oster H. 2023. Circle (s) of life: the circadian clock from birth to death. *Biology*. 12:383. doi: [10.3390/biology12030383](https://doi.org/10.3390/biology12030383).
- Palou A, Picó C. 2009. Leptin intake during lactation prevents obesity and affects food intake and food preferences in later life. *Appetite*. 52:249–252. doi: [10.1016/j.appet.2008.09.013](https://doi.org/10.1016/j.appet.2008.09.013).
- Paulaviciene IJ, Liubsys A, Molyte A, Eidukaite A, Usonis V. 2020. Circadian changes in the composition of human milk macronutrients depending on pregnancy duration: a cross-sectional study. *Int Breastfeed J*. 15:1–9. doi: [10.1186/s13006-020-00291-y](https://doi.org/10.1186/s13006-020-00291-y).
- Perez-Catalan NA, Doe CQ, Ackerman SD. 2021. The role of astrocyte-mediated plasticity in neural circuit development and function. *Neural Devel*. 16:1–14. doi: [10.1186/s13064-020-00151-9](https://doi.org/10.1186/s13064-020-00151-9).
- Pham Q, Patel P, Baban B, Yu J, Bhatia J. 2020. Factors affecting the composition of expressed fresh human milk. *Breastfeed Med*. 15:551–558. doi: [10.1089/bfm.2020.0195](https://doi.org/10.1089/bfm.2020.0195).
- Prentice A, Prentice AM, Whitehead RG. 1981. Breast-milk fat concentrations of rural African women. 1. Short-term variations within individuals. *Br J Nutr*. 45:483–494. doi: [10.1079/bjn19810127](https://doi.org/10.1079/bjn19810127).

- Pundir S, Wall CR, Mitchell CJ, Thorstensen EB, Lai CT, Geddes DT, Cameron-Smith D. 2017. Variation of human milk glucocorticoids over 24 hour period. *J Mammary Gland Biol Neoplasia*. 22:85–92. doi: [10.1007/s10911-017-9375-x](https://doi.org/10.1007/s10911-017-9375-x).
- Qin Y, Shi W, Zhuang J, Liu Y, Tang L, Bu J, Sun J, Bei F. 2019a. Variations in melatonin levels in preterm and term human breast milk during the first month after delivery. *Sci Rep*. 9:17984. doi: [10.1038/s41598-019-54530-2](https://doi.org/10.1038/s41598-019-54530-2).
- Qin Y, Shi W, Zhuang J, Liu Y, Tang L, Bu J, Sun J, Bei F. 2019b. Variations in melatonin levels in preterm and term human breast milk during the first month after delivery. *Sci Rep*. 9:1–5. doi: [10.1038/s41598-019-54530-2](https://doi.org/10.1038/s41598-019-54530-2).
- Reppert SM, Weaver DR, Rivkees SA, Stopa EG. 1988. Putative melatonin receptors in a human biological clock. *Science*. 242:78–81. doi: [10.1126/science.2845576](https://doi.org/10.1126/science.2845576).
- Saad MF, Riad-Gabriel MG, Khan A, Sharma A, Michael R, Jinagouda SD, Boyadjian R, Steil GM. 1998. Diurnal and ultradian rhythmicity of plasma leptin: effects of gender and adiposity. *J Clin Endocrinol Metab*. 83:453–459. doi: [10.1210/jc.83.2.453](https://doi.org/10.1210/jc.83.2.453).
- Sánchez CL, Cubero J, Sánchez J, Franco L, Rodríguez AB, Rivero M, Barriga C. 2013. Evolution of the circadian profile of human milk amino acids during breastfeeding. *J Appl Biomed*. 11:59–70. doi: [10.2478/v10136-012-0020-0](https://doi.org/10.2478/v10136-012-0020-0).
- Selvalatchmanan J, Rukmini AV, Ji S, Triebel A, Gao L, Bendt AK, Wenk MR, Gooley JJ, Torta F. 2021. Variability of lipids in human milk. *Metabolites*. 11:104. doi: [10.3390/metabo11020104](https://doi.org/10.3390/metabo11020104).
- Serón-Ferré M, Mendez N, Abarzua-Catalan L, Vilches N, Valenzuela FJ, Reynolds HE, Llanos AJ, Rojas A, Valenzuela GJ, Torres-Farfan C. 2012. Circadian rhythms in the fetus. *Mol Cellular Endocrinol*. 349:68–75. doi: [10.1016/j.mce.2011.07.039](https://doi.org/10.1016/j.mce.2011.07.039).
- Singhal A, Lucas A. 2004. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet*. 363:1642–1645. doi: [10.1016/S0140-6736\(04\)16210](https://doi.org/10.1016/S0140-6736(04)16210).
- Sinkiewicz-Darol E, Adamczyk I, Łubiech K, Pilarska G, Twaruzek M. 2022. Leptin in human milk—one of the key regulators of nutritional programming. *Molecules*. 27:3581. doi: [10.3390/molecules27113581](https://doi.org/10.3390/molecules27113581).
- Sorensen NL, Maloney SK, Pillow JJ, Mark PJ. 2020. Endocrine consequences of circadian rhythm disruption in early life. *Curr Opin Endocr Metabolic Res*. 11:65–71. doi: [10.1016/j.coemr.2020.02.001](https://doi.org/10.1016/j.coemr.2020.02.001).
- Stenvers DJ, Scheer F, Schrauwen P, la Fleur SE, Kalsbeek A. 2019. Circadian clocks and insulin resistance. *Nat Rev Endocrinol*. 15:75–89. doi: [10.1038/s41574-018-0122-1](https://doi.org/10.1038/s41574-018-0122-1).
- Suwaydi MA, Lai CT, Rea A, Gridneva Z, Perrella SL, Wlodek ME, Geddes DT. 2023b. Circadian variation in human milk hormones and macronutrients. *Nutrients*. 15:3729. doi: [10.3390/nu15173729](https://doi.org/10.3390/nu15173729).
- Suwaydi MA, Lai CT, Rea A, Wlodek ME, Geddes DT. 2023a. Circadian variation of human milk hormones and macronutrients: implications for sampling and analysis strategies. *Proceedings*. 84:15. doi: [10.3390/proceedings2023084015](https://doi.org/10.3390/proceedings2023084015).
- Temizsoy E. 2022. Preterm Bebeklerin Beslenmesinde Kronobiyolojik Yaklaşım Modeli: Sirkadiyen Beslenme. *Yoğun Bakım Hemşireliği Dergisi*. 26:27–34.
- Thomas KA, Burr RL, Spieker S, Lee J, Chen J. 2014. Mother-infant circadian rhythm: development of individual patterns and dyadic synchrony. *Early Hum Dev*. 90:885–890. doi: [10.1016/j.earlhumdev.2014.09.005](https://doi.org/10.1016/j.earlhumdev.2014.09.005).
- van der Voorn B, de Waard M, van Goudoever JB, Rotteveel J, Heijboer AC, Finken MJ. 2016. Breast-milk cortisol and cortisone concentrations follow the diurnal rhythm of maternal hypothalamus-pituitary-adrenal axis activity. *The J Nutr*. 146:2174–2179. doi: [10.3945/jn.116.236349](https://doi.org/10.3945/jn.116.236349).
- Victoria CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. 2016. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 387:475–490. doi: [10.1016/s0140-6736\(15\)01024-7](https://doi.org/10.1016/s0140-6736(15)01024-7).
- Vilches N, Spichiger C, Mendez N, Abarzua-Catalan L, Galdames HA, Hazlerigg DG, Richter HG, Torres-Farfan C. 2014. Gestational chronodisruption impairs hippocampal expression of NMDA receptor subunits Grin1b/Grin3a and spatial memory in the adult offspring. *PLOS ONE*. 9:e91313. doi: [10.1371/journal.pone.0091313](https://doi.org/10.1371/journal.pone.0091313).
- Voiculescu SE, Le DD, Roşca AE, Zeca V, Chiţimuş DM, Arsene AL, Drăgoi CM, Nicolae AC, Zăgrean L, Schöneberg T. 2016. Behavioral and molecular effects of prenatal continuous light exposure in the adult rat. *Brain Res*. 1650:51–59. doi: [10.1016/j.brainres.2016.08.031](https://doi.org/10.1016/j.brainres.2016.08.031).
- Wharfe MD, Mark PJ, Waddell BJ. 2011. Circadian variation in placental and hepatic clock genes in rat pregnancy. *Endocrinology*. 152:3552–3560. doi: [10.1210/en.2011-0081](https://doi.org/10.1210/en.2011-0081).
- White RD. 2017. Circadian variation of breast milk components and implications for care. *Breastfeed Med*. 12:398–400. doi: [10.1089/bfm.2017.0070](https://doi.org/10.1089/bfm.2017.0070).
- Wong SD, Wright KP Jr, Spencer RL, Vetter C, Hicks LM, Jenni OG, LeBourgeois MK. 2022. Development of the circadian system in early life: maternal and environmental factors. *J Physiol Anthropol*. 41:22. doi: [10.1186/s40101-022-00294-0](https://doi.org/10.1186/s40101-022-00294-0).