I.A. Belyaeva, L.S. Namazova-Baranova, T.V. Turti, E.P. Bombardirova, M.D. Mitish, T.V. Potekhina
Scientific Center of Children's Health, Moscow, Russian Federation

Role of Breastfeeding in Preventing Long-Term Metabolic Disorders: Review

Author affiliation:
Belyaeva Irina Anatol'evna, PhD, Head of the premature infant unit at the Scientific Center of Children's Health (Federal State Budgetary Research Institution)
Address: 2/1 Lomonosovskiy Av., Moscow, 119991; **tel.:** +7 (499) 134-15-19; **e-mail:** belyaeva@nczd.ru

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The literature review is dedicated to the preventive role of breastfeeding in preserving long-term health of individuals and the population in whole. The issue is urgent due to high prevalence of multifactor metabolic diseases (obesity, pancreatic diabetes, hypertonic disease etc.) in adolescents and adults; these socially significant have started to set on in younger persons in the recent years. The article presents results of the studies dedicated to the association between the nature of the infant's feeding and risk of metabolic pathology conducted in the recent decades in various countries. Most works put premature infants in the high risk group, as the diets involving special formulas contributing to "catching-up" growth of neonates with low birth weight are statistically significantly associated with high risk of long-term cardiovascular diseases. According to numerous studies, artificial feeding significantly increases the risk of excess weight and obesity, hypertonic disease and atherogenic dyslipidemia. Possible mechanisms of realization of hereditary susceptibility to metabolic disorders in the setting of artificial feeding are enhanced insulin burst paired with further development of insulin resistance; preventive role of breast milk is associated with the hormones therein, which program the individual's metabolism. Along with that, breastfeeding provides metabolic and immunological programming by means of forming optimal intestinal microbiota in a child. All the studies indicate importance of prolonged breastfeeding during infancy, which is why medical administrative support provided by medical personnel of medical and preventive facilities is important for preventing hypolactasia. District pediatricians and nurses not only control, but also organize the process of breastfeeding; when necessary, they recommend special devices intended to optimize lactation (breast pumps, nipple shields); if breast latching is not feasible – feeding with extracted breast milk using bottles and pacifiers reproducing natural breast sucking mechanism.
Keywords: *breastfeeding, premature infants, infants, breast milk, metabolic programming, metabolic syndrome, obesity.*

RELEVANCE

It is known that in Russia, cardiovascular pathology and the metabolic disorders closely related thereto (since recently known as the "metabolic syndrome") are a leading cause of morbidity, disability and mortality among the working-age population. The studies carried out in different countries determined that pre-clinical manifestations of the metabolic syndrome are formed during a person's adolescence or even childhood immediately from neonatality [1-3], which is why pediatricians are tasked to prevent and diagnose such manifestations as early as possible.
The primary components of the metabolic syndrome are abdominal obesity, glucose tolerance disorder with type 2 diabetes, arterial hypertension, and atherogenic dyslipidemia. The common pathogenetic mechanism of metabolic syndrome formation is insulin resistance, i.e. reduced sensitivity of target cells to insulin, which, in its turn, reduces glucose transport to cells and facilitates development of compensatory hyperinsulinemia [4]. Recently, hyperuricemia, fibrinolysis dysfunction, hyperandrogenia, microalbuminemia, and fatty liver have become

considered components of the metabolic syndrome [5]. Two or three components of the metabolic syndrome may be identified in a single patient: for instance, every third obese teenager has arterial hypertension or initial signs of type 2 diabetes [6].

Given multifactorial etiology of metabolic disorders, they are classified as socially significant multifactorial diseases. The role of hereditary aptitude in the formation of such disorders has been identified. The state-of-the-art clinical genetics is capable of predicting possible ways to diagnose such aptitude as early as possible and to correct metabolic disorders in advance [7]. However, both clinicians and geneticists do admit that most multifactorial diseases with hereditary aptitude only occur in the postnatal ontogenesis in the presence of facilitating environmental factors which impact formation of the phenotype via the epigenetic control over gene expression as well as via environmental (family-based and population-related) and stochastic influence [8]. The most significant of those is the nutrition factor. Although the mechanisms of gene-environmental impact within this area of focus have not yet been studied sufficiently, most researches mention insufficient adaptivity of the human genome, which is why many multifactorial diseases occur in increasingly younger patients living in a globally changing environment [8-11].

One of the most prevalent multifactorial metabolic disorders is obesity, the new epidemic of the XXI century. In the industrially developed countries, the percentage of excessively fat children doubles each 30 years. 25-30% of all 7-17-year-old children and teenagers have excessive weight, and a half of these children (almost 15% of the pediatric population) suffer obesity [12, 13]. What gives rise to anxiety is the increasing frequency of excessive weight in under-2 children. Throughout the last 30 years, the percentage of such children doubled from 6% to 11% [14]. In Russia, excessive weight (11.8%) and obesity (2.3%) in children are observed less often, yet in some cities the prevalence of obesity may amount up to 8.8% [15].

When it comes to obesity as the most frequent type of metabolic pathology, the main external factor that facilitates the occurrence of burdened genome is the nutrition factor. This factor is crucial during the so-called critical phases of a person's development. These "ontogenetic windows" are periods when metabolic processes are most flexible and the direction of metabolic shifts can be "imprinted". This has given rise to the term "metabolic programming" in recent years as applied to embryos and neonates [16]. During such periods, children are affected by every external impact. Both heavy neonates and underweight infants (especially premature infants) form a specific risk group in terms of delayed metabolic disorders [17-20].

BREASTFEEDING – PREVENTION OF DELAYED METABOLIC DISORDERS

The peculiarities of how initial breastfeeding of infants may prevent delayed lipid metabolic disorders became a subject of research as soon as industrial production of breastmilk surrogates began. The first articles on excessive weight gain and aptitude to excessive lipopexia in surrogate-fed infants were published almost one hundred years ago. In the recent decades there has appeared ample evidence that breastfeeding helps to prevent risks of delayed lipid metabolic disorders in children and teenagers [21].

A series of follow-up studies has shown that breastfeeding is accompanied by reduced risk of cardiovascular diseases, hypercholesterolemia, obesity, type 2 diabetes and arterial hypertension [22-24]. Such advantages may be degraded by social and biological discrepancies in differently-fed children. However, the cause and effect linkage has been confirmed, particularly for premature infants [25-28]. For instance, premature infants who were fed with the mother's or a donor's breastmilk, had a reduced arterial pressure, reduced serum cholesterol, reduced resistance to insulin and leptin (a hormone related to high obesity risks in the following years) by the age of 13-16 years [25-28]. Significance of the breastfeeding preventive effect is comparable to or even outperforms other non-pharmacological interventions affecting obesity risk factors in maturity [29]. Another evidence of the cause-and-effect linkage between breastfeeding and lower risks of metabolic disorders has been found in the framework of an analysis that identified the dose-dependent effect of the obtained results: the more breastmilk a neonate consumes, the lower

is the risk they will have the metabolic syndrome as a teenager. Similar conclusions have been made by other researchers [30], who proved that the duration of breastfeeding is reverse-proportional to the risk of excessive body weight. It is pointed out that each month of breastfeeding during the first year of life reduces the risk of delayed obesity or excessive weight by 4%. N.I. Parikh et al. [31] have noted the correlation between breastfeeding, reduced body mass index (BMI), and increased concentration of high-density lipoproteins in adults.

Therefore, although the results of follow-up studies may still be considered implausible, the combination of such evidence and the results of randomized studies involving premature infants does represent relevant evidence that breastfeeding reduces risks of metabolic syndrome development.

Premature infants have been studied [25-28] to compare the results of feeding patients with non-enriched breastmilk and specialized milk formula for premature infants. Meanwhile, the standard formula was compared with a specialized milk formula for premature infants. The studies have shown that diets that facilitate hastened weight gain in neonates are further accompanied by high risks of cardiovascular diseases. The infants who received growth-stimulating nutrition had higher risks of development of the primary metabolic syndrome components in the following age periods.

This conclusion has been made not exclusively for premature infants, but also for underweight term infants who were also randomly distributed into groups (fed either with specialized protein-enriched formulae or with the standard formula). The follow-up has shown that the patients of the first group had a higher diastolic pressure at the age of 6-8 years [29]. Further analysis of these studies has resulted in a suggestion that nutritional formulae used to induce growth do result in delayed insulin resistance and arterial hypertension both in premature infants and term infants [26, 28].

Lipid metabolism

The biological mechanisms, by means whereof breastfeeding features a preventive effect and reduces the risk of future obesity, are being widely discussed. Many researchers believe that a breastfed child receives a balanced combination of the primary nutrients (proteins and calories first), which facilitates harmonic physical development and helps to reduce the body fat percentage [14, 21, 32-34]. They also mention the role of balanced hormonal responses in breast-fed children contrary to formula feeding that induces insulin emission [21, 35, 36]. Finally, there are data proving that breast-fed children adapt to vegetarian complementary feeding faster; this reduces the further caloric load [14].

Results of a full-scale meta-analysis prove significance of this linkage between the type of feeding and the frequency of further lipid metabolic disorders. It is thereby mentioned that the prophylactic component of breastfeeding depends neither on obesity diagnostic criteria (the body mass index exceeding the 90-95th or 97th percentile) nor on the age at which lipid metabolic disorders are identified, as the scope of the meta-analysis included 5-66 year-old patients [14, 30].

Especially interesting are the studies that relate obesity development risks not only to the nature of the initial feeding, but also to excessive food consumption by pregnant women, as well as the presence of prenatal risk factors such as vegetovascular dystonia, especially when complicated by preeclampsia combined with premature birth [37].

It is mentioned that timely correction of a pregnant or nursing woman's diet helps to prevent obesity in her children [33, 38].

It has been recently found out that breastmilk contains a range of hormones (leptin, adiponectin, insulin, ghrelin, resistin, obestatin, peptide YY and glucagon-like peptide-1) that may impact metabolism in breast-fed infants as well as the regulation of appetite in the post-neonatal periods, thus defining the further aptitude to obesity. It is suggested that the concentration of such hormones in breastmilk correlates to the mother's BMI. For example, the systematic review by N.J. Andreas et al. [39] is dedicated to the analysis of studies, the subject whereof was the

correlation between mothers' BMI and the concentration of appetite-regulating hormones in their milk. The positive correlation of mothers' BMI and breastmilk leptin concentration is mentioned as it has been identified by most studies under analysis.

It is known that leptin is secreted mostly by adipocytes proportionally to the total amount of body fat tissue and, therefore, it correlates positively with the BMI [40]. The concentration of leptin in the infant's blood serum also correlates to the mother's BMI [41]. Therefore, it has been shown that the infants born by excessively weighing mothers are very likely to become obese as well.

The data presented in this review in relation to other hormones were either contradictory or implausible; the authors believe such a situation is caused by faulty design and insufficient sample amount in some of these studies. Another limitation is the non-standardized sampling of breastmilk probes: some researchers only analyzed foremilk or hindmilk, whilst other researchers analyzed fully expressed breast milk. It is crucial, as the concentration of hormones in breastmilk may change during a single feeding as well as throughout a single lactation period [42].

However, certain studies have identified that similarly to leptin, the concentration of adiponectin in the mother's blood serum correlates to her BMI [43], and the concentration of hormones in breastmilk positively correlates to both mother's and child's serum concentration [42, 43].

The amount of adiponectin in breastmilk may be biologically significant for the child: it has been found out that its concentration in breastmilk correlates negatively to children's obesity. The data show that high concentrations of this hormone in breastmilk are related to decreased body weight during the child's first six postnatal months [44]. Besides, Luoto et al. have stated that the concentrations of adiponectin in the colostrum were significantly higher in mothers whose children weighed normally at the age of 10 years, as compared to mothers whose children weighed excessively at the same age [45]. Another evidence therefor is the recent discovery of adiponectin receptors in the human intestines [46]. It proves that the hormone of the breastmilk fat tissue is absorbed systematically in neonates, is biologically active and capable of programming a child's metabolism. Adiponectin correlates negatively to prolactin [47], and the secretion of prolactin is reduced in obese patients; this may increase the concentration of adiponectin and result in its being secreted into breastmilk.

The data on the correlation between the mother's BMI and the concentration of insulin in breastmilk have been obtained when studying breastmilk of diabetes-affected mothers. There has been identified a positive correlation between blood serum insulin levels and breastmilk insulin levels [48]; it has been proved that the concentration of insulin in blood serum is increased if the mother's BMI is increased (due to insulin resistance) [49].

It has been suggested that there is a positive correlation between obesity and ghrelin concentrations in serum. Correlations between mother's ghrelin concentrations in blood serum and breastmilk, as well as in the child's blood serum, have been discovered. It is suggested that breastmilk is the source of ghrelin for the child [50].

Obese patients have an increased blood serum concentration of resistin, which is why it is reasonable to suggest that breastmilk resistin concentration correlates positively to the mother's BMI. This suggestion was not proved by the study carried out by F. Savino et al., who did not discover any correlation between the mother's BMI and breastmilk resistin concentration [51]. However, these conclusions cannot be considered final, as the number of women under research was insufficient.

The concentration of peptide YY and glucagon-like-peptide-1 (GLP-1) as well as their correlation to the mother's BMI were analyzed only in one study. No correlation between the concentration of these hormones in breastmilk and the mother's BMI has been identified. However, the researchers note that when it comes to GLP-1, the correlation between the BMI and blood serum GLP-1 concentration has not yet been identified, which is why it is not surprising that the concentration thereof has not been identified in breastmilk, where it will most likely be less expressed. The concentration of peptide YY in breastmilk may correlate negatively

to the mother's BMI, if no other factor with a stronger impact on the concentration of this hormone in breastmilk is present.
Thus, recent studies prove that enteral intake of hormones with breastmilk may correlate to systemic effects on the body, which confirms the hypothesis that breastmilk programs the infant's metabolism during the postnatal period [52].

Microflora status

The data on how the nature of the neonate's microflora defined primarily by the maternal factors is related to the risk of the development of lipid metabolic disorders in children are of interest. For instance, it is mentioned that neonates with high level of clostridia and Staphylococcus aureus and reduced bifidum flora titers comprise the risk group in terms of excessive weight formation [53].
Breastfeeding is known to have an impact on the formation and development of intestinal microflora in infants [54], and breastmilk is recognized as one of the most important postnatal factors, which modulates the metabolic and immunological programming having a long-term effect on the child's health [55]. Recent studies have discovered new data on the formation of microbiota in breastmilk [56], which prove that the factors of maternal health may have an impact on the composition and activity of microflora.
Excessively weighing and obese pregnant women may have a formed vicious circle of unfavorable metabolic development, if such intestinal microflora responsible for excessive weight and obesity or excessive weight gain during pregnancy is transferred to the child [57, 58].
R. Cabrera-Rubio et al. have conducted a study [59] to research breastmilk microbiota at three time points of lactation in mothers with different BMI and different weight gain during pregnancy who delivered children in different ways.
The study has identified the correlation between the mother's BMI and the composition of her breastmilk microbiota. High BMI values are correlated to increased *Lactobacillus* concentration in the colostrum. Similarly, increased amount of *Staphylococcus* and decreased amount of *Bifidum bacteria* in breastmilk six months after the delivery are related to the mother's increased BMI.
Excessive weight gain during pregnancy was also related to increased amounts of Staphylococcus and Staphylococcus aureus in breastmilk during the first month of lactation as well as increased amount of *Lactobacillus* and decreased amount of *Bifidum bacteria* in breastmilk after six months of lactation.
Apparent discrepancies of taxonomic composition of breastmilk bacteria were identified in the mothers who had natural childbirth as compared to those who had caesarean section. The mothers who had experienced surgical delivery had a significantly altered breastmilk microflora, wherein *Leuconostocaceae* amount was decreased and *Carnobacteriaceae* amount was increased, as compared to the women who had had natural childbirth. This discrepancy is apparent even in the colostrum and persists in breastmilk in the 1st and the 6th month of lactation.
The amount of bacteria in the colostrum of the mothers who had planned or emergency surgical delivery did not differ. However, the transitional and ripe breastmilk of the mothers who had had an emergency caesarean section was compositionally similar to milk of those who had had a natural childbirth as compared to women who had undergone a planned caesarean section.
Thus, the results of the study by R. Cabrera-Rubio et al. show that the mother's anthropometric data (first and foremost, the BMI) prior to her pregnancy and excessive weight gain during the pregnancy correlate to the taxonomic composition and microbiota diversity of breastmilk. The colostrum and the first lactation month breastmilk of obese mothers had a decreased bacterial diversity as compared to normally weighing mothers, yet there was no discrepancy in the milk probes taken at the age of 6 months. The correlation between intestinal microflora and BMI has been identified in obese pregnant women who had excessive weight gain during pregnancy: the taxonomic composition of the mother's microbiota has, by means of breastfeeding, an impact on how intestinal microbiota is formed in children.

The studies have shown that there are significant discrepancies of breastmilk microflora bacterial composition dependent on the BMI and weight gain during pregnancy, which proves the idea that obesity has an impact on the breastmilk microbiota taxonomic composition. Taking into account that breastmilk bacteria are among the first bacterial cells to enter the infant's gastrointestinal tract, changes of the milk bacterial composition may be the factor capable of transferring peculiarities of the mother's bacterial composition to her children. The presented data may indicate an additional mechanism that clarifies the increased obesity risks in children born by obese or excessively-weighing mothers.

What is more, according to the research data of R. Cabrera-Rubio et al., it is evident that breastmilk of mothers who had a planned caesarean section is, in terms of composition, significantly discrepant from breastmilk of mothers who had an urgent surgical delivery or childbirth *per naturalis*. The discrepancies are identifiable already in the colostrum and persist in breastmilk in the 1st and the 6th lactation month, which indicates that shifts in bacterial composition have a long-term effect. It is suggested that physiological (e.g. hormonal) changes taking place in the mother's body during labor may have an impact on microbiota composition. Taking into account high risks of such diseases as allergic rhinitis, bronchial asthma, and coeliac disease in children delivered via caesarean section [60, 61], the potential impact on breastmilk bacterial composition should be further evaluated. Considering the fact that breastmilk microbiota composition may have crucial consequences for the infant's health, its potential changes should be studied to make recommendations on the optimization of children's nutrition.

Therefore, one can admit that breastfeeding has a protective effect in relation to the risk of further obesity, yet its impact on the development of excessive weight is not that apparent. However, the said protective effect can be nullified dependent on the genetic and social-economic factors [21]. For instance, studies carried out in Brazil involving students from both private and public schools have not confirmed any relevant prophylactic effect of breastfeeding in terms of obesity [62].

Insulin resistance and type 2 diabetes

As a rule, lipid metabolic disorders are closely related to the other components of metabolic syndrome, i.e. the lability of vascular tone and glucose tolerance disorder, i.e. insulin resistance. Type 2 diabetes is known to be one of the most prevalent diseases in adults. However, it has been noted in recent years that this pathology tends to have manifestations in younger people, sometimes even in adolescents. Scientists suggest that early formula feeding is crucial for such shifts, whilst breastfeeding has a protective effect on the immature endocrine function of the pancreas [21].

Subject to discussion are possible mechanisms of breastfeeding that reduce the risk of type 2 diabetes development:

1) polyunsaturated fatty acids of breastmilk facilitate the reduction of insulin resistance of cell membranes and prevent the following reaction chain: compensatory hyperinsulinism — age-dependent deterioration of β-cells [21, 63, 64];
2) formula-fed children have higher concentration of basal insulin and neurotensin as compared to modulated insulin and glucagon, which facilitates an early formation of insulin resistance [21, 65];
3) breast-fed children have an optimal non-fat-to-fat percentage ratio, which makes for an indirect prevention of insulin resistance formation [63, 66, 67].

However, some researches neglect that type 2 diabetes risks are related to early formula feeding [21].

Vascular status and arterial hypertension

There is plausible evidence that breastfeeding has a protective role in terms of vascular tone disorders, which is first and foremost related to delayed development of arterial hypertension [21] as well as atherogenic dyslipidemia. The World Health Organization expert panel mentions

the potential biological mechanisms that prevent the formation of hypertensive vascular responses. The mechanisms are as follows: reduced breastmilk sodium concentration as compared to formulae, better balanced fatty-acidic composition of natural breastmilk, and prevention of excessive weight that is indirectly related to the risk of increased arterial pressure [67, 68]. The World Health Organization has made a systematic review of meta-analyses [21], which provided plausible evidence that systolic pressure is reduced by 3.3-9.8 mm Hg in teenagers and adults who were breast-fed during the first year of life as compared to patients who were formula-fed during the same. They have also noted a relevant reduction of diastolic pressure in breast-fed children at risk, i.e. 5-11-year-old children with positive family history in terms of hypertonia. The reduction was 0.97-3.4 mm Hg as compared to formula-fed children.

The potential biological mechanisms, by means whereof breastfeeding impacts cholesterol levels and risks of atherosclerotic vascular changes, are believed to be related to the fact that breastmilk cholesterol programs the effect of lipid assimilation regulation via the coenzyme A system and provides for a ripe statin system, which slow down the accumulation of cholesterol [21, 68]. Basically, such situations also have to do with metabolic programming.

Analytical reviews show that although no relevant correlations have been identified between cholesterol levels in children and teenagers and the nature of initial feeding, the average cholesterol level of those 19-28-year-old adults who were breast-fed was 0.18 mmol/L (6.9 mg/dL) – lower than that of the formula-fed ones (3.2% reduction from the median level) [21].

CONCLUSION

Therefore, state-of-the-art studies show how important the preventative role of breastfeeding is for life quality and health of children, teenagers, and working age population, which opens up many possibilities for better health of the generation to come. This is exactly why it is the duty of pediatricians to facilitate proper and sufficiently long breastfeeding of each and every infant. Local pediatricians and nurses do not only control but also manage the breastfeeding process and, shall such need arise, advise to use special appliances for lactation optimization, i.e. breast pumps or nipple protectors. If a child cannot be breast-fed, they should help feed them with expressed breastmilk by means of Pigeon Peristaltic PLUS bottles and feeding nipples (Pigeon, Japan) that reproduce the natural mechanism of breast suction. Studies have been carried out at the Scientific Center for Children's Health that involved neonates and infants who were temporarily unable to suck their mothers' breasts. The studies have shown that use of Pigeon Peristaltic PLUS bottles with nipples provides for a significant reduction of aerophagia and colics, helps infants to learn or preserve the skills of physiological suction, and make a long and successful breastfeeding possible.

CONFLICT OF INTEREST

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