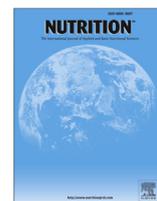




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Review

Excess body weight during pregnancy and offspring obesity: Potential mechanisms

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ABSTRACT

The rates of child and adult obesity have increased in most developed countries over the past several decades. The health consequences of obesity affect both physical and mental health, and the excess body weight can be linked to an elevated risk for developing type 2 diabetes, cardiovascular problems, and depression. Among the factors that can influence the development of obesity are higher infant weights and increased weight gain, which are associated with higher risk for excess body weight later in life. In turn, mother's excess body weight during and after pregnancy can be linked to the risk for offspring overweight and obesity through dietary habits, mode of delivery and feeding, breast milk composition, and through the influence on infant gut microbiota. This review considers current knowledge of these potential mechanisms that threaten to create an intergenerational cycle of obesity.

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Introduction

Over the past three decades, there has been a substantial increase in the number of individuals who are overweight in the United States [1], and overweight and obesity have become the most prevalent nutritional disorders of children and adolescents. Currently, more than one-third of all children in United States are overweight and more than 15% of children and adolescents are obese, a figure that is nearly triple the rate 2 to 3 decades ago [2, 3]. The health consequences of childhood obesity affect both physical and mental health. Overweight children have an increased incidence of hypertension, coronary artery disease, sleep apnea, orthopedic problems, and type 2 diabetes [1]. The psychological complications include low self-esteem, increased risk for discrimination, and poor body image.

Obesity that begins in childhood tends to be more severe and is associated with greater adverse effects than obesity in adulthood [4]. If a child is overweight by the age of 10 to 13 y, there is a 65% chance he or she will become an overweight adult [5]. Among the factors that can influence the development of childhood obesity, infant weight, and weight gain are significant determinants of future body mass. Infants with excess body weight (EBW) have an increased risk for developing obesity in adolescence and in childhood [6,7]. For example, the Growing Up Today Study in the United States revealed that each 1 kg increase in infant birth weight was associated with about a 5% increase in the chance of being overweight in adolescence [8]. In turn, infant overweight status can be linked to the weight and obesity of their mothers before, during, and after pregnancy (Fig. 1). Overweight mothers are significantly more likely to have overweight children, and the strongest predictor of child overweight status is the mother's current EBW [7,9–11]. Specifically, a number of studies have reported significantly increased odds ratios (OR) for offspring obesity in obese mothers. These ORs ranged from 3.1 among low income U.S. children in one [12], to 4.3 for U.K children at 7 y of age based on another study [13], to

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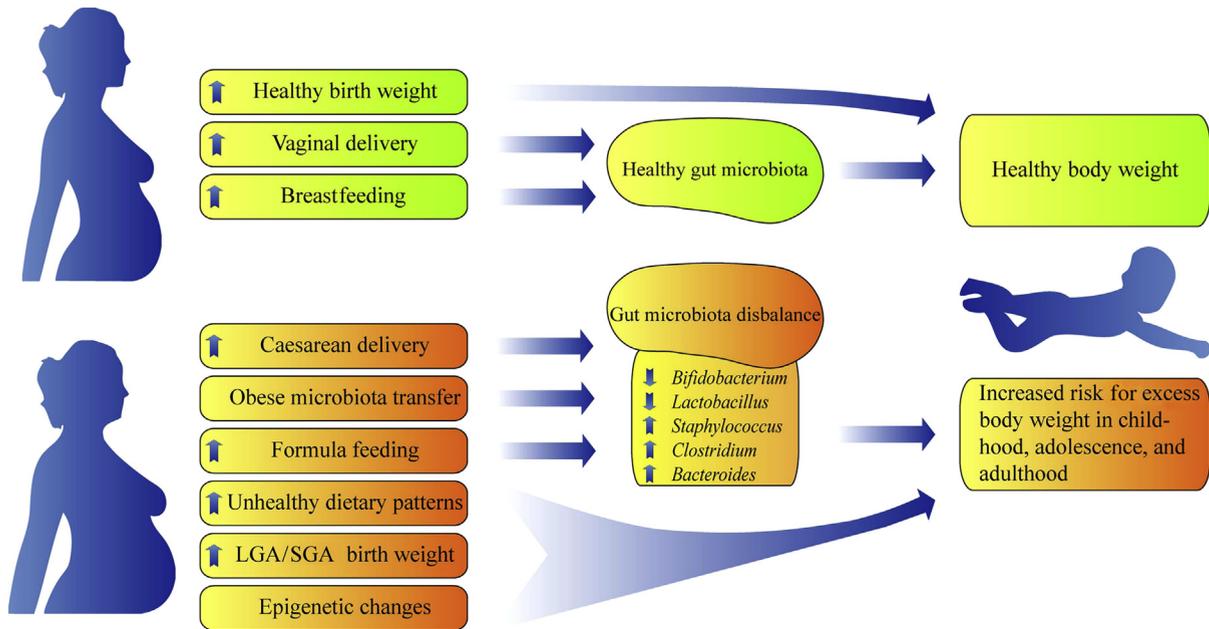


Fig. 1. Potential links between mother EBW during and after pregnancy and elevated risk for EBW in her child. Parameters that protect children from gaining excess weight in normal weight mothers are shown in the top section; parameters that can link child risk for EBW and mother's overweight status are shown in the bottom section. Vertical arrows indicate higher or lower level of each component.

above 5 for U.S. children born between 1980 and 1990 as described in a third study [10]. Among Swedish army conscripts, each unit of maternal body mass index (BMI) increased the OR of recruit obesity by 1.2 [14].

In this review, we consider currently available evidence for potential associations between maternal EBW during and after pregnancy and the risk for offspring developing obesity during childhood or later in life. Because about half of all women of childbearing age in the United States are either overweight or obese [15], and because the rate of obesity in pregnant women also has increased in recent years [16], such a link may create an intergenerational cycle of obesity.

Obesity in pregnancy

Obesity and excess weight during pregnancy are associated with a number of complications during childbirth through the influence on the intrauterine growth of the fetus. Prepregnancy obesity is linked to an increased risk for miscarriage, induced preterm delivery, and higher risk for preterm premature membrane rupture [17,18]. There also is a correlation between maternal prepregnancy BMI and the likelihood of cesarean delivery [19]. Delivery mode in turn was shown to influence the child obesity risk in some studies. For example, Brazilian adults born in the late 1970s via cesarean delivery were significantly more likely to be obese in young adulthood than those born vaginally [20]. However, maternal BMI and pregnancy complications were not accounted for, and cesarean delivery rates in this birth cohort were considerably higher than those in North America. The increasing proportions of large for gestational age (LGA) births over time also are potentially explained by concurrent increases in maternal BMI and gestational diabetes mellitus (GDM), because high prepregnancy weight in women has been associated with a statistically significantly higher risk for giving birth to LGA infants [21,22]. Moreover, the mothers, who themselves were born LGA, have an increased risk for being overweight and obese, and are more likely to give birth to LGA infants

[23]. Both LGA and small for gestational age (SGA) births and a rapid increase in weight during infancy and early childhood have been strongly related to a number of obesity-related diseases later in life [23,24]. For example, maternal over-nutrition during pregnancy can result in fetal growth restriction leading to SGA births [25], and low birth weight has been shown to influence insulin response and glucose metabolism in young adults. On the other hand, systematic evidence for the association between GDM and future offspring overweight has been inconsistent [26]. For example, glycemic control in women with GDM was not enough to reduce LGA births to acceptable limits (<10% of newborns) [27]. One study suggests that maternal overweight and GDM may both be required to cause offspring overweight [28].

One way to protect against infant birth-weight abnormalities potentially can be achieved through the modulation of dietary habits of women before and during pregnancy. There is an increasing interest in dietary patterns (DPs) during pregnancy and their effects on childbirth, as DPs capture much more than the effects of isolated nutrients considered alone. Healthier DPs during pregnancy were shown to be associated with healthier birth outcomes such as reduced risk for SGA infant births [29,30]. Remarkably, relatively little has been established regarding specific dietary factors associated with LGA and SGA birth outcomes. A positive association between higher milk consumption and LGA birth risk was shown in one study [31], whereas a negative association between coffee consumption and SGA birth risk was revealed in another [22]. Odds of giving birth to SGA infants were increased in women who, during pregnancy, consumed diets that were rich in red meat and high-fat dairy products [30]. In a Japanese study cohort, DPs during pregnancy that were rich in bread, confectionary, and soda but low in fish and vegetables were associated with a higher risk for SGA infant births [29].

The underlying biological mechanisms and pathways that are affected in the fetus and the mother by specific DPs during pregnancy are just now starting to be revealed. One of the

emerging paths that show how the mother's diet during pregnancy can affect child weight and obesity development is through epigenetic regulation of promoter activity [32,33]. Because DNA methylation may be altered in response to overall availability of amino acids and other nutrients, dietary over- or undernutrition during fetus development can create an epigenetic imprint on the fetal genome [34]. Epigenetic DNA methylation, specifically CpG methylation, of specific gene promoters in neonates was linked to child obesity risk [35]. The study found that greater methylation of retinoid X receptor- α gene in children at birth was associated with higher adiposity in later childhood. In another study conducted in sheep, undernutrition during pregnancy was associated with changes in gene promoter methylation status in fetal hypothalamus, which can potentially cause obesity development later in life [36]. The DNA methylation changes often are accompanied by modifications in histone acetylation and methylation status, which can similarly influence promoter activity. In addition, genome-wide association studies (GWASs) have been successful in identifying genetic loci associated with obesity [37,38]. However, a substantial proportion of causality still remains unexplained, limiting the use of GWAS data in obesity prevention. In this regard, ongoing pilot studies targeting specific metabolic proinflammatory polymorphism clusters (Metabolic-Obesity panel, NextGenomics, Prato, Italy) can prove to be useful in facilitating the prediction of clinical responses to obesity treatments. Epigenome-wide association studies may serve as a further complementary approach for identifying causal variation that cannot be captured by GWASs, and can potentially have prognostic value in determining odds of developing EBW later in life [35].

Maternal overnutrition also can directly influence the development of fetus adipose tissues and organs. Maternal overnutrition during pregnancy may lead to fetal overnutrition that would cause increased fetal fat deposition. This can promote an increase in the number of developing adipocytes in the fetus that would be carried for the rest of the life [39]. Infants of obese mothers also appear to have reduced energy expenditure [40]. Similar permanent changes in offspring metabolism were shown in animal studies [41]. Interestingly, significant undernutrition during pregnancy also can program the fetus for increased energy retention and weight gain as one study showed: Exposure of women during pregnancy to the Dutch famine during 1944–1945 led to a significantly higher obesity rate of their offspring at age 19 y [42].

Gut microbiota and obesity

Another avenue that links an individual's diet and body weight is the role of intestinal microbiota in human nutrition. The human gastrointestinal tract houses 10^{13} to 10^{14} microbial cells, and the composition and activity of this complex microbial system have a significant influence on health and disease [43]. A considerable number of recent publications have evaluated whether alterations of gut microbial populations can potentially contribute to the development of metabolic disorders such as obesity and type 2 diabetes [1,44,45]. Gut microbiota can contribute to obesity development by increasing the energy recovery from the diet, by changing gut transit time, or by modulating host signaling pathways involved in lipogenesis, energy storage, and inflammation. Several recent studies profiled differences in the relative abundances of different microbial groups in obese and non-obese adolescents and adults [46–50]. The initial investigations indicated that an obese status was associated with the lower relative abundance of members of

phylum Bacteroidetes accompanied by an increase in the abundance of phylum Firmicutes [46–48]. However, other reports failed to corroborate such shifts [51–53], and in some cases, higher levels of Bacteroidetes were detected in the obese cohorts [49,54]. Weight loss diets also have been shown to lead to changes in intestinal microbiota in some cases [46,55], but others revealed no such effect [53]. The obese gut microbiome is enriched in the genes coding for glycoside hydrolases—enzymes that are capable of breaking down otherwise indigestible complex plant polysaccharides [56]. As a likely consequence, the “obese” microbiota displayed an increased energy harvest from the diet [57] with an associated increased production of short-chain fatty acids (SCFAs) in the gut lumen [54]. The resulting elevated levels of SCFAs, which are readily absorbed through the intestinal mucosal surface, can promote increased lipogenesis in the liver and alter fat storage [58]. In addition to the nutrient harvesting changes, high-fat diets in mice led to a drop in the content of genus *Bifidobacterium*, a prominent gut member with beneficial functions. This decrease correlated with higher lipopolysaccharide plasma levels, thereby allowing the onset of inflammation, insulin resistance, and type 2 diabetes associated with obesity [59]. The colonization of germ-free mice with gut microbiota alters the expression of several host factors, including cellular energy control enzyme AMPK, fasting-induced adipocyte factor FIAF, and the endocannabinoid system [44,60]. SCFAs produced by colonic biota also can regulate enteroendocrine function; for example, SCFAs act on two G protein-coupled receptors Gpr41 and Gpr43 that are thought to regulate host energy balance and inflammation [61].

In summary, a body of evidence has been accumulated on the role of gut microbiota in obesity development. Although the available data is not always consistent among different human studies, specific differences in gut microbiota between obese and normal weight human populations were detected in most investigations. Better consistency was generally observed among animal studies, where gut microbiota was shown to be a prominent contributing factor to obesity development [56,62–64]. Diversity among human populations in genotypes, consumed diets, and behavioral patterns, the use of different clinical criteria and sample collection routines, as well as variability in the investigative methodologies employed can all serve as confounding factors that influence the measured microbial community structures. It also is possible that more subtle changes at the genus or species level are responsible for the altered host–microbial interactions in obese individuals [65,66].

Establishment of infant gut microbiota

During birth, the intestine of a newborn is immediately colonized by microbial cells. Initial gut colonization of infants is driven by the exposure to microbes in the vaginal canal and from traces of mother's feces (in case of vaginal delivery) or to microbes on the skin and in the air (in case of cesarean delivery) [67]. Thus, although traditional delivery sees the early infant microbiota resembling that of the vaginal canal, gut of infants born through cesarean delivery receives initial microbes from human skin that are less similar to those that normally inhabit the human gut. Specific early gut members in the vaginally delivered babies include *Streptococcus*, lactobacilli, and enterobacteria, which are followed by *Bifidobacterium* and later by other anaerobic species from phyla Bacteroidetes and Firmicutes [68–71]. These early colonizers seem to be critical for the proper maturation of the child's immune system because cesarean delivery was shown to be associated with an increased risk for

celiac disease, diabetes, and asthma [72–74]. Cesarean delivery leads to a different colonizing community often dominated by skin microbes *Staphylococcus*, *Propionibacterium*, and *Corynebacterium*, and is low in lactobacilli and bifidobacteria [20,71]. A reduction in gut *Bifidobacterium* numbers in cesarean-delivered infants may potentially explain higher obesity risk in this group.

Changes in gut microbiota during pregnancy were shown to influence early infant gut colonization. For example, several studies showed that the gut of overweight and obese pregnant women had higher levels of *Bacteroides*, *Clostridium*, and *Staphylococcus* and lower levels of *Bifidobacterium* than the gut of women of normal weight [75]. These differences were transferred to the mother's babies as the prevalence of *Bacteroides* and *Staphylococcus* also was higher in the gut of babies of overweight mothers [76]. One study found that pregnant women with EBW harbored higher numbers of *Escherichia coli* and *Staphylococcus* but lower *Bifidobacterium*, which correlated with higher infant birth weight [77]. Specific strains of *B. longum* were shared between feces of mothers and infants, presumably transferred either during delivery [78] or through breast milk feeding (see below) [79]. Mother–child contact likely serves as the primary method of transfer of keystone gut members from the genus *Bifidobacterium* because these species are not generally found in the environment [80]. Although not always corroborated by other reports [81], these studies provide preliminary evidence of the direct link between gut microbiota of mothers and their children in early infancy.

Several recent studies have pointed out the differences in infant microbiota between children that maintain normal weight and those that later develop EBW. Children that maintained healthy weight tended to have higher *Bifidobacterium* counts, whereas other microbes such as *Staphylococcus* were elevated in infants that would become overweight [66]. The authors provided a hypothesis that the protective role of bifidobacteria might be associated with their anti-inflammatory properties, whereas *Staphylococcus* may trigger low-grade inflammation leading to obesity development [66]. The plausible protective effect of higher *Bifidobacterium* numbers in the gut of children with healthy weight also was found in another study analyzing this cohort, although the difference did not reach statistical significance [82].

Postnatal associations

Postnatally, an infant's association with their mother's health and obesity can be made through breastfeeding and breast milk composition. Overweight and obese mothers are less likely to breastfeed than those with healthy weight [10], partly due to physiological difficulties with initiating breast milk production. Higher BMI is associated with a delayed onset of lactation that also usually leads to shorter breastfeeding period [83]. In turn, several recent meta-analyses and numerous clinical studies provide evidence that infant breastfeeding is associated with a lower risk for developing overweight and obesity later in life, with the level of protection dependent on the duration of breast feeding [9,10,84,85]. In developed countries, breast-fed infants gain weight slower than formula-fed babies, likely because formula-fed babies consume larger volume meals, feed less frequently, and overall obtain higher energy intake per day [86,87]. Differences in intake persist even after the solid foods are added to the diet. Such differences in daily energy intake in early childhood are associated with higher odds of developing obesity in childhood [88]. Note, however, that not all trials found an association between breastfeeding duration and offspring weight [89].

Nutrient composition of breast milk in mothers during lactation can also play a role in child weight gain control. Although milk composition seems to be generally buffered against fluctuations in maternal short-term dietary changes [90], mothers who consumed higher amounts of fatty acids were found to be more likely to have higher body fat content, and their infants were twice as likely to have body fat above 24% of body weight [91]. Similar influence of a high-fat diet on offspring obesity also was found in animal models [92], and the milk of obese rats contained more energy than that from lean rats [93]. In humans, breast milk of overweight mothers was found to contain less protein compared with the normal group [94]. Recent findings also revealed a presence of human hormones and bioactive compounds in human breast milk including leptin, ghrelin, adiponectin, obestatin, and resistin [95]. Many of these hormones are likely to play a role in the regulation of infant energy intake and metabolism, and they can serve as regulators of breast-fed infant body weight gain.

After initial colonization, the establishment of infant gut microbiota population also is dependent on whether the infant is breast or formula fed [96]. The gut biota of breast milk-fed babies usually is dominated by *Bifidobacterium*, *Streptococcus*, *Lactobacillus*, and enteric bacteria. The microbiota of formula-fed babies is more complex and is more similar to that of an adult with increased counts of Bacteroidia and Clostridia [97,98]. Similar differences were observed between formula-fed and maternal-fed young mice; in addition, formula feeding was associated with increased oxidative stress and decreased structural integrity in the intestine [99].

In addition to other nutrients, human milk also contains more than 100 different human milk oligosaccharides (HMOs), which are believed to play a vital role in the determination of early microbial gut colonizers. For example, some beneficial microbes such as members of *Bifidobacterium* are able to metabolize HMOs efficiently, whereas other gut microbes such as *Clostridium* cannot grow on HMOs [100]. Thus, breast milk HMOs facilitate initial colonization of the infant gut by “beneficial microbiota” that is critical for host pathogen protection and proper immune development. Breast milk itself provides another source of microbes that include *Bifidobacterium*, *Streptococcus*, and lactic acid bacteria [79], and breast milk oligosaccharides supply further selective nutrient source to these microbes with beneficial properties [101]. The milk of overweight mothers contains lower counts of *Bifidobacterium* but higher numbers of *Staphylococcus* [102]; this can predispose their infants to higher weight in later childhood as described in the previous section.

Infant feces and the mother's breast milk were found to contain the same strains of bifidobacteria, lactobacilli, and staphylococci [103]. Although the route of how the breast tissues and milk acquire these microbes has not yet been fully elucidated, there is emerging evidence implicating the increased microbial translocation in the mother's gut in this process [79]. Several studies showed that dendritic cells can keep some internalized intestinal bacteria and can then spread them through the lymphoid system to other tissues, including mammary glands [104,105]. These milk microbes can serve important roles in infant development including production of antimicrobial compounds, improvement of epithelial integrity, and stimulation of mucin synthesis [106].

Conclusions and outlook

Although increasing evidence is available that links mother's obesity status, delivery mode, and feeding regimen with the risk

for childhood obesity (Fig. 1), the data is sometimes inconsistent and at the current time is not sufficient to provide a definitive causative link. Nevertheless, the currently available evidence points to a troubling cycle of increasing obesity risk in developed societies, as children of obese and overweight mothers have a significantly higher chance of developing obesity themselves and in turn passing such increased risk to their own offspring.

Although obesity prevention programs have received an unprecedented level of support in the new health reform laws, obesity still remains one of the greatest health problems in many developed countries. Because it is a challenge to treat obesity effectively once established, the identification of promising interventions for obesity prevention and control is an important area of research. Increasing public education of the health consequences of obesity in both adults and children is important to achieve the success of such prevention options, especially in the light of the fact that more than half of all pregnancies are unplanned. Obese and overweight prepregnant and pregnant women can benefit from visits to a dietician and by establishing a healthy diet with moderate exercise to control gestational weight and excess weight gain. However, care should be taken not to decrease BMI significantly while in gestation, as under-nutrition during pregnancy can actually elevate the risk for offspring obesity through epigenetic regulation of fetal gene expression [36]. In addition to the dietary and physical activity changes, another potential intervention option to reduce EBW in pregnant women is via dietary probiotics [107]. Some potential benefits of probiotic supplementation to pregnant women include the reduction in the risk for LGA infant births [108] and the moderation of the initial phase of excessive weight gain by babies [109]. However, not all probiotic trials have been able to detect a positive effect [110] and more research is needed.

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