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Review Article

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The Impact of Maternal Age on Human Milk Composition

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ABSTRACT

Human milk provides both nutritional and non-nutritional benefits to infants and can meet an infant's nutritional needs for the first six months of life. Human milk composition varies during lactation and is affected by maternal factors. Most investigations have reported on associations between maternal factors such as maternal diet, nutrition, and body mass index and the composition of human milk. There is, however, little information on the association between maternal age and the composition of human milk. In this review, we provide an overview of the nutrients in human milk based on maternal age relationship between nutrients in human milk and maternal age and we highlight and identify the effect of maternal age on macronutrients and micronutrients.

KEYWORDS maternal age, adolescent, advanced maternal age, human milk, nutrient

INTRODUCTION

Human milk (HM) is considered the best source of nutrition for infants. Research in recent decades has found that breastfeeding has many short- and long-term health benefits for both infants and mothers. Breastfeeding can decrease the incidence of infections and other diseases in infants. There is strong evidence that breastfeeding can reduce the incidence of infant. There is strong evidence that breastfeeding can reduce the incidence of infant hospital admissions by 72% for diarrhea and by 57% for respiratory infections (1) as well as 58% for necrotizing enterocolitis (2). Breastfeeding is also associated with a reduction in infant mortality. A meta-analysis suggested that breastfeeding reduces the incidence of sudden infant deaths in high-income countries by 36% (2). Additionally, breastfeeding is associated with lower malocclusion and higher cognitive ability in children (1). There is increasing evidence that breastfeeding may help prevent children from becoming overweight and from developing diabetes later in life (1). For mothers, short-term effects of breastfeeding include reducing postpartum bleeding, reducing the risk of postpartum depression, being conducive to postpartum weight loss, and delaying ovulation (1). Long-term benefits include reducing the risk of breast cancer, ovarian cancer, and type 2 diabetes (1).

International authorities and organizations have adopted promotion of breastfeeding as an important public health strategy. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend that infants should be exclusively breastfed for the first six months of life. After that, infants should be breastfed while receiving complementary feeding until the age of two or older (3).

The 56^{th} World Health Assembly set a goal of increasing exclusive breastfeeding during the first six months to at least 50 percent by 2025 (4).

HM is not a static biological fluid; rather, its composition is constantly changing. The composition of HM is affected by numerous factors including environmental, genetic, and maternal characteristics. Maternal age may affect HM composition, especially extreme maternal age (adolescent mothers and advanced-aged mothers). We propose the hypothesis that metabolic and physiological functions of the mother change with age, leading to changes in lactation function of the mammary gland that may affect the composition of HM. Adolescence is defined by the WHO as spanning the age of 10-19 years. The adolescent fertility rate (AFR) is the number of births per 1,000 women aged 15-19 (5). In recent years, the fertility rate of adolescents worldwide has declined. However, a large number of women still give birth at a young age. In 2018, the global AFR was 42 (6). In Thailand, there were 44.7 births per 1,000 women in this age group (6), or approximately 130,000 adolescents giving birth each year (7). Advanced maternal age (AMA) is usually defined as pregnancy in women 35 years and older (8). Worldwide, AMA accounts for a large proportion of pregnant women and is increasing each year. A cohort study in Taiwan showed that the proportion of AMA births increased from 11.4% to 19.1% between 1990 and 2003 (9). A recent cross-sectional study of 29 countries in Africa, Asia, Latin America, and the Middle East showed that the overall prevalence of AMA was 12.3%; in Thailand the prevalence of AMA pregnant women was 15% (8).

In recent years, several studies have investigated the influence of maternal age on milk production. A study on the milk production of adolescent mothers showed that at 6 and 24 weeks after delivery, adolescent mothers produced 37% and 54% less milk, respectively, compared with adult mothers. After adjusting for variables such as the frequency and duration of breastfeeding and the timing of introduction of complementary food, differences in milk production were significant between the two groups of mothers. The study's authors speculated that the differences may be due to the immature physical development of adolescents, and that the mother's metabolic needs for growth and maintenance of body reserves may be met at the expense of her metabolic needs for milk production (10). Another study of Peruvian mothers found that for each increase of five years in maternal age, daily infant milk intake decreased by 25 grams (11). Variation in the amount of milk produced may also change the concentration of HM components. Several studies have reported associations between maternal age and the presence of certain ingredients in HM (10). However, the age groups and milk component analyses in these studies varied and information on the difference in milk composition between adolescent and advanced-age mothers remains limited. The present review provides current knowledge on the relationship between maternal age and changes in the concentration of major components in HM (such as lipid, protein, lactose, minerals, vitamins, and trace elements, etc.), as well as how maternal age affects the nutritional concentration of HM.

HUMAN MILK COMPOSITION

HM contains both nutritional components and non-nutritive biologically active factors. The nutritional components include macronutrients, namely lipids, proteins, and carbohydrates, which are the main energy-producing components in HM. Vitamins and minerals in HM are collectively referred to as micronutrients. The present study focused only on the nutritional components of HM.

MACRONUTRIENTS

Lipids and fatty acids

Lipids in HM are the main source of energy and essential nutrients such as polyunsaturated fatty acids (PUFAs), accounting for about 50% of the total energy in HM. The main component is triglyceride (TG), which accounts for 98% of the lipid fraction (12).

Fatty acids (FAs) are the main component of TG, accounting for about 95% of total fatty acid composition of total fatty acid composition (12). FAs can be classified as saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and PUFAs (13). The long-chain polyunsaturated fatty acids (LC-PUFAs) in milk, omega-3 FAs, refer to PUFA whose first double bond is located at the third carbon atom of the methyl end of the FA chain. The three main omega-3 FAs are α-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), and docosahexaenoic acid (DHA, 22:n-3). Omega-6 FAs are PUFA with the first double bond located at the sixth carbon atom of the methyl end of the FA chain which includes mainly linoleic acid (LA,18:2n-6) and arachidonic acid (AA, 20:4n-6) (13). AA in omega-6 FAs and DHA in omega-3 FAs have attracted considerable attention because many biological effects in early life seem to be mediated by LC-PUFAs which are involved in the inflammatory and immune processes (14).

Table 1 displays the relationship between maternal age and milk fat concentration. A study of lactating women in Israel compared the fat content of colostrum, transitional milk, and mature milk in AMA women (≥ 35 years, n = 48) with that of younger women (< 35 years, n = 42). The authors found that colostrum creamatocrit (CMT) was positively correlated with maternal age ($R2 = 0.11$, $p = 0.006$), while CMT in transitional milk and mature milk was not affected by maternal age (15). These findings are consistent with the results of two other studies (10,16). However, a study in Israel found higher milk fat concentration in the transitional milk of AMA mothers (≥ 37 years, n = 15) than in younger mothers (< 37 years, n = 27) (17). In mature milk, Denić et al. (18) compared the milk fat content of AMA (≥ 35 years) and adult women (< 35 years) and reported that maternal age was positively correlated with milk fat ($r = 0.821$, $p < 0.0001$). Kim et al. (19) measured the mature milk of Korean mothers (21-45 years old, n = 238) and suggested that maternal age was negatively correlated with milk fat concentration ($r = -0.14$, $p < 0.05$). A study by Motil et al. (10) did not find a significant difference in mature milk fat concentration between adolescent (16.5 ± 0.6 years) mothers and adult women (31.1 ± 3.8 years) add the age range of each of the two groups in that study. Similarly, Hascoët et al. (20) analyzed the micronutrients in the milk of 81 French mothers (aged 19-42 years) of premature infants and concluded that the milk composition had no relationship with the mother's age.

Results of studies of The effect of maternal age on FA levels have also been contradictory. Sinanoglou et al. (21) recruited 97 lactating women and collected milk samples for the first three days postpartum to investigate the demographic factors affecting the FA profile of colostrum. They found that in colostrum, MUFA and the ratio of omega-6 to omega-3 were positively correlated with maternal age, while SFA was negatively correlated with maternal age. In a large French mother-child cohort study, FAs in 934 colostrum samples were analyzed. In that study, the contents of AA and DHA in HM were reported to be positively correlated with maternal age (22). Argov et al. (17) reported that docosadienoic acid, eico-

Table 1. Milk fat concentration in different age groups

References	Site	Maternal age	N	Colostrum	Transitional milk	Mature milk	Laboratory methods	
Hausman et al. 2013	Israel	Adult (ages 19 to under 35y)	42	4.67±2.89	9.20±3.53	8.33±2.89	The creamatocrit (CMT) method	CMT (%)
Lubetzky et al. 2015	Israel	Adult (ages 19 to under 35y)	34	1.8±1.1	3.5±1.3	4.6±1.1	Infrared transmission spectroscopy	g/100 mL
		AMA (> 35y)	38	2.7±1.9*	3.9±1.4	4.1±1.1		
Denić et al. 2019	Serbia	Adult (ages 19 to under 35y)	21	2.42±0.31	NA	3.50±0.31	The modified gravimetric method	g/100 mL
		AMA (> 35y)	22	3.38±0.31*	NA	4.51±0.30*		
Motil et al. 1997	USA	Adolescents (< 19y)	11	NA	NA	3.61±0.79	The modified Jeejeebhoy method	g/100 mL
		Adult (ages 19 to under 35y)	11	NA	NA	3.48±0.86		

Data are mean ± standard deviation values. *Statistically significant ($p < 0.05$). NA, not applicable sadienoic acid, and AA in transitional milk were negatively correlated with maternal age. In mature milk, Grote et al. (23) reported that PUFAs, linoleic acid (LA), and total omega-6 FAs in HM were negatively correlated with the age of mothers. However, Mangel et al. (24) found that the FAs composition of HM in Brazilian lactating adolescents did not differ from that observed in mature milk of Brazilian adults.

The variability in the correlation between maternal age and milk fat content found in previous studies can be attributed to the influence of milk fat concentration on other factors such as lactation stage, diurnal variation, collection method, storage time, maternal dietary intake, and maternal nutrition. The fat content of HM is known to be quite variable, as it can be affected by lactation, the degree of breast emptying during feeding, diurnal variation, as well as the effect of maternal plasma circulation on fatty acids (20,25). Studies have reported that higher fat and/or protein intake in the maternal diet is associated with increased fat concentration in HM (26,27). How HM samples are stored is also reported to affect milk fat concentration due to lipolysis (25). Furthermore, the regulation of milk fat is not an isolated effect, but is rather the result of a combination of internal and external maternal factors. One study showed that maternal age and body mass index (BMI) interaction were positively correlated with milk fat content (28). Bachour et al. (29) found that lactation stage, maternal age, BMI, smoking, parity, and residential area interactions had statistically significant effects on milk fat. Another possibility is that these studies vary in their ability to control potential confounding variables, such as maternal weight and maternal dietary intake. For example, A previous study observed a positive relationship between weight gain during pregnancy and lipid content in HM (19).

Maternal dietary and supplement intake is an important factor to control for when assessing FA content. There are three sources of FAs: 1) FA up to C14:0 derived from the de novo synthesis by the mammary gland, 2) FA with a chain length greater than C14:0 comes from the maternal diet or body reserves, while 3) LA and α-linolenic acid (ALA) are essential FAs that cannot be synthesized in the human body and adequate levels depend entirely on dietary intake and body storage. As is a lack of Δ12 and Δ15 desaturases required to synthesize omega -6 and omega -3 FAs in mammalian cells (30). Several observational and intervention studies have shown that maternal intake of MUFAs, PUFAs, and LC-PUFAs is important in secreting corresponding FAs in HM (12,20,22).

Proteins

Protein is the third most abundant macronutrient in HM and is a polymer chain of amino acids connected by peptide bonds. The proteins present in HM can be roughly divided into three categories: whey, casein, and mucin (31).

Milk proteins not only provide essential amino acids for infant growth, but also provide numerous bioactive proteins and peptides. The functions of these proteins and peptides include enhancing the bioavailability of micronutrients (31), improving cognitive development (32), regulating innate and adaptive immune responses (32), and promoting intestinal growth and maturation (31).

Numerous studies have found that the concentration of milk protein at all stages of lactation is not affected by the age of the mother (16,19,20,23,29,33,34). Dritsakou et al. (33) collected 630 milk samples from 210 Greek mothers on the 3rd, 7th, and 30th days of lactation and analyzed the macronutrient content. They found that there was no correlation between the age of the mother and the protein content in colostrum, transitional milk, or mature milk. These findings are consistent with the results of Hascoët et al. (19).

Most milk proteins are synthesized in the mammary glands by free amino acids or short peptides provided by blood circulation (35). Therefore, it is speculated that the age factor may have little effect on the ability of mammary glands to synthesize proteins. However, milk protein content may be affected by lactation period (28,29), gestational age (19), smoking, maternal weight (29), and diseases such as anemia (36). A previous study reported that milk protein is negatively correlated with infant postnatal age, positively correlated with carbohydrate intake, and negatively correlated with preterm birth (19).

Lactose

Lactose is a disaccharide composed of glucose and galactose and is the principal carbohydrate in HM. Lactose is also the main component of oligosaccharides, which play a variety of roles in early human development, e.g., One study found a correlation between brain development and lactose content in milk in different types of mammals (37).

Mangel et al. (34) collected colostrum from 109 healthy mothers who gave birth to healthy full-term infants and measured the macronutrient content. It was found that the carbohydrate content of colostrum was not related to maternal age. This is consistent with the research of Lubetzky et al. (16) and Dritsakou et al. (33) Most studies failed to find a correlation between lactose content and maternal age in transitional milk and mature milk (19, 23,33). Nevertheless, a Korean cross-sectional study by Kim et al. (20) collected mature milk from 238 healthy lactating women and measured the macronutrient content and FA profile. They found that the lactose content in HM was weakly positively correlated with maternal age ($r = 0.199$, $p < 0.01$). Lubetzky et al. (16) reported similar results.

Lactose changes little throughout the lactation period .In colostrum, the lactose concentration is relatively low and then increases rapidly (33). Studies have consistently shown that lactose concentration after the first few weeks of life does not change with the lactation stage (19,23). Lactose concentration is not affected by maternal BMI (38) although it may be affected by parity (39). Other studies have found that lactose has no relationship with maternal diet and nutritional status (40). Overall, the macronutrient content of lactose is relatively stable.

MICRONUTRIENTS

Vitamins

Vitamins are a group of relatively small but essential dietary compounds needed for healthy growth, development, and maintenance of life. Their functions range from being essential cofactors of various enzymes to acting as key regulators of gene expression and antioxidant functions. They are essential for metabolism, neurodevelopment, vision, mineral homeostasis, cardiovascular health, and immunity (41). Vitamin deficiency can cause noticeable symptoms related to these processes. Vitamins can be subdivided into water-soluble and fat-soluble according to their polarity.

Limited evidence shows that the concentration of retinol and tocopherol in mature milk of lactating adolescents is lower than that of adult lactating women (42). A cross-sectional study in Serbia found that the levels of retinol and β-carotene in the colostrum of the AMA group (≥ 35 years) were significantly higher than those of the younger group (< 35 years), while there was no difference in the levels of retinol in mature milk between the two groups (18). Other influencing factors, e.g., gestational age (43) and parity (44), are positively correlated with HM retinol concentration. Additionally, vitamin A in HM is easily degraded by light. It has been reported that when HM is exposed to light, vitamin A concentrations can decrease by up to 70% (45). Research on the mechanism of tocopherol absorption and transport in the mammary gland is limited. It has been reported that the level of vitamin E concentration in preterm milk is lower than in full-term milk (46) and that the concentration of vitamin E in foremilk is lower than in hindmilk (47).

Minerals

The minerals in HM are divided into two main categories: 1) the macrominerals, such as calcium, magnesium, phosphorus, potassium, sodium, and chlorine; and 2) the trace minerals, such as copper, iron, zinc, selenium, and iodine. The mammary gland has a remarkable ability to strictly regulate the concentration of specific minerals in HM. The concentration of calcium, magnesium, phosphorus, zinc, iron, and copper in HM is strictly regulated and maintained by breast epithelial cells during breastfeeding. The levels of these minerals in HM are independent of the maternal mineral status and have no significant correlation with maternal dietary mineral intake (48).

Few maternal factors affect the concentration of calcium, magnesium, phosphorus, iron, or copper in HM. In the studies evaluated in this review, maternal age did not affect the concentrations of calcium, magnesium, iron, copper, potassium, or phosphorus in HM at any stage of lactation (49,50). However, this is not true for zinc. Lin et al. found that older mothers (> 30 years) had higher levels of zinc in their colostrum compared to young mothers (20-30 years) (49). Another study demonstrated that in women under 30 years old (n = 25) had higher levels of zinc in their colostrum and transitional milk than older women (> 30 years, n=14), an average value of 6.19 µg/mL and 4.69 µg/ml, respectively ($p < 0.05$) (50). Severi et al. (51) reported that there was no difference in zinc content in mature milk of adolescents and adult women. Rodríguez et al. (52) reported a negative correlation between maternal age and zinc content in HM which may be related to the effect of gene mutation on the function of zinc transporter 2 (ZnT2), which imports zinc into secretory vesicles in mammary epithelial cells (MECs) and regulates the transfer of zinc into milk during lactation (53).

A Hypothesis Regarding the Effects of Maternal Aging Pathophysiology on HM Composition

The formation of the HM components is very complex. They are secreted and synthesized by the lactocytes in the alveoli of mammary glands by multiple highly coordinated systems. The components of HM originate from three sources: maternal storage, synthesis of lactocytes, and maternal diet (54). The physiological and metabolic functions of maternal storage change with increasing age, which may affect maternal nutrient reserves and mammary gland synthesis, although the precise mechanism is still unclear. In addition, maternal age is also related to changes in maternal diet habits and eating behavior. All of these can lead to changes in lactation performance and HM content.

Dietary intake

Although diet has a negligible effect on the total fat concentration in HM, numerous studies have demonstrated that diet is one of the most important factors affecting FAs in milk. Diets rich in LC-PUFA fats will greatly increase the concentration of linoleic acid in HM (22). In addition, compared with a high-fat diet, a high-carbohydrate diet results in a higher content of medium-chain FAs (C6-C14) in HM, confirming that the carbon of FAs synthesized de novo in the mammary glands mainly comes from dietary carbohydrates (55). Moreover, the breast cannot synthesize vitamins (including both water-soluble vitamins and fat-soluble vitamins), thus these nutrients must come from food. The vitamin content of HM is directly related to the mother's vitamin status (48). Adolescents (age 10 to 19) generally have less healthy dietary habits compared to adult women, consuming more sugar-sweetened beverages resulting in fewer key vitamins and minerals (such as vitamin A, riboflavin, vitamin B12, folate, iron, calcium, magnesium, potassium, zinc, and iodine.) than recommended by nutritional guidelines (56).

Nutritional status

There is potential competition for nutritional needs in adolescent mothers due to the dual nature of adolescent physiological development and lactation. This poses a double metabolic challenge for adolescent mothers (24). Many girls are undernourished or nutritionally marginalized during pregnancy (57). A systematic review of the nutritional intake of adolescent mothers indicated that adolescent mothers may not be able to meet all their nutritional needs (55). A study by Lunn et al. (58) showed that the serum levels of prolactin in malnourished mothers are higher. This may be because children of malnourished mothers may need to feed more frequently, for longer periods of time, and possibly exert more effort to meet the demand for HM. The most important control of plasma prolactin during lactation is through the lactation reflex arc (59). A recent study found that maternal anemia was associated with a significant decrease in milk fat ($p = 0.025$) and a significant increase in milk protein ($p = 0.001$) (36).

Mammary gland secretion and synthesis

Previous studies of well-nourished adolescent mothers found that the concentrations of retinol and tocopherol in milk were independent of the concentrations in serum, but the concentrations of retinol and tocopherol in milk of adolescent mothers were lower than in adult mothers (18,42). This may be related to

Table 2. Association between maternal age on macronutrients, fatty acids, and micronutrients in HM

No.	References	Population	Gestational age	Method of HM collection	Collection time	Measurement			Main result
						Macronutrients	Fatty acids	Micronutrients	
1	Meneses et al., 2008	Adolescents : age 14-19y	Full-term,	Full expression	8:00-10:00		EFA, LC-PUFA		No difference in DHA levels in milk between Brazilian adolescents and adults.
2	Azeredo et al., 2008	Adolescents : age 14-19y	Full-term,	Full expression	8:00-10:00			Retinol, tocopherol carotenoid,	The content of retinol, carotene, and tocopherol in mature milk of adolescents is lower than the reported value in HM of the adult mother in western developed countries.
3	Argov et al., 2017	Younger mother: age < 37y; Older mother: age≥ 37y	Preterm and term	NA	NA	Fat	Fatty acids		Docosadienoic acid, eicosadienoic acid, and AA in transitional milk were higher in younger women. HM fat was lower in younger women.
4	Lubetzky et al., 2015	AMA: age 35-43y; Adults: age 27-34y	Full-term,	NA	Morning 21:00-24:00	Fat, protein, lactose, and energy			HM fat in colostrum and lactose in mature milk was higher in AMA. No difference in HM fat at 7 days and 2 weeks postpartum between groups.
5	Sinanoglou et al., 2017	Mother age 24-42y	Preterm and term	Post-feed	12:00-13:00		Fatty acids		Older mothers had lower SFA, higher MUFA and ω-6/ω-3 ratio in colostrum
6	Lin et al., 1998	Younger: age 20-30y Older: age >30 y	Full-term,	Full expression	9:00-11:00			Calcium, Magnesi-um, Iron, Copper, Zinc	Zinc in colostrum was higher in older mothers (>30 y). No difference levels of calcium, magnesium, iron, copper in milk between groups
7	Dritsakou et al., 2017	Mother age: 31.9 ± 6.8 y	Preterm and term	Full expression	24 h	Fat, protein, carbohydrates, energy			HM fat content positively correlated with maternal age
8	Armand et al., 2018	Mother: age 29.6±4.7y	Full-term,	Mid-feed	NA		LA, ALA, AA, DHA		AA and DHA levels in colostrum positively correlated with maternal age
9	Kim et al., 2017	Mother: age 31.6±3.2 (21-45) y	Full-term,	Full expression	NA	Fat, protein, lactose, energy	Fatty acids		Maternal age negatively correlated with milk fat; positively correlated with milk lactose, and not correlated with fatty acids.

Table 2. Association between maternal age on macronutrients, fatty acids, and micronutrients in HM (continue)

No.	References	Population	Gestational age	Method of HM collection	Collection time	Measurement			Main result
						Macronutrients	Fatty acids	Micronutrients	
10	Grote et al., 2016	Mother: age 32.4±4.4y	Full-term	Pre-and post-feed	NA	Lipids, protein, carbohydrates	Fatty cids		Levels of PUFAs, LA, and total omega6 fatty acids were all lower in older mothers.
11	Mangel et al., 2017	Mother: age 20-42 y	Full-term	Pre-feed	8:00-13:00	Fat, carbohydrate, protein, energy			Maternal age was inversely correlated with fat; not related to the protein or carbohydrate content in colostrum.
12	Bachour et al., 2012	Mother: < 25y, 25 < age ≤ 30, 30 < age ≤ 35, >35y	NA	Pre-feed	Morning	Lipids, Protein, (SIgA)			HM proteins and SIgA were not affected by age. However, milk protein content was affected by the interaction of maternal age, BMI and smoking (p = 0.048) and the interaction between age and BMI (p = 0.015) - Lipid content was affected by the interaction of lactation stage, age, BMI, smoking, number of fetuses, and residential area (p = 0.028).
13	Hascoët et al., 2019	Mother: age 29 (19–42) y	Preterm	Full expression	24 h	Fat, protein carbohydrate,			No correlation between milk composition and maternal age.
14	Hausman et al., 2013	AMA: age ≥35 y Adults: age <35 y	Preterm and term	NA	Morning 21:00-24:00	Fat			-HM fat in colostrum positively correlated with maternal age. -HM fat at 7 days and 2 weeks were not affected by maternal age.
15	Severi et al., 2013	Adolescents: age 13-19 y Adults: age 24-35y	NA	Pre-feed	NA			Zinc	No difference zinc content in milk for both groups
16	Motil et al., 1997	Adolescents: age <19y Adults: age 31.1±3.8y	Full-term	Full expression	24 h	Fat, protein, lactose,		Calcium, Sodium, Potassium, Phosphorous, and Volume	Adolescents produced less milk than adults (P <0.05), while the sodium concentration in milk was significantly higher. There was no significant difference in the concentration of milk nutrients between the two groups.

Table 2. Association between maternal age on macronutrients, fatty acids, and micronutrients in HM (continue)

No.	References	Population	Gestational age	Method of HM collection	Collection time	Measurement			Main result
						Macronutrients	Fatty acids	Micronutrients	
17	Baldeón et al., 2014	Mother: age 14–27y	Full-term	NA	6:00–8:00		FAAs		Maternal age did not have a significant linear relationship with any of the FAAs
18	Silvestre et al. 2000	Older: age > 30 y Younger: age ≤ 30y	Full-term	Pre-feed	11:00–16:00			Iron, Copper, Zinc	The zinc content in milk of younger women was higher than in elderly women.
19	Rodríguez et al., 2000	Adults: age 21–35y	NA	Pre- and post-feed	NA			Iron, Copper, Zinc	Maternal age was inversely correlated with zinc concentration in human milk
20	Orun et al., 2012	NA	NA	Full expression	NA			Copper, Zinc	Maternal age was not related to the concentra-tion of zinc and copper in HM
21	Denić et al., 2019	AMA: age ≥35 y Adults: age <35 y	Full-term	Full expression	7:00–10:00			Retinol, β-carotene	The content of total fat, retinol and β-carotene in the AMA mothers were significantly higher.

AA, arachidonic acid (C20:4n6); AMA, advanced maternal age; ALA, α-linolenic; BMI, body mass index; DHA, docosahexaenoic acid; EFA, essential fatty acid; FAAs, free (protein-unbound) amino acids; FFQ, food frequency questionnaire; HM, human milk; LA, linoleic acid; LC-PUFA, long-chain polyunsaturated fatty acid; MUFA, Monounsaturated fatty acid; NA, not available; SFA, saturated fatty acid; SIgA, Secretory Immunoglobulin A; y, year;
Pre-feed refers to the beginning of the nursing episode; post-feed refers to the end of the nursing episode.

the decreased ability of adolescent mammary glands to regulate these nutrients. The relatively immature reproductive development of an adolescent mother has a significant impact on her ability to lactate. There is evidence that adolescent mothers are not as capable as adult women in producing enough milk to meet the needs of their infants (10).

In advanced-age mothers (over the age of 35), involution occurs in which breast epithelial tissue is gradually replaced by fat (60), which leads to a decrease in the ability of the mammary glands to synthesize and secrete milk. Another possibility is that insulin sensitivity decreases with age as insulin is a hormone that promotes uptake of glucose by mammary epithelial cells. Glucose is one of the major precursors of milk synthesis and is closely related to milk production and milk composition (61). It has been reported that the milk fat concentration of AMA mothers is higher than that of other adult women (18). This may be related to changes in fat metabolism with age. Briefly, changes in the breast microenvironment at an advanced age may result in secretory failure or insufficient lactation, leading to changes in milk composition.

CONCLUSIONS

The key findings of this study are that maternal age does not affect the concentration of HM protein or lactose at different stages of HM and does not seem to be related to the concentration of calcium, magnesium, copper, phosphorus, or potassium in HM. There is no conclusive evidence of a relationship between maternal age and changes in fat and fatty acid concentration in HM. Additionally, vitamins in HM are mainly affected by the mother's dietary intake rather than the maternal age.

To date, most studies of the relationship between maternal age and HM composition have evaluated macronutrients, while there have been few studies on micronutrients. It is also important to note the variability in research design among papers included in this study. The age groupings were not uniform and there was obvious heterogeneity, so it was difficult to conduct a quantitative analysis. Moreover, most studies lacked control of confounding factors, leading to inconsistent observations (Table 2). There are still many unanswered questions about the effect of maternal age on the composition of HM, such as the influence of age-related metabolic changes on the variability of milk fat, fatty acids, and fat-soluble vitamins. More rigorous research is needed to clarify these relationships, information which is essential for the provision of optimal nutritional interventions for mothers particularly those in these two age groups.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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