Can hormones contained in mothers’ milk account for the beneficial effect of breast-feeding on obesity in children?

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Summary
Nutrition and growth during infancy are an emerging issue because of their potential link to metabolic health disorders in later life. Moreover, prolonged breast-feeding appears to be associated with a lower risk of obesity than formula feeding. Human milk is a source of various hormones and growth factors, namely adipokines (leptin and adiponectin), ghrelin, resistin and obestatin, which are involved in food intake regulation and energy balance. These compounds are either not found in commercial milk formulas or their presence is still controversial. Diet-related differences during infancy in serum levels of factors involved in energy metabolism might explain anthropometric differences and also differences in dietary habits between breast-fed (BF) and formula-fed (FF) infants later in life, and may thus have long-term health consequences. In this context, the recent finding of higher leptin levels and lower ghrelin levels in BF than in FF infants suggests that differences in hormonal values together with different protein intake could account for the differences in growth between BF and FF infants both during infancy and later in life. In this review, we examine the data related to hormones contained in mothers’ milk and their potential protective effect on subsequent obesity and metabolic-related disorders.

Introduction
Nutrition and growth during infancy are now under close scrutiny because of their possible link to obesity and metabolic disorders in later life. However, the mechanisms that link early growth and nutrition with long-term obesity risk are not well defined. Obesity is a chronic condition, frequent in both developed and developing countries, that affects both adults and children. Overweight and obesity in childhood result primarily from an energy imbalance whereby dietary energy intake exceeds energy expenditure, but the dynamics of this imbalance are complex and not fully understood. One of the driving forces behind obesity is increased appetite, which is controlled in the arcuate nucleus of the hypothalamus via a complex process involving hormones, such as leptin and ghrelin that act as mediators between the adipose tissue, the gastrointestinal tract and the brain.

Interestingly, the pathways involved in appetite regulation mature early in postnatal life. Indeed, patterns of foetal and neonatal growth influence appetite regulation as shown by the finding that a low birth weight and rapid postnatal weight gain up-regulate appetite. While up-regulation of appetite may be advantageous in the short term, it could promote obesity in the long term. This could to a certain extent explain the link between early growth and the risk of metabolism-related diseases later in life.

It is well known that growth pattern and body composition in the first period of life differ between breast-fed (BF) and formula-fed (FF) infants. Formula feeding is associated with a greater weight and length gain after 3 months of age. Moreover, a dose–response relationship has been observed between formula intake and both length and weight gain with the greatest effects occurring between 3 and 6 months of age. Butte et al. reported that BF infants have a higher fat mass than FF babies in the first months of life. It has been suggested that differences in growth pattern and body composition between BF and FF infants might be because of a different endocrine response to feeding or to bioactive substances present in breast milk that could influence infants’ response to energy intake and metabolism.

Leptin, ghrelin, adiponectin, resistin, and obestatin have recently been identified in breast milk. These hormones, which are involved in energy balance regulation, may play a role in the regulation of growth and development in the neonatal period and infancy, and could influence the programming of energy balance regulation in childhood and adulthood.

In this review, we examine the data related to hormones contained in mothers’ milk and their potential protective effect on subsequent obesity and metabolic-related disorders.
Nutritional programming

The concept that nutrition in infancy could influence later health first emerged in the 1960s with the pioneering study of McCance, who observed that, in rats, nutrition acts during a critical, early postnatal window to program later body size. In 1974, Dörner proposed that hormones, metabolites and neurotransmitters during a critical window in early development may program brain development and body functions as well as risk for diseases in human adulthood. Forty years of animal experiments and epidemiological studies in humans have shown that early nutrition is a key factor for health later in life, thereby supporting the concept of ‘nutritional programming’.

Low birth weight and rapid catch-up growth during the early postnatal period have been associated with a subsequent higher ratio of fat mass to lean mass, a greater central fat deposition and insulin resistance and consequently an increased risk of adverse outcomes, namely obesity, cardiovascular diseases and type 2 diabetes. The link between growth acceleration and later obesity was confirmed by two systematic reviews: one of 15 studies that demonstrated an association between rapid growth during the first years of life and the prevalence of obesity in during life, and the other of 24 studies (22 cohort and two case–control studies) showing that infants at the highest end of the distribution for weight or body mass index (BMI) or who grow rapidly during infancy are at increased risk of subsequent obesity. In a cohort study, rapid weight gain during infancy and early childhood predicted larger BMIs and waist circumferences in young adulthood and taller adult height. Moreover, weight gain between 0 and 6 months was inversely related to rapid weight gain between 3 and 6 years, indicating that weight gain in early childhood tended to slow down in individuals who rapidly gained weight in infancy.

Considering that much of the evidence on nutritional programming in humans comes from animal models, there is a need for observational studies and clinical intervention trials to determine whether there is a causal association between early nutrition and later health.

Breast-feeding and childhood obesity

The view that early nutrition could affect long-term health, and the observation of different growth patterns and body composition between BF and FF infants prompted nutrition researchers to ask the question: does breast-feeding protect against the development of obesity? However, while breast milk is undoubtedly the best source of nutrients for the newborn and protects against infectious diseases during the breast-feeding period, whether it has long-term health benefits has not been unequivocally demonstrated. A case–control study by Kramer was one of the first studies to suggest that breast-feeding protected against later obesity. Armstrong et al., in a large cohort study of Scottish children suggested that breast-feeding was associated with a reduction in childhood obesity risk. Subsequently, epidemiological surveys showed a protective effect of breast-feeding, when compared with formula feeding, on the long-term overweight risk in children. Moreover, a meta-analysis of 17 studies (16 cohort studies and one case–control study) revealed that the longer the duration of breast-feeding, the lower the risk of overweight in later life.

Various hypotheses have been proposed to explain how breast-feeding protects against faster weight gain and consequently against later obesity. BF babies can self-control the amount of milk they consume, and so they may learn to self-regulate their energy intake better than FF infants. Furthermore, a higher protein intake in FF infants could determine a higher risk of later obesity by causing an earlier adiposity rebound. A higher protein intake from skimmed cow’s milk by stimulating serum insulin-like growth-factor I (IGF-I) levels in infancy could promote later obesity. Similarly, associations between an earlier age at weaning and a greater risk of later obesity may reflect the influence of a greater nutrient and particularly protein intake with weaning on growth rate in infancy. Another study showed that a mother’s prepregnant BMI, duration of breast-feeding and timing of complementary food introduction are associated with infant weight gain from birth to 1 year of age. Breast milk contains many bioactive factors (lactoferrin, oligosaccharides, long-chain polyunsaturated fatty acids, glycoproteins and secretory IgA antibodies) that do not function primarily as nutrients, but that may control nutrient use, protect infants from pathogens and play a role in regulating metabolic pathways. Moreover, breast milk contains other biologically active factors, namely hormones, growth factors and cytokines, which are involved in energy balance regulation and seem to play a role in infant nutrition and growth. Epidermal growth factor and IGF-I are two major milk-derived peptide growth factors, which are relatively resistant to proteolysis and stable in the gastrointestinal tract. Furthermore, specific receptors have been identified in gastrointestinal mucosa, suggesting a role of these hormones in stimulating growth and development of the gastrointestinal tract. It remains unclear whether hormones, more recently identified in breast milk and which we will deal with in the present review, are resistant to proteolysis in the gastrointestinal tract and absorbed across the intestinal mucosa.

Hormones in mother’s milk implicated in nutritional programming

The hormones identified thus far in breast milk are listed in Table 1.

Leptin

Structure. Leptin, the product of the obesity (ob) gene on chromosome 7q31.3, is a 167-amino acid peptide discovered in 1994 and mainly synthesized by the white adipose tissue proportionally to the amount of body fat mass. Leptin is also produced by mammary gland and is secreted by epithelial cells in milk fat globules.

Role in appetite, energy homeostasis and body composition. Leptin functions directly in the regulation of food energy intake and expenditure. At the level of the central nervous system, leptin exerts an anorexigenic effect by signalling satiety and decreasing the sensation of hunger. Leptin exerts an anorexigenic effect by activating anorexigenic pro-opiomelanocortin (POMC)/cocaine...
ampheta\-mine-regulated transcript neurons in the hypothalamic arcuate nucleus, and inhibiting orexigenic NPY/AgRP neurons.

The physiological role of leptin was first investigated in the ob/ob mouse model that has a single-base mutation leading to a nonfunc-\-tional leptin protein. ob/ob mice had low leptin concentrations and became obese when they ate ad \-libitum. Humans with leptin defi-\-ciency caused by genetic mutations are affected by congenital obesity and endocrine abnormalities, similar to the ob/ob mouse.3\-5 The administration of exogenous leptin to leptin-deficient children resulted in a decrease in their energy intake and a dramatic loss of fat mass, whereas lean body mass was unaffected.3\-6 However, administration of exogenous leptin failed to reduce adiposity signifi-\-cantly in most cases of human obesity characterized by increased adipocyte leptin content and high circulating leptin levels – a condition known as 'leptin resistance'.3\-7 The administration of exogenous leptin to leptin-deficient children resulted in a decrease in their energy intake and a dramatic loss of fat mass, whereas lean body mass was unaffected.3\-6 However, administration of exogenous leptin failed to reduce adiposity significantly in most cases of human obesity characterized by increased adipocyte leptin content and high circulating leptin levels – a condition known as 'leptin resistance'.3\-7

A large body of experimental data suggests that control of energy homeostasis, food intake and body composition by leptin begins in early life, when the hormone also controls foetal growth and develop-\-ment. Growth during foetal life is linked with specific changes in leptin levels: small-for-gestational age (SGA) neonates have lower leptin levels at birth than appropriate-for-gestational age (AGA) ones, and large-for-gestational age (LGA) neonates have higher leptin levels than the other infants.3\-8 The observation of a surge in leptin soon after birth in mice suggests that leptin is essential for the development of the hypothalamic pathways involved in the regu-\-lation of energy balance and appetite, and that this activity could be restricted to a critical neonatal window.3\-9

Interestingly, there is evidence that serum leptin concentration reflects body fat mass in adults, in children, during foetal life4\-0 and also in infants.4\-1

Leptin in breast milk. It is now well established that leptin is a component of mothers’ milk. Casabiell et al. identified leptin in human milk, and reported that, in nursing rats, leptin is trans-\-ferred via milk to the stomach and then to the infant rat circulation.4\-2 Smith-Kirwin et al. showed that the leptin gene is expressed in the mammary gland of lactating women and that leptin is produced by mammary epithelial cells.3\-5 Bonnet et al. showed through immunohistochemistry that the cellular location of the leptin protein differed between gestation and lactation stages: leptin protein was detected in mammary adipocytes during early stages of pregnancy, and in epithelial cells (mainly on their apical membrane) just before parturition, and in myoepi-\-thelial cells during lactation; moreover, secretory epithelial cells may transfer leptin from the blood to milk.3\-3 Thus, leptin can be secreted into milk by the mammary gland and it can be transferred from the blood. Leptin receptors have been identified in gastric epithelial cells and in the absorptive cells of mouse and human small intestine,4\-4 which suggests that leptin could pass from milk to infant blood.

Leptin concentration, assayed by radioimmunoassay, was found to be higher in whole than in skimmed samples of human milk,3\-5 probably because a portion of leptin could be associated with the milk fat droplet or fat-associated proteins. Milk leptin concentra-\-tion was shown to be higher in colostrum than in transitional milk (4–5 days postpartum milk).4\-6 Leptin is present also in preterm human breast milk at levels similar to those in term breast milk, although levels can be lower after preterm than after term delivery.4\-7

Houseknecht et al. were the first to report that leptin in breast milk correlated with maternal plasma leptin concentration, although breast milk leptin concentration was lower than maternal plasma leptin levels. They also observed a positive correlation between breast milk leptin concentration and maternal BMI, sug-\-gesting that BF infants nursed by overweight/obese mothers might be exposed to higher amounts of leptin than infants nursed by lean mothers.3\-5 More recently, leptin concentrations in breast milk were found to correlate positively with maternal circulating leptin levels, maternal BMI and the mothers’ adiposity.4\-8 A positive correlation has also been reported between breast milk leptin levels and infant plasma leptin.4\-9 We have observed higher serum leptin concentrations in BF infants than in FF babies in the first months of life and also a positive correlation between serum leptin concentration in BF infants and maternal BMI.4\-2

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Table 1. Breast milk hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Amino acids</th>
<th>Gene</th>
<th>Year of discovery</th>
<th>Sources</th>
<th>Receptor</th>
<th>Main functions</th>
<th>Year of discovery in breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>167</td>
<td>7q31.3 (gene Ob)</td>
<td>1994</td>
<td>White adipose tissue, placenta, mammary gland, other sites</td>
<td>Ob-receptor</td>
<td>Anorexigenic effect</td>
<td>1997</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>244</td>
<td>3q27 (gene apM1)</td>
<td>1995</td>
<td>Adipose tissue</td>
<td>Adipo-R1 Adipo-R2</td>
<td>Improvement of insulin sensitivity, increase in fatty acid metabolism, anti-inflammatory and anti-atherogenic properties</td>
<td>2006</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>28</td>
<td>3p25-26</td>
<td>1999</td>
<td>Stomach, intestine, pancreas, other sites</td>
<td>Growth hormone secretagogue-receptor-1a</td>
<td>Orexigenic action; stimulation of GH secretion; stimulation of acid gastric secretion and motility</td>
<td>2006</td>
</tr>
<tr>
<td>Resistin</td>
<td>114</td>
<td>3p25-26</td>
<td>2001</td>
<td>Adipose tissue</td>
<td>Unknown</td>
<td>Regulation of insulin sensitivity</td>
<td>2008</td>
</tr>
</tbody>
</table>

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Is milk-borne leptin a link between maternal body composition and neonatal growth and development? Dundar et al. were the first to show that leptin is involved in the growth of BF infants. They suggested that the production of leptin in breast tissue might be regulated physiologically depending on need and the state of the infant. They found that SGA infants grew more rapidly during the first postnatal 15 days than AGA and LGA infants, and that human milk leptin levels were significantly lower in the SGA group.

Milk-borne leptin has been implicated not only in growth, but also in short-term appetite regulation in infancy, especially during early lactation. Oral administration of leptin at doses close to the physiological concentration in milk reduced food intake in newborn rats, and was absorbed by the rat’s stomach during neonatal development thereby triggering down-regulation of endogenous leptin production. Consequently, oral intake of leptin supplied by maternal milk could play a role in the short-term control of food intake in neonates by acting as a satiety signal.

Breast milk leptin could exert a long-term effect on energy balance and body weight regulation. Indeed, by acting on the brain during a critical neonatal period that coincides with the naturally occurring leptin surge, the hormone promotes the formation of neural circuits that control food intake and adiposity later in life. The presence of leptin in the breast milk of nonobese mothers at 1 month of lactation was found to be negatively correlated with BMI at 18 and 24 months of age, suggesting that milk leptin may regulate body weight gain during the first months of life. In a study of rat pups monitored into adulthood, animals given physiological doses of oral leptin during lactation had lower body weight and fat content than untreated animals, which suggests that leptin could have long-term effects on body weight regulation. More recently, leptin-treated animals were found to have lower body weight in adulthood, to eat fewer calories, to have higher insulin sensitivity and to show a lower preference for fat-rich food than untreated animals, which suggests that leptin could have long-term effects on body weight regulation.

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One would expect to find leptin in milk formula because whey proteins added to the formula are isolated from skimmed bovine milk and leptin associated with milk fat globules would be removed during the skimming process. Lage et al. using radioimmunoassay reported significant and variable leptin concentrations in edible commercial bovine milk, and noted that concentrations were higher in infant formulas. However, radioimmunoassay is not appropriate for the detection of leptin in infant formulas because supplemented iron, emulsifiers and other additives contained in formulas could confound the assay. Therefore, further research is required to determine whether leptin is present in milk formula.

Ghrelin

Structure and functions. Ghrelin, a 28-amino acid peptide produced primarily in the stomach, is involved both in the short-term regulation of feeding and in the long-term regulation of weight and energy metabolism. The human ghrelin gene is localized on chromosome 3p23–26. It is mainly produced in the oxyntic mucosa of the stomach by enteroendocrine X/A-like cells. A portion of ghrelin possesses a fatty acid modification, an n-octanoylation, at Ser 3; the remainder is unacylated (desacyl ghrelin). The acylated form, also known as active ghrelin, is thought to be essential for binding to the growth hormone secretagogue receptor 1a (GHSR-1a), and stimulates GH secretion in humans.

Role in appetite, energy homeostasis and body composition. Ghrelin has many endocrine and nonendocrine functions; it is involved in energy balance regulation, and it stimulates food intake in rats and humans. The orexigenic action is mediated by three distinct pathways: (i) circulating ghrelin reaches and activates the orexigenic NPY/AgRP neurons in the arcuate nucleus of the hypothalamus that are implicated in the central control of meal initiation, and inhibits neurons expressing POMC that suppresses appetite; (ii) circulating ghrelin or ghrelin produced locally in the stomach acts via afferent vagal fibres that innervate the nucleus tractus solitarius, which then relays ghrelin to the hypothalamus; and (iii) ghrelin is produced locally in the hypothalamus by ghrelin neural cells.

Unlike leptin, ghrelin increases food intake and decreases energy expenditure. Leptin exerts a tonic dual restraint both on gastric ghrelin secretion peripherally and on activation by ghrelin of the orexigenic neurons centrally.

Ghrelin is released in a pulsatile fashion, with a nocturnal peak. Although several dietary and hormonal factors influence ghrelin concentration, in adults, ghrelin has a meal response: it increases 1–2 h before a meal and returns to trough levels 1–2 h after a meal. Ghrelin secretion increases under negative energy-balance conditions, such as acute energy restriction and anorexia nervosa, and decreases under positive energy-balance conditions, such as food intake and obesity. In newborns, levels of ghrelin were higher in SGA babies than in AGA babies. Reduced ghrelin suppression and higher postprandial ghrelin levels in SGA infants could result in a sustained orexigenic drive and could contribute to postprandial catch-up growth in these infants.

Ghrelin also exerts adipogenic activity, and is involved in the long-term regulation of body weight. Administration of ghrelin induced body weight gain and adiposity in rodents by stimulating food intake and reducing fat utilization and energy expenditure. Kitamura et al. reported high ghrelin levels during the early neonatal period. In term infants, plasma ghrelin was inversely associated to birth weight and body length. This contrasts with a more recent study in which ghrelin levels did not correlate significantly with anthropometric parameters in newborns. In another study, ghrelin significantly increased during the first 2 years of life, after which it decreased until the end of puberty, at which point it reached adult levels. We found a direct correlation between the circulating level of ghrelin and age, weight and length in both BF and FF infants, and a negative correlation between circulating ghrelin levels and weight gain in BF infants. We observed higher values in FF infants in the first months of life, and more recently a positive correlation between circulating ghrelin levels and fasting time in the first 6 months of life in infants fed exclusively with formula.

Ghrelin in breast milk. Ghrelin is a component of breast milk. The levels of ghrelin were found to be lower in colostrum, and in
transitional and mature milk than those typically found in plasma, which suggests that ghrelin comes from the plasma. There is compelling evidence that ghrelin in breast milk is synthesized and secreted by the breast. In fact, ghrelin occurs in both term and preterm human breast milk; its levels are higher in whole milk than in skim milk, and higher in breast milk than in plasma. Acylated ghrelin has also been reported in breast milk; its concentrations increase during lactation and are significantly related with serum ghrelin concentrations in BF infants.

Dass et al. recently demonstrated growth hormone secretagogue-receptor (GHSR) immunoreactivity within the enteric nervous systems of rat and human stomach and colon. These GHSRs may be activated by ghrelin released into the blood from the large deposit within the stomach. In addition, the presence of both ghrelin and the receptor within neuronal and non-neuronal structures of the gut suggests that local supplies of ghrelin can act at least in a paracrine manner within both the stomach and the large intestine. Ghrelin may have the potential to operate within the gut both via the enteric nervous system and via vagus nerve-dependent mechanisms.

Considering that ghrelin is involved both in short-term regulation of food intake, by stimulating appetite, and in long-term body-weight regulation, by inducing adiposity, ghrelin in breast milk could be one of the factors through which breast-feeding may influence infant feeding behaviour and body composition.

Adiponectin

Structure and functions. Adiponectin, discovered in 1995, is the most abundant adipose-specific protein and its multiple functions have started to emerge in recent years. This protein circulates in very high concentrations in human serum. A reduction in adiponectin expression has been associated with insulin resistance, whereas administration of adiponectin is accompanied by an increase in insulin sensitivity. In humans, adiponectin levels are inversely related to the degree of adiposity and positively associated with insulin sensitivity as Rasmussen-Torvik et al. showed recently in adolescents. 

Circulating adiponectin levels correlate negatively with the degree of adiposity also in children aged between 5 and 10 years. In contrast, in full-term neonates, during the first few days of life, serum and plasma adiponectin levels correlate positively with birth weight and length, neonatal adiposity and circulating levels of leptin. Furthermore, adiponectin concentrations in cord blood are higher than those reported in adolescents and in adults. In preterm infants, serum adiponectin levels are lower than those in full-term infants and correlate positively with body weight. Blood adiponectin levels increase with postnatal age in premature infants, suggesting a rapid, as yet unexplained, metabolic adaptation to premature extrauterine life.

Adiponectin in breast milk. Martin et al. recently reported that immunoreactive adiponectin levels in human milk were significantly higher than leptin levels, and that they decreased with the duration of lactation. Bronsky et al. looked for adipose tissue-generated proteins that are related to lipid metabolism in breast milk and found adiponectin, adipocyte fatty acid binding protein and epidermal fatty acid binding protein. Interestingly, adiponectin was found to be more abundant in cord blood than in either breast milk or maternal serum. Given the biological properties of adiponectin, its presence in breast milk and the expression of adiponectin receptor 1 in the small intestine of neonatal mice, not only adipose tissue-produced adiponectin but also milk adiponectin may affect infant growth and development.

Recently discovered hormones in breast milk

Resistin

Resistin is a cytokine identified in 2001 that is secreted by adipocytes. Resistin mRNA encodes a 114-amino acid polypeptide with a 20-amino acid signal sequence. Resistin has been implicated in the development of insulin resistance in mice; the effects of resistin on insulin sensitivity in humans are less well known. In the perinatal period, resistin does not seem to be directly involved in the regulation of insulin sensitivity and adipogenesis. Mouse serum levels of resistin decreased with fasting and increased after re-feeding. Circulating resistin levels were found to be elevated in both genetic (ob/ob and db/db) and diet-induced mouse obesity and insulin-resistance models.

Resistin is expressed in the human placenta and it may play a role in the regulation of energy metabolism during pregnancy. Umbilical serum resistin levels are positively correlated with maternal serum resistin levels and negatively with neonatal birth weight, while Cortellazzi et al. observed decreasing resistin levels with advancing gestation in women with normal BMI. In a cohort study that included overweight and obese women, Jansson et al. found an increase in maternal serum resistin level between the first and third trimesters, and a positive correlation between first-trimester resistin level and birth weight, independently of BMI and dietary variables.

Resistin was recently identified in human milk, and its concentration decreases during lactation. Both milk and serum resistin concentrations in breast-feeding mothers correlated positively with oestradiol, progesterone, pro lactin, thyroxine, triiodothyronine, cortisol, leptin and C-reactive protein concentrations. Moreover, serum resistin concentrations in BF infants were higher than in the breast milk, and serum of their mothers. It is conceivable that resistin is another breast milk hormone involved in the metabolic development of infants.

Obestatin

Obestatin is a 23-amino acid peptide derived from the ghrelin peptide precursor preproghrelin and produced by the cells lining the human stomach and small intestine. This hormone was initially found to reduce food intake, body weight gain and gastric emptying and to suppress intestinal motility thereby exerting effects opposite to those of ghrelin. However, these findings have been questioned by other studies; it has been observed that obestatin is involved in inhibiting thirst and anxiety, improving memory, regulating sleep, inducing cell proliferation and increasing exocrine
pancreatic secretion. Increased plasma obestatin levels have been observed in subjects with anorexia nervosa, in whom obestatin seemed to be a marker of acute and chronic changes in nutritional state. Obestatin was recently identified in breast milk, and there are no data concerning its relationship with infant metabolic development.

Conclusions
Early nutrition could exert both short- and long-term effects on the programming of metabolic development and growth. Epidemiological surveys indicate that breast-feeding protects against obesity in later life, although the precise magnitude of this association remains unknown. Breast milk contains the hormones leptin, ghrelin, adiponectin, resistin and obestatin, which play a role in energy balance regulation. These hormones may be involved in the regulation of growth and development in the neonatal age and infancy and could influence the programming of energy balance regulation in childhood and adulthood. Thus, as shown in Fig. 1, these hormones may represent the link between breast-feeding and protection against obesity in later life.

Competing interests/financial disclosure
Nothing to declare.

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