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Do maternal morbidities change the nutritional composition of human milk? A systematic review

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Abstract *This paper aims to identify the effects of maternal morbidities on the nutritional composition of human milk. This systematic review of the literature employed a PRISMA's protocol for searching, selecting, and extracting data. The flowchart proposed for bibliographic search resulted in 1,582 papers, of which 14 were selected for this work. The papers selected for this review were published between 1987 and 2016. Nine studies found significant differences in the nutritional composition of the milk of mothers with diabetes mellitus, arterial hypertension, or overweight compared to the control group. Most studies have shown that the presence of chronic diseases leads to changes in the nutritional composition of human milk. The main results showed a lower concentration of lactose and fat in the milk of women with diabetes mellitus. Concerning hypertension, higher levels of total protein were found in colostrum and mature milk. A higher fat and energy content was observed in overweight mothers. It is imperative that these women have continuous nutritional monitoring to minimize the impact of these morbidities on the nutritional composition of breast milk.*

Key words *Chronic disease, Human milk, Macronutrients*

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Introduction

Studies have shown an increased prevalence of diabetes mellitus, hypertension and overweight among women[1-3] over the years.

Concerning diabetes mellitus, a multicenter study conducted between 1999 and 2005 found that 21% of pregnancies were complicated by this disease[2]. In Brazil, about 7% of pregnant women have increased gestational glycemia[3]. On the other hand, systemic arterial hypertension affects 5% to 10% of pregnancies[4]. Regarding overweight, a study carried out in six Brazilian capitals revealed that 28% of women started pregnancy with a weight above the recommended level[1].

Diabetes mellitus and hypertension during pregnancy can cause severe maternal and fetal complications, including deteriorated hypertension, preeclampsia, eclampsia, HELLP syndrome, restricted intrauterine growth, preterm delivery, premature placental abruption, and fetal death, and is one of the primary causes of maternal and perinatal morbimortality[4].

Not unlike this scenario, overweight in pregnancy can also lead to many negative consequences for fetuses (hemorrhages, macrosomia, asphyxia) and women (gestational diabetes mellitus, arterial hypertension, pre-eclampsia, eclampsia and higher weight retention postpartum)[5].

Besides the adverse effects cited, some studies have shown that these chronic diseases may also lead to changes in the nutritional and immunological composition of human milk[6].

Although human milk has been the subject of several studies, the influence of chronic diseases on its nutritional composition has not yet been well elucidated, and results are different, which is why it is still the target of several studies.

As a result, this study aims to identify the effects of the morbidities in question (diabetes mellitus, hypertension, overweight) on the nutritional composition of human milk.

Methods

A systematic review of the literature was performed using a pre-established protocol for searching, selecting and extracting data. The papers were identified by bibliographic search in databases Medline (through PubMed), Lilacs and SciELO (through the Virtual Health Library – BVS Brazil), Scopus and Embase. The description of this systematic review was based on the Preferred Reporting Items for Systematic Reviews (Prisma)[7] guideline (Figure 1).

The association of diabetes mellitus, arterial hypertension and overweight with the nutritional composition of human milk was evaluated through the following descriptors: ("Human Milk") AND ("Diabetes Mellitus" OR "Diabetes Gestational"), ("Human Milk") AND ("Hypertension" OR "Hypertension, Pregnancy-Induced"), ("Human Milk") AND ("Overweight" OR "Obesity").

A search was conducted by two independent researchers and finalized in September 2016. There was no delimitation of publication period or language restriction.

The bibliographic search returned 1,582 papers. Of these, 56 were selected for full-text reading. After extensive selection, only 14 manuscripts were chosen for this work. The others were excluded because they addressed themes that were not of interest to this study. Also, we searched for other papers in the references of the selected papers for this study, but no new manuscripts were found.

The selected papers were compared against the following axes: sample size, mean age of the participants, type of design, maternal morbidity, milk evaluation period, human milk macronutrient analysis method, confounding factors controlled in the analysis and main results observed.

Results

The literature search resulted in 14 papers published between 1987 and 2016. Most studies (n = 5) were conducted in North America (United States), followed by South America (Brazil), Europe (Greece, Finland and the Netherlands), Asia (Lebanon) and Oceania (Australia). Regarding the studied population, age ranged from 17 to 43 years, and three papers did not inform the age group of the participants. The lowest sample consisted of 11 participants, and the most significant sample was 305. Regarding the language, one paper was written in Portuguese and the other in English (Table 1).

Concerning the morbidities, nine papers evaluated diabetes mellitus[8-17], one evaluated hypertension[18] and four overweight[17,19-21]. Only one paper evaluated both diabetes and overweight (Table 2).

The most commonly used technique for fat content analysis was gravimetry, followed by

Ciência & Saúde Coletiva, 24(7):2491-2498, 2019

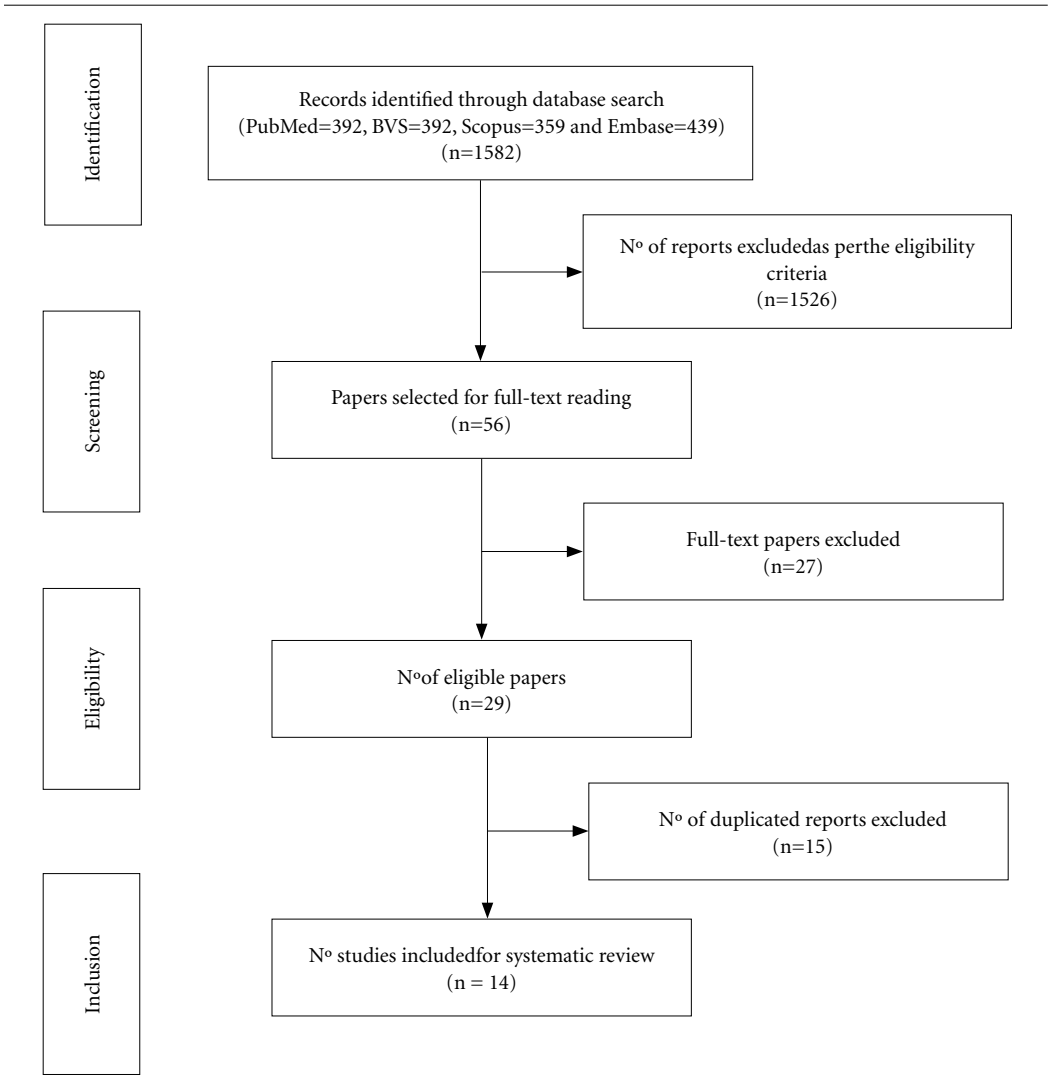

Figure 1. Flowchart of the paper selection process - PRISMA.

calorimetry. For the analysis of the total protein content, the most common procedure was the Kjeldahl method. Only one study analyzed all macronutrients (fat, protein and carbohydrate) and total energy in a single procedure, and for this analysis, the author used the spectrophotometric technique from the Human Milk Analyzer – Miris (Table 2).

Regarding the time of evaluation of human milk, most studies (n = 6) analyzed all phases of milk (colostrum, transitional milk and mature milk), five analyzed only colostrum, two only mature milk and one analyzed the transition and mature milk. The number of milk analyses ranged from 1 to 7 times (Table 2).

Regarding the design used, most (n = 11) used longitudinal observational studies. Information on confounding factors controlled in the analysis was obtained in 12 studies, and the most prevalent were maternal age, gestational age at delivery, type of delivery, tobacco use, parity, and newborn birth weight. Seven papers did not mention exclusion criteria in their methods (Table 3).

Regarding the results of the selected papers, it was observed that nine studies found significant

Table 1. Year of publication, origin, sample size and age of participants of selected studies, 1987-2016.

Authors	Year of publication	Country	Sample (n)	Age (years)
Butte et al.[8]	1987	USA	47	29[1]
Bitman et al.[9]	1989	USA	14	23-39[2]
Arthur et al.[10]	1989	Australia	44	24-40[2]
Neubauer et al.[11]	1993	USA	77	NA
Beusekom et al.[12]	1993	Netherlands	11	23-30[2]
Jackson et al.[13]	1994	USA	77	NA
Lammi-Keefe et al.[14]	1995	USA	43	NA
Oliveira et al.[15]	2008	Brazil	30	22[1]
Morceli et al.[16]	2010	Brazil	45	18-35[2]
Bachour et al.[17]	2012	Lebanon	66	29[1]
Massmann et al.[18]	2013	Brazil	23	18-35[2]
Makela et al.[19]	2013	Finland	100	17-43[2]
Fujimori et al.[20]	2015	Brazil	68	18-36[2]
Dritsakou et al.[21]	2016	Greece	305	32[1]

[1] Mean age. [2] Minimum and maximum age.

differences in the nutritional composition of the milk of mothers with diabetes mellitus, hypertension, or overweight. A lower concentration of lactose (n = 3) and fat (n = 4) was observed concerning diabetes mellitus and one paper found lower protein value and higher energy value. The other papers selected (n = 2) did not find statistical differences concerning macronutrients (fat, protein, carbohydrate) and total energy. The only study that evaluated the nutritional composition of milk of women with arterial hypertension found that colostrum and mature milk from hypertensive mothers had higher levels of total protein. Regarding overweight, two studies concluded that mothers with obesity had higher fat and energy content, and the other two studies did not find statistical differences (Table 3).

Discussion

In this section, we will discuss and emphasize the main results of the papers selected for this systematic review that have investigated the possible effect of chronic diseases (diabetes mellitus, arterial hypertension or overweight) on the nutritional composition of human milk.

Insulin inadequacy in diabetes mellitus can directly affect the quantity and quality of human milk[15,16]. The results of the studies that have investigated this issue are different.

Beusekom et al.[12] did not observe significant differences between glucose, lipid and sodium levels in mature milk of diabetic women. Similarly, Butte et al.[8] found no change in lactose and protein (colostrum, transition and mature milk) among people with diabetes. Authors believe this result may be partly explained because the selected diabetic women have controlled glycemia.

However, Neubauer et al.[11] found lower lactose and higher protein on the second and third day postpartum among people with diabetes. Oliveira et al.[15] also observed lower lactic concentration in the group of diabetic women during the first five days postpartum.

Dritsakou et al.[17] identified higher levels of fat in the milk of diabetic women. This may be partly explained by the abnormal lipid metabolism in diabetics, which is marked by an elevation of lipoprotein lipase and lipolysis. It is worth noting that 50% of diabetics were diagnosed with overweight. However, the authors did not control any possible confounding factors.

Contrary to the findings made explicit above, Jackson et al.[13] and Morceli et al.[16] observed that the amount of fat in the human milk of diabetic women was lower compared to the control group. Despite the results' unanimity, different methods were used to evaluate the nutritional composition of human milk.

Another point worth mentioning is the influence exerted by diabetes mellitus on milk volume. Lactation is marked by two phases – lactogenesis I and II. Phase I begins at the 20th gestation week and may be marked by increased lactose and alpha-lactalbumin. Phase II occurs between 24 and

Chart 1. Morbidity, method used to evaluate the composition of human milk and analyzed milk phase, 1987-2016.

Authors	Disease	Method used to evaluate human milk composition	Analyzed milk phase
Butte et al.[8]	Type 1 DM[1]	The total protein was determined by the Kjeldahl method, lactose by enzymatic hydrolysis and fat by gravimetry after extraction with methylene chloride by the modified Roese-Gottlieb method	Mature Milk
Bitman et al.[9]	Type 1 DM[1]	The total protein was determined by the bicinchoninic acid method and fat by chromatography	Colostrum
Arthur et al.[10]	Type 1 DM[1]	Lactose was determined by enzymatic hydrolysis	Colostrum
Neubauer et al.[11]	Type 1 DM[1]	Total protein was determined by the Kjeldahl method, lactose was determined using the industrial model analyzer 27	Colostrum, Transition Milk and Mature Milk
Beusekom et al.[12]	Type 1 DM[1]	Total protein was determined by the bicinchoninic acid method, fat and lactose by chromatography	Colostrum, Transition Milk and Mature Milk
Jackson et al.[13]	Type 1 DM[1]	Total fat was determined by gravimetry using the modified Folch method	Colostrum, Transition Milk and Mature Milk
Lammi-Keefe et al.[14]	Type 1 DM[1]	Total fat was determined by gravimetry using the modified Folch method	Colostrum, Transition Milk and Mature Milk
Oliveira et al.[15]	Type 1 DM[1]	Lactose was dosed according to the colorimetric method	Colostrum
Morceli et al.[16]	DM[1]	The total protein was determined by the colorimetric method, lipids and total calories were determined through the creamatocrit	Colostrum
Bachour et al.[21]	Overweight	Total protein was determined by the Bradford method and total fat by gravimetry using the modified Folch method	Transition Milk and Mature Milk
Massmann et al.[18]	SAH[2]	The total protein was determined by the Biuret colorimetric method	Colostrum, Transition Milk and Mature Milk
Makela et al.[19]	Overweight	Total fat was determined by chromatography	Mature Milk
Fujimori et al.[20]	Overweight	The fat and the total energetic value were determined by the creamatocrit and total protein by the Biuret colorimetric method	Colostrum
Dritsakou et al.[17]	Gestational DM[1] and Overweight	Miris® Human Milk Analyzer	Colostrum, Transition Milk and Mature Milk

[1] Diabetes Mellitus. [2] Arterial hypertension.

48 hours postpartum and is marked by increased lactose. Oliveira et al.[15] found an 18-hour delay in the diabetic group to complete the transition from phase I to phase II of lactogenesis, which hindered the establishment of breastfeeding. Similar to the specified, Bitman et al.[9], Arthur et al.[10] and Neubauer et al.[11] observed that the transition from phase I to II of lactogenesis was delayed among diabetic patients with inadequate glycemic control, which led to reduced milk volume from the third to the seventh day postpartum.

The delayed lactogenesis transition in diabetic patients can be partially explained by the action of insulin in the uptake of glucose by the mammary gland. Therefore, the control of glucose in diabetic women is of paramount importance for the achievement of an adequate nutritional composition of human milk as well as for the establishment of breastfeeding[16].

Chart 2. Type of study, controlled confounding factors and main results, 1987-2016.

Authors	Type of study	Confounding factors controlled in the analysis	Results
Butte et al.[8]	Case-control	Age, height, gestational weight gain, parity, newborn birth weight	The concentrations of total protein, lactose, fat and energy did not differ from the concentrations found in the milk of the reference population
Bitman et al.[9]	Case-control	Not informed	The fat content of the milk secreted by the diabetic woman tended to be lower compared to the control group; the values of protein and lactose did not differ
Arthur et al.[10]	Case-control	Maternal age and gestational age	The lactose content of the milk secreted by the diabetic woman was lower on the 1st and 2nd day postpartum
Neubauer et al.[11]	Cohort	Gestational age, delivery type, newborn gender and if already breastfed	The milk of women with diabetes had less lactose and a higher concentration of protein on the 2nd and 3rd day postpartum
Beusekom et al.[12]	Case-control	Gestational age, delivery type, newborn birth weight	Mean total fat was lower in the milk of women with diabetes, but there was no difference in lactose and total protein values
Jackson et al.[13]	Case-control	Maternal age, gestational weight gain, parity, schooling, gestational age, delivery type, newborn gender and time of previous breastfeeding	The mean total fat was lower in the milk of women with diabetes on the 2nd and 3rd day postpartum.
Lammi-Keefe et al.[14]	Case-control	Gestational age, delivery type, newborn gender and if already breastfed	There was no significant difference in lipid content between the three groups throughout the study
Oliveira et al.[15]	Cohort	Maternal age, pre-gestational body mass index, weight gain during gestation, type and number of deliveries and gestational age of newborn	Both groups showed increased concentration of lactose from 1 to 5 days postpartum. A lower concentration of lactose was observed in colostrum in the group of women with diabetes.
Morceli et al.[16]	Cross-sectional	Tobacco use, arterial hypertension and glycemia	Total protein concentration was similar between normoglycemic and diabetic mothers. Fat concentration was significantly lower in the colostrum of diabetic mothers, but the total energy value did not differ
Bachour et al.[21]	Cohort	Maternal age, tobacco use, parity, lactation stage, residential area and use of medicines	Protein concentration was lower and fat concentration was higher in mature milk of overweight mothers
Massmann et al.[18]	Cohort	Tobacco use, diabetes and mean pressure during gestation	Colostrum and mature milk from hypertensive mothers had higher levels of total protein
Makela et al.[19]	Cross-sectional	Maternal age, schooling, household income, gestational weight gain and maternal diet	The total fat content of the milk did not differ between overweight and normal weight women
Fujimori et al.[20]	Cross-sectional	Maternal age, gestational age, tobacco use, hypertension, pre-gestational body mass index, gestational or chronic diabetes	The fat and energy content was higher among obese women when compared to the eutrophic group, whereas the protein content did not show differences
Dritsakou et al.[17]	Cohort	Not informed	The fat and energy content of both colostrum and transition milk were higher in overweight women, whereas in mature milk only higher fat levels were estimated. Women with diabetes had higher energy values in colostrum, transition milk and mature milk, and lower values of protein in transition and mature milk

Ciência & Saúde Coletiva, 24(7):2491-2498, 2019

Hypertension is often associated with metabolic, functional, or structural changes in target organs. Also, it is considered one of the diseases that causes more harmful effects to the maternal, fetal and neonatal body[22,23].

When we observed the impact of hypertension on the nutritional composition of human milk, only the study conducted by Massmann et al.[18] was selected. In this study, the authors concluded that colostrum and mature milk from hypertensive mothers had higher levels of total protein. However, the effects of changes in blood pressure on the nutritional composition of human milk are still not fully understood, especially for mothers who have had hypertension-aggravated pregnancies[24].

Regarding the influence of overweight on the nutritional composition of human milk, Bachour et al.[21] found that the nutritional composition of the milk of overweight women had a lower amount of protein. According to the authors, this change may be partially explained by a higher level of oxidative stress among overweight patients.

Fujimori et al.[20] and Dritsakou et al.[17] found higher levels of fat and energy in the milk of overweight women. However, Makela et al.[19] concluded that the milk fat content did not change. It is noteworthy that the milk of these overweight women had a higher amount of saturated fatty acids, reduced amount of omega 3 and a high proportion of omega 6 compared to omega 3.

In short, most studies have shown that the presence of chronic diseases leads to changes in the nutritional composition of human milk. The main results were: 1) three papers that evaluated the nutritional composition of human milk of women with diabetes mellitus found a lower concentration of lactose[10,11,15], and four of fat[9,12,13,16]. Concerning hypertension, a higher total protein concentration was found in both colostrum and mature milk[18]. In the case of overweight, half of the studies observed a higher fat and energy content in the milk of these mothers[17,20].

The different results among the selected studies can be partly explained by the numerous methodological differences, such as sample size, the method used in the evaluation of human milk, control of confounding factors, nutritional components evaluated, lactation stage (colostrum, and transition and mature milk).

It is noteworthy that while chronic diseases cause nutritional changes in human milk, it is universally agreed that breastfeeding should be strongly encouraged exclusively until the 6th month of life of the newborn and that, from then on, breastfeeding is maintained for two years or more, together with appropriate complementary foods.

It is of the utmost importance that women have continuous nutritional monitoring in prenatal and postpartum care to have effective control of blood glucose, blood pressure and gestational weight gain in order to minimize the impact of diabetes mellitus, arterial hypertension and overweight on the nutritional composition of milk, as well as on the early establishment of breastfeeding.

Collaborations

YNV Amaral participated in the design, methods, analysis, data interpretation and paper drafting. D Marano participated in the design, methods, analysis, data interpretation and final drafting of the paper. LML Silva participated in data analysis and paper drafting. FVM Soares participated in the analysis, data interpretation and final drafting of the paper. MEL Moreira participated in data interpretation and the approval of the version to be published.

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