Review Article

Maternal BMI, gestational weight gain and postnatal weight gain: the way forward to prevent childhood obesity

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Background: Maternal obesity, excessive gestational weight gain (GWG) and rapid weight gain (RWG) in infancy are found to be modifiable risk factors of obesity and non-communicable diseases in children. The lack of long-term sustainability and the cost of secondary prevention of obesity urge for action to identify strategies for primary and primordial prevention.

Aims: Our aim is to summarize the wealth of evidence from human as well as animal studies on the mechanistic role of maternal obesity and GWG on offspring adiposity and plausible preventive interventions at individual as well as community level.

Review Results: Maternal factors like obesity, nutrition, lifestyle and GWG can alter the intrauterine milieu that result in DNA methylation of fetal metabolic genes and exposure of the developing fetus to abnormal levels of leptin and adiponectin. Community-wide research from western countries show that postpartum weight reduction, antenatal lifestyle modifications, physical activity during pregnancy and early lifestyle interventions during the first two years of life are effective in preventing childhood obesity.

Conclusion: Epigenetic modifications and adipokines play a pivotal role in the maternal-offspring transmission of obesity risk. In addition, RWG in infancy leads to later childhood obesity. Interventions to achieve normal preconceptual BMI, GWG and prevent RWG in infancy have the potential to prevent the development of obesity.

Clinical Significance: Globally, prevention of childhood obesity should focus on identification of cost-effective, feasible and sustainable programs. Research from low and low-middle-income (LMI) countries are expected to contribute to the policy-makers on development of an appropriate framework to be implemented at ground level.

Keywords: childhood obesity, maternal obesity, gestational weight gain, DNA methylations, adipokines, rapid weight gain in infancy, obesity prevention

INTRODUCTION

The rising prevalence of obesity in children and adults is a global health concern1. Obesity has been determined as a key factor in the etiology of several non-communicable diseases (NCD) including cardiovascular disease, type 2 diabetes, non-alcoholic steatohepatitis and several types of cancer[1]. The persistence of childhood obesity with its associated metabolic derangements into adulthood is widely evident[2].

Childhood obesity also induces a significant personal, societal and economic burden at local as well as global level[3].

While the increasing trends of body mass index (BMI) have plateaued in most of the high-income countries, the obesity prevalence continues to escalate in the low and low-middle income countries particularly in East and

South Asia for both sexes, and Southeast Asia for boys[4]. At present, management of childhood overweight and obesity is based on lifestyle modification interventions. Most studies published to date have demonstrated either a low or short-term positive effect[4,5]. In addition, management of obesity and associated complications involve a large health care cost per person apart from loss of income at both individual and societal level over a lifetime, indicating the need for cost-effective preventive strategies. Hence, it is important to elucidate the origins of obesity and identify the opportunities to prevent its occurrence both at primary and primordial levels.

While the western lifestyle with high fat, high sugar diet with refined carbohydrates and sedentary behavior are thought to contribute to the global shift towards an obese phenotype, strong evidence has emerged to support that the developmental origins of obesity as well as metabolic syndrome are linked with in utero programming of metabolic genes. Maternal obesity and increased GWG are considered to adversely influence the intrauterine environment[3,6,7].

The aim of this review is to summarize the evidence for the association between maternal factors such as BMI and GWG with offspring adiposity and to explore potential mechanisms mediating this relationship. We also highlight the possible interventions available to modulate the early origins of childhood obesity.

The recently published WHO report on ―Ending childhood obesity‖ reflects that those specific opportunities for effective prevention of obesity and associated NCDs exist at different stages in the life cycle namely pre-pregnancy and pregnancy, infancy and early childhood, and adolescence which is also the pre-pregnancy period for girl child[3].

Impact of maternal obesity on offspring adiposity and cardiometabolic risk

Maternal BMI at the time of conception has been identified across several studies as a strong predictor of offspring adiposity[8,9,10]. A meta-analysis carried out by analyzing data from 162,129 mothers and their offspring from 37 pregnancy and birth cohort studies from Europe, North America, and Australia[11], identified that higher maternal pre-pregnancy BMI and gestational weight gain were associated with an increased risk of childhood overweight/obesity, with the strongest effects seen at later ages of childhood.

Increased prevalence of adult obesity has resulted in higher BMI among pre-pregnant females. A significant proportion of women, entering pregnancy, also suffer from non-communicable diseases such as Type II diabetes mellitus and hypertension which can affect the intrauterine environment of the growing fetus12. Higher maternal BMI increases the risk for both large and small for gestational age babies (LGA and SGA) whereas low maternal BMI is associated with small for gestational age babies (SGA)[13,14]. Both high and low birth weights are known to be associated with childhood obesity and metabolic syndrome

World Health Organization (WHO) reports that the prevalence of obesity during pregnancy ranges from 1.8% to 25.3% [1]. According to the European Perinatal Health Report more than 30% of pregnant women are obese in most European countries15. A global estimation of overweight and obesity in pregnant women based on panel data between 2005 and 2014 reported that India has the highest percentage of overweight and obese females. China also had 1.06 million obese pregnant women, and the number increased by 71.2% within ten years[16].

The prevalence of overweight and obesity among Sri Lankan women have been reported by the WHO as 26.8% and 7.4% respectively. However, there are no published data among women of child bearing age[17].

Evidence has accumulated over the years to prove that higher maternal BMI and increased GWG are independently associated with offspring adiposity during early childhood[18,19]. Starling et al estimated the associations of maternal pre-pregnancy BMI and increased GWG at different periods of pregnancy with neonatal adiposity[20]. They concluded that maternal pre-pregnancy BMI, overall and period specific (early, mid and late pregnancy) GWG, were positively and independently associated with neonatal adiposity.

The mechanistic role of maternal obesity in fetal metabolism

While the association between maternal BMI and offspring adiposity is well established, the exact mechanisms mediating this relationship are still not clear.

Maternal obesity potentially influences the fetal growth via mechanisms induced by an altered genetic, biochemical and hormonal environment. Evidence has accumulated to prove that adipokines and epigenetic changes of fetal metabolic genes play a pivotal role in the causal pathway of childhood obesity[21].

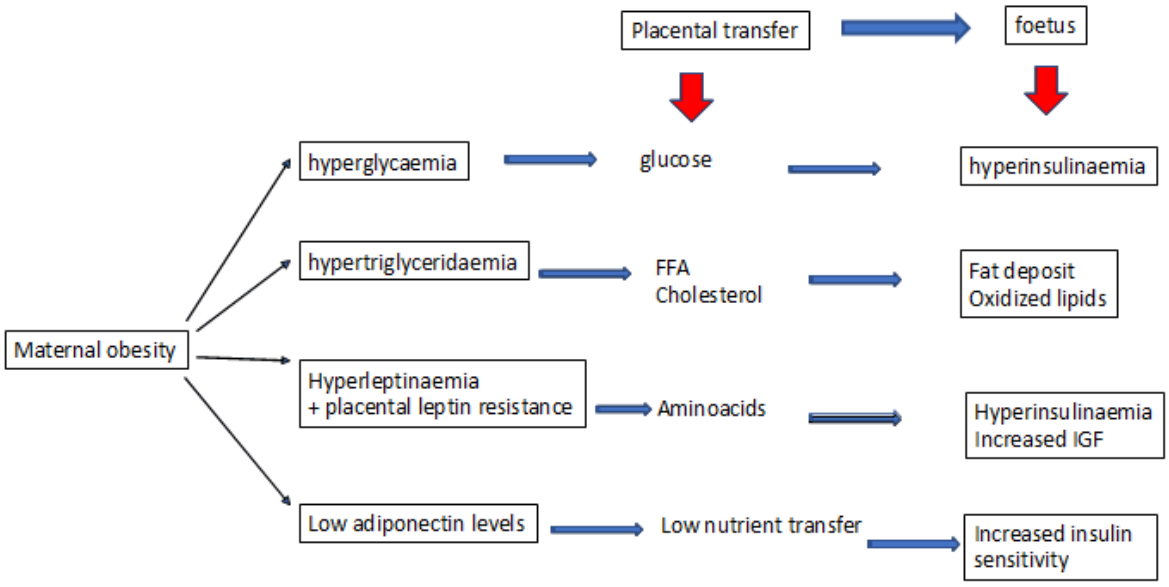

Figure 1: Postulate causal mechanisms of increased adiposity in offspring of obese mothers

Obesity during pregnancy is characterized by a state of hyperglycemia, hypertriglyceridemia and hyperinsulinemia associated with insulin resistance. This altered endocrine milieu results in increased plasma levels of free fatty acids, hence placental transfer and enhancement of fetal fat deposit[22].

Studies have shown that gestational weight gains both greater and lesser than the Institute of Medicine (IOM) recommendation have adverse metabolic effects on the offspring, irrespective of the pre-pregnancy BMI. Tam et al observed a 'U' shape relationship between maternal gestational weight gain and increased risk of insulin resistance, hypertension and low insulin sensitivity index in children whose mothers had gestational weight gains out of the IOM recommended range irrespective of the pre-pregnant BMI[23].

Subjects	Type of study	Maternal/cord blood variable	Offspring metabolic marker	Association	Reference
Newborns of mothers with normal or high BMI (n=61)	Cross-sectional	Cord blood leptin	Neonatal adiposity	Positive	Josefson et al[27]
Normal weight and obese pregnant mothers (n=121)	Cross-sectional	Cord blood leptin Maternal BMI	Neonatal adiposity Fetal insulin resistance Fetal insulin resistance	Positive Positive Positive	Catalano et al[28]
Mother-child pairs (n=76)	Cross sectional	Cord blood leptin	Weight gain in first five years	Positive	Anna Telschow et al[29]
Children at 3years and 7 years(n=510)	Cross sectional	Cord blood leptin	Early childhood weight gain	Positive	Boeke et al[30]
Mother-child pairs (n=186)	Cross sectional	Cord blood Leptin levels	Birth weight	Positive	Shekhawat PS et al[31]
Mother-child pairs (n=638)	Prospective cohort study	Cord blood leptin	Birth weight	Positive	Polyxeni Karakosta et al[32]
obese and non-obese mothers (n=133)	Prospective cohort study	Maternal BMI	Plasma Adiponectin	Negative	Maricella Haghiac et al[33]

Table 1: Association between maternal adiposity markers / cord blood adipokines with offspring metabolic markers

Cord blood adipokines and offspring obesity

Adipose tissue is now recognized as an endocrine organ, which secretes numerous bioactive peptides known as adipokines[24].

These adipokines have numerous roles in metabolic regulation including blood glucose homeostasis and energy balance regulation. Leptin is an adipokine which is important in regulation of body weight via regulation of appetite and energy expenditure. Cord blood leptin is recognized widely as an accurate biomarker of neonatal adiposity. In pregnancy, leptin is important in regulating satiety and energy metabolism and placentation. Adiponectin, an insulin-sensitizing adipokine, is less well studied than leptin. Maternal obesity is characterized by high leptin with low adiponectin levels.

Increased GWG is also associated with higher umbilical cord blood leptin levels independent of pregestational BMI status[25]. Low levels of adiponectin have shown to be associated with increased fetal growth[26].

Animal studies have shown that administration of adiponectin causes reduction in placental nutrient transfer by downregulating the expression of placental nutrient transporters. Adiponectin also inhibits the insulin/IGF-1 signaling mechanism[27]. A positive correlation between maternal and cord blood hyperleptinaemia with offspring adiposity has been demonstrated across several studies. However, there are studies that have revealed either a weak or absence of such correlation. Most of the studies have had small sample sizes. Table 1 summarizes the studies that have evaluated the association of maternal and cord blood adipokines with offspring adiposity.

The Avon longitudinal study of parents and children (ALSPAC study) is the largest published study to date which is a UK birth cohort followed up to 17 years of age. It showed that higher cord blood leptin levels were associated with higher z-scores of fat mass, waist circumference and BMI at 9 years of age. However, they concluded that the association was weak[34]. The study conducted by Shekhawat et al found that both LGA and IUGR infants were hyperleptinaemic[32]. Further studies are expected to enhance the understanding of the long-term effects of adipokines on offspring health and the interventions to minimize these effects.

Epigenetics and offspring adiposity

Epigenetics, the study of modifications to DNA that alter gene expression without changing gene sequence has been identified as another mechanism contributing to the early life development of excess adiposity and an adverse metabolic phenotype[35].

Epigenetic processes alter the openness of the transcriptional machinery to a particular gene, thereby determining whether the gene is active in a given cell at a given time or not. Another important fact is that although the DNA sequence of genes in an individual (the genome) is largely stable, the epigenome has the potential to be reversibly modified by exposure to a range of nutritional and environmental factors. Recent research has shown that maternal obesity, excessive GWG, maternal glycaemia, nutritional quality and physical activity during pregnancy are potential contributors of epigenetic changes (Table 2).

Intrauterine exposure to high levels of lipids as well as oxidative stress can lead to epigenetic changes in fetal metabolic genes that induce obesity in the offspring and related diseases later in life[36,37,38,39]. Table 2 summarizes the association of DNA methylation with maternal factors and offspring health.

Two recently published studies have focused on the impact of maternal nutrition before and during pregnancy on DNA methylation in the offspring[40]. The first study used a Gambian mother-child cohort to show that maternal malnutrition was associated with altered DNA methylation of growth and metabolism related genes in the infants[41]. The second study applied adult offspring from the Dutch Hunger Winter cohort to investigate the effect of prenatal exposure to an acute period of severe maternal under nutrition on DNA methylation of genes involved in growth and metabolism in adulthood. The results highlighted that the impact on the epigenome was significant with exposure during early gestation.

The UK newborn epigenetics study (NEST) that was conducted to determine the effect of maternal pre pregnancy obesity and fetal DNA methylation on offspring metabolic health revealed that methylation of

multiple CpG sites of the TAPBP were associated with higher blood pressure centiles at 4-5 years of age, though the results did not reach statistical significance[42].

Subjects	Maternal factor	Methylated gene and methylated site	Offspring adiposity marker	Association	Reference
Mother-child dyads (n=259)	Hyperglycaemia	placental *LEP* DNAm (25 5'-C-phosphate-G-3' (CpG) sites)	Adiposity at 3years	Positive	Gagné-Ouellet V et al[40]
Mother-child pairs (n=114)	Pre-pregnancy BMI	Placental *LEP* DNAm	Offspring birth weight, adiposity	Positive	Kadakia R et al[41]
Cord blood (n = 877) 12-month (n = 734)	Preeclampsia Hyperglycaemia	*LEP*DNAm in cord blood	Offspring birth weight	Positive	Mansell T et al[42]
Mother-child pairs (without gestational diabetes) (n = 172)	Hyperglycaemia	PRDM16, BMP7, CTBP2, and PPARGC1α gene loci Cross sectional study Cross sectional study Cross sectional study	Cord blood leptin	Positive	Côté S et al[43]
Obese mothers with a non-obese control sample (n=50)	Pre-pregnancy BMI	LEP promoter ADPOR2	Leptin Adipoleptin	Negative	Perrine Nogues et al[44]
Multiple birth cohorts (n=1040)	Preecclampsia Smoking	Multiple CpG sites HMBOX1 gene	Offspring birth weight	Positive	E Antoun et al[45]
Mother-infant pairs (n=484)	Maternal physical activity	*PLAGL1* DMR	Offspring birth weight	Negative	Lauren E McCullough et al[46]

Table 2: Association between maternal factors with cord blood DNA methylation and offspring adiposity

Association of maternal lifestyle factors with offspring adiposity

Regular physical activity during pregnancy is shown to be associated with improved fetal growth. A meta-analysis of randomized controlled trials show that supervised prenatal exercises reduce the odds of having a large for gestational age baby by 31% [50]. McCullough et al explored the association between prenatal physical activity, birth weight and offspring DNA methylation of metabolic genes among 484 mother-infant pairs. They found that infants born to mothers with longer non-sedentary times had lower birth weights compared to mothers with shorter non-sedentary times. The study also gives evidence that maternal physical activity leads to epigenetic changes of the fetus that potentially improve long-term health of the offspring[47]. Anna Telschow et al[30] has reported that the cord blood leptin level is influenced by maternal physical activity. Therefore, they suggest that an active and healthy maternal lifestyle may play a pivotal and beneficial role in the offspring's weight development. However, larger studies are needed to provide further understanding on the effect of maternal lifestyle on offspring adiposity and metabolic health.

The association between postnatal growth acceleration and childhood obesity

Rapid postnatal weight gain particularly during infancy and the second year of life has shown to be associated with later obesity [51,52].

The UK Millennium Cohort study (n=10,637) demonstrated higher BMI trajectories in children who experienced rapid weight gain in early life[53]. While epigenetic mechanisms have been implicated in the development of NCDs in later life through fetal programming, recent epidemiological research points out that nutritional manipulation during early infancy could prevent accelerated post-natal growth and associated adverse metabolic health outcomes [54].

The 1990 IOM report placed an emphasis on birth outcomes that are chiefly related to low birth weight, which was a particular concern at that time and infant nutrition was focused more on achieving catch up growth. Catch up growth in SGA infants is defined as achieving a height at 2 years of age of more than -2SD for chronological age [55].

Clinical trials done on preterm as well as term newborn infants have suggested that nutrient-enriched, calorie dense diet is associated with rapid post-natal growth and later development of insulin resistance and high blood pressure [56,57]. Therefore, the current trend in early childhood nutrition has moved towards the impact on the long-term health outcomes rather than weight gain alone [58].

Prevention of childhood obesity through early life interventions

The aim of this review is to highlight the importance and the windows of opportunity that exists during the pre-conceptual period, pregnancy and postnatal life to apply well designed interventions to modulate the early origins of childhood obesity.

Figure 2 shows some of the plausible strategies that have shown potential to modify the unfavourable trajectories during these critical periods of life.

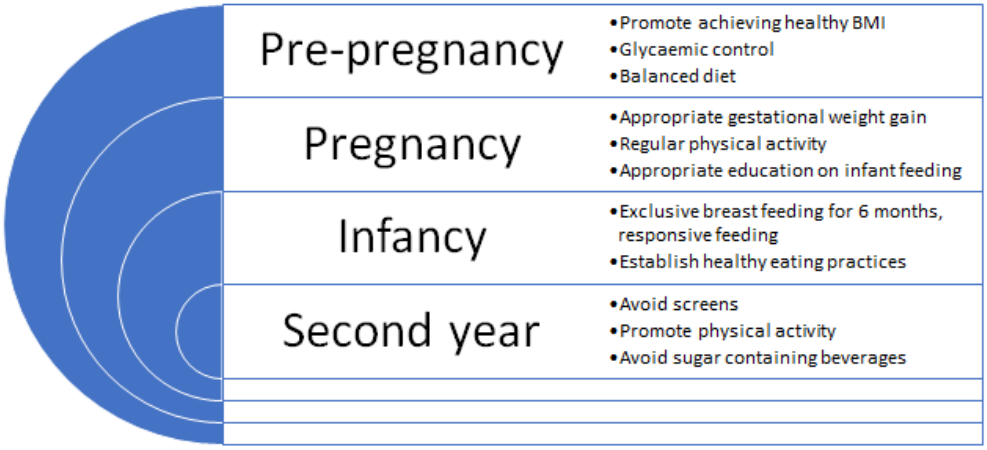

Figure 2: Strategic prevention of childhood obesity through interventions during the periods of developmental plasticity

Implementation of such preventive measures will need a well-planned integrated multicomponent approach involving multiple stakeholders through re-setting of societal standards [59,60].

Interventions to prevent pre-conceptual obesity

The affliction of a fate of later-life risk of obesity upon the newborn infant creates a vicious cycle at epidemic level. Therefore, prevention of maternal obesity takes priority in reversing the tide on the obesity epidemic. Systematic reviews on diet and lifestyle interventions and drugs like metformin to manage weight during pregnancy have not shown promising outcomes, highlighting that the interventions during the 2nd and 3rd trimesters of pregnancy could be too late [61,62]. Prevention of maternal obesity should therefore focus on the reduction of BMI prior to conception. Post-partum period can be considered as a window of opportunity to implement weight control/reduction interventions and encourage women to obtain a healthy BMI prior to the next pregnancy. The basis behind this is, obesity associated lipogenesis and adipose tissue inflammation that leads to altered intrauterine metabolic and endocrine milieu start in the first trimester itself, meaning that, interventions in later stages of pregnancy may be rather too late to be effective [63]. Randomized controlled trials exploring the possible impact of antenatal lifestyle modification on offspring's birthweight and infant adiposity showed a significant reduction in the number of high birth weight newborns and reduced subscapular skinfold thickness at 6 months of age [64] .

In 2009, the IOM revised the GWG guidelines, on the basis of the incidence of obesity in the reproductive age. The recommendation was to primarily meet the obligatory accrual of water and protein [65]. The IOM allows interventions to reduce weight during lactation and states that losing as much as 2kg/month does not affect the milk volume but daily energy restriction should not exceed 1800 kcal. Studies have shown that such weight loss can safely be achieved in obese lactating women by an energy deficit of 500kcal/ day along with 4 days per week of aerobic exercises [66,67,68,69].

Current recommendations from western countries include supervised weight reduction prior to conception and bariatric surgery. The application of these interventions to low- and middle-income countries need further evaluation considering the availability of expertise and facilities [70,71].

Interventions to prevent rapid weight gain in infancy

Exclusive breast feeding within the first 6 months of life is considered with high priority in obesity prevention. Many studies have revealed that the benefit of breast milk is not only nutritional, but rather has biological effects that influence an individual's long-term health and development. Breast feeding in comparison to formula feeding has an attenuating effect on increased weight gain and this protective effect of breast feeding on later obesity has been repeatedly shown across the studies [72,73].

The effect of the timing and composition of complementary feeding on childhood obesity have not been elucidated yet. However, avoiding over feeding and excess energy consumption are important in preventing high weight gain during complementary feeding.

The baseline results of the NOURISH randomized trial on feeding intervention to prevent RWG identified formula feeding and feeding to schedule as modifiable risk factors [74].

Similarly, lifestyle interventions addressing nutrition and physical activity during early life particularly in infants who were exposed to adverse intrauterine conditions would potentially prevent accelerated weight gain and future risk of obesity. The US "INSIGHT" randomized controlled trial that assessed the effectiveness of responsive parenting on preventing RWG, revealed a significant slowing of weight gain in the intervention group [75].

Together, the available evidence points out the potential of nutritional manipulation in early years in the prevention of later obesity.

The way forward to prevent childhood obesity

Low and middle-income countries need to take prevention of childhood obesity with high priority due to the foreseeable scale of burden of NCD in this region. The BMI cut-offs for the Asian population may affect the policy-making in these communities. Considering the variations in body compositions between ethnicities and the higher prevalence of gestational diabetes at a relatively low BMI for Asian populations, WHO is yet to endorse lower criteria for the classification of obesity in Asian women [76,77]. Additionally, the relationship between metabolically healthy obesity in pregnancy and offspring health need further evaluation [78].

It appears that interventions during the preconceptual period, pregnancy and the first two years of life can have a considerable impact on childhood obesity. A latest review of prenatal interventions states that initiation of combined interventions early in pregnancy may decrease adiposity in the offspring [79].

However, information is lacking on preventive strategies from low and low-middle income countries which should be developed based on further research in their own communities.

Obesity being a public health problem spread across all types of communities, lifestyle modification will remain the mainstay of treatment and prevention. Bariatric and metabolic surgery may not be an attractive option in most LMI countries due to lack of facilities and expertise. National level implementation of policies through governmental leadership to reform obesogenic environments, attitudes towards healthy eating and physical activity of children would pave the way towards permanent societal changes [80,81].

Finally, the most cost-effective approach to curb the obesity epidemic and strengthen the human capacity would be to establish a robust preventive program focusing on primordial prevention which could not only prevent childhood obesity, but also build up a metabolically healthier adult population.

Our intension through this review is to encourage community-wide research from LMI countries to explore the best ways for primordial prevention of child hood obesity.

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