Review article

Early nutrition and later excess adiposity during childhood. A narrative review.

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Short title: A review on early predictors of excess adiposity in childhood.

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Abstract

BACKGROUND: Studies on childhood obesity mainly focus on the genetic component and on the lifestyle that may be associated with the development of obesity. However, the study of perinatal factors in their programming effect towards future obesity in children or adults is somewhat more recent and there are still mechanisms to be disentangled.

SUMMARY: In this narrative review, a comprehensive route based on the influence of some early factors in life in the contribution to later obesity development is presented. Maternal pre-pregnancy BMI and gestational weight gain has been pointed out as independent determinants of infant later adiposity. Lifestyle interventions could have an imact on pregnant mothers throught epigenetic mechanisms capable of redirecting the genetic expression of their children towards a future healthy weight and body composition and dietary-related microbiome modifications in mothers and newborn might also be related. After birth, infant feeding during the first months of life is directly associated with its body composition and nutritional status. From this point of view, all the expert committees in the world are committed to promote exclusive breastfeeding up to 6 months of age, and to continue at least until the first year of life together with complementary feeding based on healthy dietary patterns such as Mediterranean Diet.

KEY MESSAGES:

To develop future effective programs to tackle early obesity, is necessary not only by controlling lifestyle behaviors likeinfant feeding but also understanding the role of other mechanisms like the effect of perinatal factors such as maternal diet during pregnancy, epigenetics or microbiome.

Introduction

Obesity is a complex multi-factorial condition [1]. Therefore, it is crutial to understand the role and the weight of each genetic and non-genetic related factors on its onset and development. When its onset occurs during childhood, represents a significant risk factor of obesity and obesity-related complications in adulthood specific perinatal factors. The knowledge on the impact of the first 1000 days of life for programming the development of future health is still quite recent [2] and new knowledge, about metabolic pathways and the role of epigenetic mechanisms and the gut microbiome, would be essential in this regard. To answer all these questions, this review focused on systematic reviews, original papers and scientific reports try to fill and summarize all these gaps to identify early opportunities to tackle childhood obesity. The literature search was systematic at first, but reduced according to expert opinions.

Following the above mentioned strategy, together with the main topics found in the screening of the available literature, this narrative review is finally focused on *Nutrition during pregnancy and child adiposity programming, New evidence on metabolic pathways, Postnatal determinants of excess adiposity and the influence of early nutrition on microbiota and later obesity risk.*

Nutrition during pregnancy and child adiposity programming

We have recently reviewed that maternal pre-pregnancy BMI and gestational weight gain are both positively and independently associated with neonatal and infant adiposity [3]. In addition, in a recent meta-analysis with 162,129 mothers and their children from 37 pregnancy and birth cohort studies from Europe, North America, and Australia, it was shown that the proportions of childhood overweight/obesity prevalence attributable to maternal overweight, maternal obesity, and excessive gestational weight gain ranged from 10.2% to 21.6% [4]. Indeed, maternal BMI was stronger predictor of childhood obesity than paternal BMI [3] since the demethylations of the zygote during pregnancy delete some of the paternal epigenetic marks [5]. Nevertheless, mothers being the main caregivers in many cultures/countries are also an important factor to explain the higher association of maternal BMI than paternal BMI [6].

The best example to evaluate the effects of maternal obesity on fetal metabolic programming in humans comes from the studies comparing siblings born from mothers with obesity, before and after gastrointestinal bypass surgery. Children born after

maternal surgery presented lower prevalence of macrosomia (1.8 vs. 14.8%), and severe obesity at adolescence than their siblings born before surgery (11 vs. 35%) [7].

As still there are some knowledge gaps or contradictory findings in this respect, cohort studies evaluating differences among siblings according to maternal pre-pregnancy BMI are of major interest as well as studies considering the different associations between the offspring according to maternal and paternal BMI.

Diet and physical activity based interventions during pregnancy may reduce gestational weight gain and lower the odds of caesarean section [8, 9]. Pregnant women need to increase just about 10-15% of the energy in their diet, and not to eat by two while to think by two (10). to have an adequate gestational weight gain for a healthy pregnancy as recommended by the World Health Organization (WHO) and be informed that it is even more important to start pregnancy with a BMI in the normal range (18.5 to 24.9 kg/m^2) [11].

When considering specific macronutrients, for instance, high glycemic index diet during pregnancy is associated with a higher prevalence of large for gestational age, and greater adiposity in the offspring at birth [12]. Consistently, increased odds of overweight/obesity in offspring at 5 and 6 years were found in large cohort studies in mothers with higher intakes of sugar during pregnancy [13]. However, intervention studies on maternal dietary glycemic index during pregnancy have achieved modest success in decreasing excessive gestational weight gain [9], reduce infant adiposity measured as subscapular thickness and produce sustained improvement in maternal diet at 6 months postpartum [14], and reduced birth weight above 4000 g but not child growth and adiposity at 3-5 years in the offspring in the Limit Trial [15]. Maternal fat and protein intakes were not consistently associated with infant BMI peak and childhood BMI from 18 moths to 4 years old [16]. Higher maternal protein intake at the expense of carbohydrate or fat intake at 26-28 wk gestation was associated with lower abdominal internal adiposity in neonates from the GUSTO study [17] but also with higher risk of gestational diabetes mellitus in pregnant women [18]. Furthermore, in the generation R study, higher protein intake during pregnancy was associated with a higher fat-free mass in children at the age of 6 years, but not with their fat mass [19]. Maternal intake of saturated fat or sugar have been related to body fat mass at 5 years [13]. Moreover, low maternal plasma n-3 and high n-6 polyunsaturated fatty acid concentrations during pregnancy were also associated to higher obesity risk or body fat in children [20]. These results may suggest the convenience to

assure adequate intakes of macronutrients and specifically polyunsaturated fatty acids during pregnancy.

Mediterranean diet (MedDiet) is a dietary pattern characterized by a high consumption of fruits and vegetables, and hence seems appropriate to achieve the extra amounts of vitamins and minerals required because of gestation. Some studies evaluated the effect of MedDiet during pregnancy on different outcomes (Table 1 [19-44]). Some of them indicate that higher adherence to the MedDiet pattern during pregnancy may be protective for the development of obesity and adiposity in early childhood, while others do not show significant effects (Table 1). In addition, MedDiet pattern was positively associated with lipoprotein and homocysteine concentrations [41], and insulin resistance in newborns [42], and negatively associated with gestational diabetes incidence [27] (Table 1). The induction of epigenetic modifications represents a possible explanation for these findings [43], since various micronutrients may influence pregnancy outcomes by altering both maternal and fetal metabolism due to their roles in modulating oxidative stress, enzyme function, signal transduction and transcription pathways that occur early in pregnancy [43].

These dietary recommendations should be taken into account when implementing nutritional intervention programs, in order to prevent nutritional deficiencies that might adversely impact the health of the mother and the newborn [45].

Indeed, more intervention studies evauating groups according selected levels of adherence to MedDiet pattern are needed to stablish further conclusion and recommendations for pregnant women, since the results of associations in cohort studies are promising. In addition, a new index of MedDiet pattern adapted during pregnancy could be of major interest, since a-priori scores are attributed for components already not consumed by pregnant females, such as alcohol, or recommended for daily or weekly consumptions, such as whole dairy products and fish, respectively.

New evidence on metabolic and molecular pathways

Maternal obesity and inadequate nutrition might modulate key genes expression in the offspring. For example, high protein intake induced changes in infant metabolome, increasing plasma concentrations of the branched-chain amino acids and consequently insulin levels. These changes seem to inhibit fat oxidation and thereby enhance body fat deposition and the risk of adiposity [46].

Epigenetic control is essential for embryonic and early postnatal development, and its deregulation play a role in the etiology of several developmental syndromes [47]. Evidence suggests that early life exposure to suboptimal nutrition during pregnancy can affect transcriptional regulation through epigenetic alterations, in adipose tissue, brain, liver, and pancreas [48], contributing to the long-lasting consequences on offspring health.

Adipose tissue is one of the most active metabolic and endocrine tissues that synthesizes and secretes a wide variety of molecules. Dietary-induced gut microbiota modification may modulate epigenetic gene-expression of adiponectin and resistin through its metabolites such as folate, biotin, and short-chain fatty acids [49]. In fact, antibiotics modify gut microbiota and increase transcription of the adiponectin and resistin genes in mice fed a high-fat diet by modifying promoter DNA methylation, thus leading to increased fatty acid oxidation and less body weight gain [50]. Therefore, more studies are needed to understand the molecular epigenetic and metabolomic mechanisms involved in the obesity risk associated to early-nutrition, in order to achieve improved personalized advices.

Postnatal determinants of excess adiposity

Infant feeding

Nutrition plays an important role from very early in life and not only in terms of growth and development, but also in terms of risks of diseases later in life if not adequate. Considering nutrition during the early postnatal period, breastfeeding is considered by pediatric organizations as the ideal nourishment for infants during their first year of life [51].

In 2014, a systematic review concluded that there is still a controversy in respect to overweight-obesity prevention and breastfeeding, as there is a large number of aspects that may confound this association [52]. In 2017, a randomized controlled trial including 17046 breastfeeding mother-infant pairs cocluded that breastfeeding does not prevent obesity neither in childhood nor in adolescence [53]. However, this study had a number of limitations (such us the observed higher rates of breastfeeding duration in the control group) that make its conclusion not generalizable [52]. Besides, a longitudinal study in USA in 2017 including 1234 children, concluded that breastfeeding at month 1 was associated with a 36% lower risk for childhood obesity from 24 months, and that the

longer duration of breastfeeding was correlated with a lower prevalence of childhood obesity [54]. This study has as limitations that data were collected decades ago and might be slightly biased while as strength it includes a number of socioeconomic status variables. In fact, the compendium of social and economic characteristics of children´s environment affecting at individual, household, community, or society levels may affect more negatively individuals´ health, including body composition as early as in the gestational period [55]. Indeed, early life risk factors of later excessive weight gain, such as parental smoking and excessive maternal weight gain during pregnancy, gestational diabetes, prematurity, high and low birthweight, caesarean section or not being breastfed are normally grouped in determined socio-economic patterns [56]. Consequently, children from families in a vulnerable social position are prone to accumulate several risk factors predisposing to lower health future status including inadequate body composition.

Around the sixth month of life, and not early than fourth months, complementary food and beverages (CFBs) introduction should start [57]. This period continues up to two years of child age when it is considered that the transition to family feeding habits is finished. In relation to the importance of the introduction timing for later body composition, the literature is not overwhelming. A recent position paper [58], concluded that the introduction of CFBs between the ages of 4 and 5 months compared with the introduction at 6 months is not associated with a different body composition in healthy full-term infants. Little evidence suggests higher odds of overweight/obesity when the introduction of CFBs took place before 4 months; and insufficient evidence exists regarding introduction at age ≥7 months. Therefore, large observational cohorts from bith would be highly recommended to clarify these questions [59].

In relation to CFBs, energy is the most determining factor for fat deposition, so it must be adequate for infants requirements [60]. It is important to assure the amount of proteins do not exceed the current recommendations because it may induce metabolic programming of both rapid weight gain and increased obesity risk later (Early Protein Hypothesis) [60].

Besides, it seems the perinatal period is relevant in terms of food preference choices development which may also contribute to excess fat deposition later during childhood. In this respect, the role of parental (or caregivers) feeding practices, as well as the early and continuous exposition to all (but especially) healthy foods, continue inspiring

research through familiarization via taste lessons, cooking, or playing activities on acceptance [61].

Early infant growth

Risk factors tend to track from early life through to adulthood. When consider elevated BMI as risk factor for cardiovascular diseases, for example, it seems that individuals experience only small changes in BMI classification trajectories throughout their life [62]. Besides, the question whether birth weight is a predictor of later overweight/obesity remains unclear. In a representative sample of Norwegian adolescents from the Medical Birth Registry of Norway, longitudinal data showed that associations between birth weight and overweight/obesity were modest at 15–20 years of age, whereas the influence of BMI at 2–4 and 5–7 years on overweight/obesity at 15–20 years was moderate to strong [63].

In addition, rapid weight gain (RWG) during the first months of life, has been also recognized as an important determinant of childhood obesity [64]. A recent nationally representative study in Taiwan [65] found that the association between RWG and the risk of subsequent overweight or obesity was independent of the specific time interval during which RWG occurred before the age of two. In a representative cohort of Spanish children followed since birth [66], BMI for age z-score and weight for age z-score trajectories were significantly higher in rapid weight gainers during the first semester of life compared to their counterparts. These associations were independent of the type of feeding.

Influence of early nutrition on microbiota and later obesity risk

The microbiota consists of a wide variety of microorganism that colonizes all the compartments of the body. The imbalance of microbiota composition is known as dysbiosis, and it is strongly associated with early nutrition, impacting on the individual's later health and the risk of non-communicable [67] and metabolic diseases such as obesity [68]. The gut microbiota potentially plays a role in dietary energy harvest and energy storage in the host. Indeed, it is considered a novel factor involved in body weight management, and a contribution of the intestinal microbiota in the onset of obesity has been suggested [69].

Maternal diet during pregnancy establishes long-lasting effects on offspring gut microbial composition, with potential health implications [70].

Preclinical evidence has suggested that gut microbiota immaturity may lead to childhood undernutrition and growth failure [71]. On the other side, gut microbiota has been implicated in the origin of obesity, since in children with obesity have different microbiota than normal weight children, and the microbial intercorrelation network was also altered [72]. Furthermore, some gut bacterial derived metabolites as the short-chain fatty acids found in fecal samples are also more abundant in children with obesity suggesting a higher substrate utilization and energy production from the intestinal microbiota. This confirms that gut microbiota may be important for energy metabolism during obesity development [73]. Indeed, the well-known relation between microbiota-deribed short chain fatty acids (SCFAs), inflammation and obesity might explain the molecular mechanisms implicated in (74, 75), since SCFAs are key molecules able to increased the host capacity to harvest excess energy from the diet, exerting metabolic effects on the via multiple complementary pathways [76]. It has been demonstrated that the most important determinants of the gut microbiota composition in infants are the mode of delivery, gestational age, infant hospitalization, antibiotic administration and also the type of infant feeding [67, 77]. In fact, there is a clear clustering of components of newborn-infant microbiota that depends on the type of feeding [human milk versus formula milk] [78]. Breastfeeding is a key factor in the healthy metabolic, immunological, and microbiological programming of the infant's health that is driven by the interaction between milk components and also the mother microbiota [67]. Observational studies have shown that the composition of human milk has an important influence on subsequent infant growth and body composition [73].

Therefore, more studies are needed to find out if there is a link between the type of feeding, the microbiome, and later obesity.

Within food components that may affect these mechanisms, human milk oligosaccharides (HMO) may influence the newborn development and infant growth [79], and the majority of ingested HMO are energetic substrates for specific gut bacteria [79, 80] which might also influence the microbime profile. Within HMO, lacto-N-tetraose has been linked to growth, and its presence in human milk is associated with increased fat mass percentage at five months of age [81]. Furthermore, the higher risk of obesity in infants with overweight and excessive weight gain mothers may also be influenced by the interaction between breast milk cytokines and microbiota [82].

Later on, solid food greatly influences the microbial ecology after weaning. The influence of dietary composition on children microbiota has been described [83]. The Western diet rich in fat and energy is associated with dysbiosis [84], and specific gut microbiota profiles facilitate the extraction of calories from the diet and their storage in the host adipose tissue [85]. Hence, early dietary manipulation represents a strategy to promote a beneficial gut microbiota and to improve health and weight control [86].

Therefore, knowledge of how early nutrition influence on gut microbiota will help in the design of new nutritional strategies to prevent the development of obesity. These new strategies could be based on the development of new formula-milk or solid-food enrich with probiotics or prebiotics that can modulate gut microbiota ecology.

CONCLUSIONS

Perinatal period represents in many aspects a good opportunity to increase the awareness of families and to apply the adequate health policies to prevent later obesity. The impact of the first 1000 days of life for programming later obesity risk can be explained by a number of metabolic, epigenetic and metagenomics mechanisms that have been recently explored. From a clinical point of view, factors such as maternal pregestational BMI, should be monitored for instance by controlling glycemic index of their diets or try to better adhere to the Mediterranean diet, althought results on reducing infant adiposity are not yet confirmatory. Also, breastfeeding at least during the first semester of life and even better after first year together with the delay in the introduction of complementary feeding until after the fourth month at least, must be recommended from primary care with special emphasis in social vulnerable families.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have designed, wrote and reviewed the final content of this manuscript.

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Table 1. Classification (protect vs no effect) of studies showing the association between the adherence to Mediterranean diet during pregnancy and either maternal or fetal outcomes

Variable	**Protect**	**No effect**
Birthweight, Adiposity	**11** [Timmermans et al. 2012 (19); Chatzi et al 2012, 2017 (21, 22); Smith et al. 2015 (23); Monteagudo et al. 2016 (24); Parlapani et al. 2017 (25); Gómez-Roig et al. 2017 (26); Assaf-Balut et al. 2017 (27); Martínez Galiano et al. 2018 (28); Peraita-Costa et al. 2018 (29); Fernández-Barres et al. 2019 (30)]	**5** [Saunders et al. 2014 (31); Fernández-Barres 2016 (32); Castro-Rodriguez et al. 2016 (33); Tomaino et al. 2020 (34); Peraita-Costa et al. 2020 (35)]
Gestational Diabetes & Preeclampsia	**7** [Assaf-Balut et al. 2017, 2018 (27, 36); Parlapani et al. 2017 (25); Al Wattar et al. 2019 (37); Olmedo-Requena el al. 2019 (38); García de la Torre et al. 2019 (39); Melero et al. 2020 (40)]	
Biomarkers	**2** (Gesteiro et al. 2012, 2015 (41, 42); Gonzalez-Naham et al. 2017 (43)]	**1** [Mantzoros et al. 2010 (44)]

None study has described adverse effects