Maternal and Infant Implications of Excessive Gestational Weight Gain among Obese Pregnant Women

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Abstract

The global obesity epidemic affecting women of reproductive age is a well-established contributor to adverse maternal and infant outcomes. Overweight and obese pregnant women are more likely to experience excessive gestational weight gain (EGWG). EGWG is associated with higher postpartum weight retention, lactation failure and long-term risk of weight-associated diseases including type 2 diabetes mellitus (T2DM) and metabolic syndrome. Furthermore, maternal EGWG is an independent predictor for childhood obesity in affected offspring.

In 2009, the United States Institute of Medicine (IOM) published new recommendations for gestational weight gain to determine adequate weight gain intervals according to the pre-pregnancy body mass index (BMI). Recent observational studies have consistently shown that the majority of overweight and obese pregnant women gain weight above the current IOM recommendations. Non-pharmacologic interventions such as diet and exercise are currently first-line strategies in the management of obesity and prevention of EGWG. However, the evidence supporting clinical effects of these interventions is scarce and in many ways conflicting.

We review in detail the effects of EGWG among obese and overweight pregnant women on both maternal and infant outcomes and propose new areas of future research on novel interventions to prevent EGWG in this high risk population.

ABBREVIATIONS

EGWG: Excessive Gestational Weight Gain; T2DM: Type 2 Diabetes Mellitus; IOM: Institute of Medicine; BMI: Body Mass Index

INTRODUCTION

Obesity is a major public health problem [1]. In the United States, more than half of pregnant women are overweight and one third are obese [2]. Furthermore, 8% of all women of reproductive age have class 3 obesity (body mass index >40 kg/m²) putting them at risk of adverse pregnancy outcomes [3]. Sedentary lifestyles, poor nutritional habits and lack of prenatal care further steepen the slope of weight gain during pregnancy. In 2009, the United States Institute of Medicine (IOM) published new recommendations for gestational weight gain according to the pre-pregnancy body mass index (BMI) to optimize obstetrical outcomes (Table 1) [4]. Approximately 35% of normal weight women and 60% of overweight and obese women gain more than the specified recommendation during pregnancy [5–9].

MATERNAL MORBIDITY RELATED TO OBESITY AND EXCESSIVE GESTATIONAL WEIGHT GAIN

Maternal obesity is an independent risk factor for adverse pregnancy outcomes including: increased risk for pregnancy-related hypertension, gestational diabetes mellitus (GDM), complications during labor and delivery, increased postpartum weight retention, higher weight status in subsequent pregnancies, increased risk for unsuccessful breastfeeding and subsequent obesity related diseases later in life such as type 2 diabetes mellitus (T2DM) and cardiovascular disease [4,10] (Box 1). The frequency and severity of these adverse outcomes is further increased when obese women gain weight above the recommended ranges [4].

Preeclampsia is a condition affecting approximately 5% of all pregnancies, marked by hypertension and proteinuria, which can lead to significant morbidity and mortality. Importantly, up to 50% of the study population was obese or gained excessive weight during the first 28 weeks of gestation was a significant predictor of GDM. The anabolic effects of gestational weight gain (EGWG) on the development of glucose intolerance and therefore GDM. It is well established that women classified according to the 1998 National Institute of Health (NIH) obesity classes. The researchers found that overweight and obese women had significantly unadjusted OR of 2.25 to 4.25 times higher, respectively, than normal weight women for pregnancy-related hypertension disorders and 1.25 to 3.45 times higher for preeclampsia. In a study of 481 Danish women, the authors found a statistically significant trend for development of pregnancy-related hypertension (P < 0.001) with increasing weight using < 5 kg as the reference for weight gain. Finally, a U.S. study examined birth certificate data for 120,251 obese women classified according to the 1998 National Institute of Health (NIH) obesity classes. The researchers found that the amount of weight gain associated with minimal risk for preeclampsia differed by class of obesity but that, in all classes, a gain of less than 15 pounds was protective. As a note, women with hypertension and preeclampsia may have significant edema due to their underlying condition, thus increasing their weight. Therefore, the excessive GWG may be secondary to the hypertension, rather than the cause of it.

Antepartum morbidity

There is biologic plausibility for an effect of excessive gestational weight gain (EGWG) on the development of glucose intolerance and therefore GDM. It is well established that women who are obese at the time of conception tend to develop a more pronounced insulin resistance and are at greater risk of developing GDM (OR 8.56; 95% CI 1.17-1.92) among women who entered pregnancy at a BMI ≥ 35 kg/m² [19]. Gaining more than 16 kg during pregnancy was associated with increased likelihood of developing preeclampsia (OR 1.50; 95% CI 1.17-1.92) among women who entered pregnancy at a BMI ≥ 35 kg/m² [19].

Intrapartum morbidity

Current evidence supports a strong association between EGWG and gestational hypertension, preeclampsia, and eclampsia. The risk for pregnancy-related hypertension is greater among women who enter pregnancy overweight or obese. Preeclampsia is about three times as prevalent among overweight and obese women [15,16]; and the severity of the disease is more pronounced as BMI increases [17]. Indeed, obese women with EGWG are 10 times more likely to develop gestational hypertension than their normal weight gain counterparts [18]. A prospective cohort study from Sweden examined the relationship of weight gain by pregravid BMI on pregnancy outcomes for 245,526 women who delivered term infants between 1994 and 2002 [19]. Gaining more than 16 kg during pregnancy was associated with increased likelihood of developing preeclampsia (OR 1.50; 95% CI 1.17-1.92) among women who entered pregnancy at a BMI ≥ 35 kg/m². In a retrospective cohort study of 603 women in Canada, Brennand et al., found that overweight and obese women had significantly unadjusted OR of 2.25 to 4.25 times higher, respectively, than normal weight women for pregnancy-related hypertension disorders and 1.25 to 3.45 times higher for preeclampsia [20]. In a study of 481 Danish women, the authors found a statistically significant trend for development of pregnancy-related hypertension (P < 0.001) with increasing weight using < 5 kg as the reference for weight gain [21]. Finally, a U.S. study examined birth certificate data for 120,251 obese women classified according to the 1998 National Institute of Health (NIH) obesity classes. The researchers found that the amount of weight gain associated with minimal risk for preeclampsia differed by class of obesity but that, in all classes, a gain of less than 15 pounds was protective. As a note, women with hypertension and preeclampsia may have significant edema due to their underlying condition, thus increasing their weight. Therefore, the excessive GWG may be secondary to the hypertension, rather than the cause of it.

Box 2: Complications of Obesity and Excessive Gestational Weight Gain on the Child.

A. Short-Term Neonatal Morbidity

- Stillbirth
- Perinatal death
- Increased rates of large for gestational age fetuses and macroglossia

B. Long-Term Child Morbidity

- Increased risk for long-term obesity
- Higher incidence of metabolic-related conditions (i.e. type 2 diabetes mellitus, hypertension, cardiovascular disease)
- Increased lifetime risk of attention-deficit hyperactivity disorder

Table 1: Institute of Medicine Weight Gain Recommendations During Pregnancy§.

<table>
<thead>
<tr>
<th>Pre-pregnancy Weight Category</th>
<th>Body Mass Index*</th>
<th>Recommended Range of Total Weight Gain†</th>
<th>Recommended Rates of Weight Gain in the 2nd and 3rd Trimesters§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>28-40</td>
<td>1 (1-1.5)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
<td>25-35</td>
<td>1 (0.8-1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>15-25</td>
<td>0.6 (0.5-0.7)</td>
</tr>
<tr>
<td>Obese (includes all classes)</td>
<td>≥ 30</td>
<td>11-20</td>
<td>0.5 (0.4-0.6)</td>
</tr>
</tbody>
</table>

*Body mass index is calculated as weight in kilograms divided by height in meters squared or as weight in pounds multiplied by 703 and divided by eight in inches.
†Range in pounds.
§Data presented as mean range (pounds/week).

and increased risk for dystocic labor patterns ultimately leading to operative delivery [4]. Obese women are more likely to require induction of labor, in greater part due to increased prevalence of prolonged gestations, comorbidities such as hypertensive disorders and diabetes [22]. Several studies report a modest association between EGWG and failure of labor induction as well as significant increase in the length of labor [21,23-27]. Indeed, in a trend analysis of a longitudinal retrospective study, Johnson et al. found a higher risk of labor abnormalities with increased weight gain, suggesting that a difference of 10 pounds corresponds to an OR of 2 (P < 0.001) after adjusting for BMI, patient care (private vs. non-private), parity, infant sex, hypertension and macrosomia [28]. A retrospective case-control study in Ireland also found that EGWG was a significant predictor of shoulder dystocia (OR 2.0; 95% CI 1.6-2.2; P = 0.015) [29].

Substantial research has been conducted on the association between obesity, EGWG and mode of delivery. Almost universally, obesity has been shown to be associated with increased rates of planned or emergent cesarean delivery [30]. In a large population-based study limited to primary cesarean deliveries, Rosenberg et al. found a significant association between gestational weight gain and cesarean delivery (aOR 1.38; 95% CI 1.34-1.41) [31]. Two additional studies in multiparous women accounted for route of prior delivery. One study identified the progression of aOR of cesarean delivery for every 5 pounds of gestational weight gain to be 1.09 (95% CI 1.07-1.11) [32]. The second study calculated the attributable risk for cesarean delivery of gaining more than 16 kg to be 6.9% [33]. Jensen et al. reported that, compared with cesarean delivery for obese women gaining < 5 kg, the aOR for cesarean delivery among women gaining ≥15 kg was 3.60 (95% CI 1.60-7.80) [21]. In addition, the use of instrumental delivery is not uncommon for delays in labor among obese women, particularly those with EGWG [19,24,27,34-35]. Intrapartum fetal distress has also been reported as more likely, and a reason for emergent cesarean delivery in this group of women [36].

High BMI at the time of conception and EGWG also affect those who attempt a trial of labor after cesarean (TOLAC). Obese women who gained more than 40 pounds during pregnancy were also less likely to achieve a successful vaginal birth after cesarean (VBAC) than women who gained ≤40 pounds (OR 0.65; 95% CI 0.42-0.98) [37]. This study controlled for previous normal spontaneous vaginal delivery, previous VBAC, diabetes, induction, birthweight > 4,000 grams, recurrent indication, one layer closure, pregnancy complications and BMI.

Postpartum morbidity

Obesity and EGWG is associated with a myriad of complications in the postpartum period. EGWG is positively associated with excessive weight retention in the puerperium and with interpregnancy weight gains [38-43]. In fact, each kilogram of gestational weight gain at ≤20 weeks, 21-30 weeks, and 31 weeks to term was significantly associated with an increase of 0.86 (±0.05), 0.68 (±0.07), and 0.49 (±0.07) kg at 6 weeks postpartum, respectively [38]. In a study that measured body weight, body fat mass and skinfold thickness from 13 weeks’ gestation through 6 months postpartum showed that, compared with normal-weight women, obese women with EGWG have significant increases in total skinfold thickness between 36 weeks’ gestation and 6 months postpartum, and in waist-to-hip ratio between 6 weeks and 6 months postpartum [44]. Another study reported that among women within the upper tertile for gestational weight gain (mean 16.0 ± 3.7 kg), approximately 39% had an increase in BMI category at 1 to 3 months postpartum compared to only 5% among women within the lower and middle tertiles for gestational weight gain (mean 3.7 ± 2.9 kg and 9.4 ± 1.3 kg, respectively) [45]. This trend persisted in the intermediate term (3 months to 3 years postpartum), and affected future pregnancies [39,40,44,46]. In a cross-sectional study, Hunt et al. examined the effect of self-reported weight gain from multiple pregnancies on the development of morbid obesity in a group of morbidly obese women, who were not morbidly obese prior to their first pregnancy and compared them to population-based controls [43]. Women who became morbidly obese gained significantly more weight during their first pregnancy than controls (16.4 kg vs. 12.6 kg, respectively; P < 0.05), and they retained significantly more weight after their first and second pregnancies than controls (7.1 kg and 5.9 kg vs 3.1 kg and 2.9 kg, respectively; P < 0.05). Breastfeeding performance and duration of lactation were also affected by obesity and EGWG, contributing in part to the risk for retained weight postpartum [47-49].

Long-term maternal morbidity

A direct association between EGWG among overweight and obese gravidas and metabolic disorders including T2DM, chronic hypertension, cardiovascular disease and cancer is biologically plausible, although still unclear [4,50,51]. It is well established, however, that obesity is associated with increased morbidity and mortality from these chronic illnesses. In a recent analysis from prospectively collected data, Rooney et al. studied 484 women to estimate the impact of perinatal weight change on obesity, postpartum weight-gain, and development of obesity-related illnesses up to 15 years after pregnancy [51]. The authors reported that across all BMI categories at the 15-year follow-up, 38% of obese women developed T2DM against only 2% of those with normal weight. Furthermore, 51% of obese women were diagnosed with heart disease against only 17% of those with normal weight. Conceivably, the longer the follow-up, the greater the possibility that other lifestyle factors affected the impact of EGWG on the development of disease. However, the authors found that the ability to control weight during pregnancy correlated well with weight control in the long-term. The authors therefore concluded that EGWG and failure to lose weight postpartum were strong indicators of persisting obesity and were indirectly associated to metabolic diseases later in life.

There is a modest association between EGWG and risk of maternal breast cancer. Specifically, a retrospective cohort study of 2,089 Finnish women showed a positive relationship between weight gain in the upper tertile (>15 kg) and post-menopausal breast cancer risk after adjustment for pre-pregnancy BMI (RR 1.62; 95% CI 1.03-2.53) [52].

INFANT MORTALITY RELATED TO MATERNAL OBESITY AND EXCESSIVE GESTATIONAL WEIGHT GAIN

For many years, maternal obesity has been classically...
associated with alterations in fetal growth patterns, increased risk of stillbirth and perinatal death. It is important to note, however, that in recent years researchers have recognized that EGWG leading to higher birth weight is also associated with later obesity and its consequences in affected offspring (Box 2). The ways in which EGWG could influence obese-related child health outcomes are linked to fetal developmental programming, allowing pregnancy to be a unique timeframe for intervention [4].

**Short-term neonatal morbidity and morbidity**

High pre-pregnancy BMI has classically been associated with increased rates of stillbirth and perinatal death. However the association of EGWG with both of these outcomes is less clear [4]. Biological pathways are conjectural, and it is not possible to disentangle the intrinsic effects of obesity and EGWG. Indeed, biologic plausibility links EGWG with obesity-related diseases in pregnancy that mediate an association with stillbirth and perinatal death, such as GDM or pregnancy related hypertensive disorders [53]. Chen et al., examined maternal pre-pregnancy BMI and gestational weight gain among 4,265 infant deaths and 7,293 controls [54]. When obese women gained weight above the IOM recommendations, the aOR for infant deaths was 2.87 (95% CI 1.98-4.16) when compared to controls.

The effects of pre-pregnancy BMI, gestational weight gain, obesity and diabetes in pregnancy on fetal growth are well documented [4]. Recently, Kim et al., reviewed 660,396 Florida birth certificates and hospital discharge data to estimate the contribution of EGWG on the rates of large for gestational age (LGA) infants by race or ethnicity [55]. The authors found that the prevalence of LGA was 17.3% among women with GDM, 13.5% among those with EGWG, and 12.6% among those who were overweight or obese. In obese women in different BMI categories (normal, overweight, obese class I, obese class II and obese class III) with no diabetes and adequate gestational weight gain, LGA prevalence was 5.7%, 7.0%, 8.6%, 11.5% and 13.9%, respectively. The prevalence of LGA was highest among class III obese Asian/Pacific Islanders (29.2%) Whites (24.9%) and Hispanics (18.4%). These results led the authors to conclude that, across all race or ethnic groups, the factor that contributed the least to the fraction of LGA neonates was GDM (2.0-8.0%); and the factor contributing the most was EGWG (33.3-37.7%).

**Long-term infant morbidity**

It has been hypothesized that relative amounts of adiposity and lean mass in fetal and neonatal life are important in setting long-term cardio-metabolic trajectories [4]. In a recent study by Catalano and Ehrenberg, which combined data from diabetic and non-diabetic woman (total n = 415), gestational weight gain was directly associated with both lean and fat mass at birth [56]. The latter results are consistent with those of Udall et al., who found a direct association between gestational weight gain and the sum of 8 neonatal skinfold measurements among 109 non-diabetic mothers delivering term infants; an association that was independent of pre-pregnancy weight, gestational age, smoking, and family history of diabetes [57].

Excessive weight gain during infancy is associated with obesity and obesity-related diseases later in life. Oken et al., analyzed data from a prospective study of predominantly non-low-income pregnant women and their children in Massachusetts [58]. Among 1,044 mothers included in this analysis, 51% gained excessive, 35% adequate and 14% inadequate weight during pregnancy. Compared with inadequate gestational weight gain and after controlling for key covariates, adequate and excessive gains were associated with ORs of 3.77 (95% CI 1.38-10.27) and 4.35 (1.69-11.24), respectively for obesity at 3 years of age. In addition, by analyzing total weight gain in 5-kg increments, the authors found higher BMI z-scores, higher sums of triceps and subscapular skinfold thickness, and higher systolic blood pressure in children born to women who had EGWG. In another study, Li et al., empirically derived three weight gain trajectories through childhood and found that EGWG was a predictor of early-onset overweight that persisted throughout childhood [60]. Adjusting for maternal BMI and other factors, the authors found that total weight gain of at least 45 pounds (versus 25-35 pounds) was associated with a relative risk of 1.7 for being in the early-onset rather than in the normal trajectory class. Similarly, Moreira et al., found that total gestational weight gain was directly associated with childhood overweight as defined by the International Obesity Task Force standards [61-62]. Overall, each 5-pound increment in gestational weight gain was associated with an OR of 1.09 (95% CI 1.06-1.13) for obesity.

The effects of maternal obesity and EGWG seem to extend beyond the cardio-metabolic morbidities in the offspring. Two lines of evidence link EGWG to cancer. In a meta-analysis by Hjalgrim et al., the authors estimated that the odds for acute lymphoblastic childhood leukemia (ALL) were higher (OR 1.26, 95% CI 1.17-1.37) for infants with birth weight over 4,000 grams compared to non-macrosomic counterparts [64]. Although not statistically significant, results were of similar magnitude for acute myelogenous leukemia (AML). Similarly, using birth certificates and after multivariate logistic regression analyses, McLaughlin et al., found that total gestational weight gain > 14 kg conferred an increased risk for ALL (OR 1.31; 95% CI 1.07-1.60) [65]. In this study, no association was noted between EGWG and AML. The authors speculated that EGWG could result in higher fetal exposure to insulin-like growth factor 1 (IGF-I), which in turn may increase the risk of childhood ALL. Based on these results and because of the established relationship between obesity, EGWG and macrosomia, it is plausible that EGWG may be related to childhood leukemia.

Observational studies show direct associations between EGWG and development of breast cancer in the offspring [66-68], presumably due to aberrant circulating hormone levels. EGWG was associated with lower levels of maternal progesterone and of sex hormone-binding globulin (-0.7%; 95% CI -1.5-0.0) at 16 weeks and (-1.2%; 95% CI -2.0 to -0.4) at 27 weeks for every 1 kg increment in gestational weight gain [69]. This finding provides some support for the hypothesis that EGWG could lead to elevated breast cancer risk in the offspring.
Adverse effects on neurodevelopment associated with obesity and EGWG have also been described, although the literature on the topic is scarce. Because the human brain develops rapidly during both gestation and early postnatal period, it has been postulated that maternal body fat reserves and gestational weight gain can influence fetal neuroplasticity, particularly during organogenesis. After multivariate linear regression analyses, Rodriguez et al. showed that among women with a high-prepregnancy BMI, EGWG (measured weekly and in 100 g increments) was associated with increased odds of child attention deficit hyperactivity disorder (ADHD) (OR 1.24; 95% CI 1.07–1.44) [70]. The mechanisms for these effects are unknown, although the authors speculated on the possibility of neurotoxin transfer from maternal adipose tissue to the developing fetal brain.

INTERVENTIONS TO REDUCE EXCESSIVE GESTATIONAL WEIGHT GAIN AND RETAINED GESTATIONAL WEIGHT POSTPARTUM

Unfortunately, the best strategy to prevent EGWG has not been defined. Recent reviews and meta-analyses of the literature have concluded that dietary and physical activity interventions produce generally only small reductions in gestational weight gain [71–76]. This is particularly true among overweight and obese women who also have a lower adherence to exercise programs [77].

Lifestyle modifications focused on nutrition and exercise are first-line therapies for prevention and control of diabetes in obese, non-pregnant women [78,79]. Numerous trials demonstrate that educational counseling sessions may have some immediate effects, but are not able to sustain behavioral changes that produce long-term health benefits [14]. Similar studies have been conducted in the postpartum period.

A Cochrane review was recently published in 2007 [80]. Six randomized controlled trials involving 245 women showed that women who exercised did not lose significantly more weight than women in the usual care. Women who took part in a diet program or who had diet and exercise lost significantly more weight than women with usual care, [mean weight difference: diet alone group -1.70 kg (CI -2.08 to -1.32) vs. diet and exercise group -1.93 kg (CI -2.96 to 0.89)]. Others have shown that such lifestyle interventions were effective in increasing the proportion of women who were able to achieve their pre-pregnancy weight and thus eliminate their retained postpartum weight [74,81]. An important finding among all these studies is the high dropout and attrition rate which likely contributes to the inability to achieve sustained weight loss. Despite the multiple randomized controlled trials conducted to reduce postpartum weight retention, the authors unanimously suggest that new innovations need to be investigated to achieve weight loss including medical therapies.

These reviews concurred that there was an urgent need for high quality randomized controlled trials (RCTs) that conform to known standards for methodological quality (i.e. CONSORT). Further studies are needed to examine mechanisms linking successful lifestyle modifications as well as novel pharmacologic interventions to reduce EGWG among obese women.

DISCUSSION AND CONCLUSION

Improvement of maternal, fetal and child health are major public health goals. One of the most serious issues that practitioners and researchers have faced over the past four decades is the increase in the prevalence of obesity among women of childbearing age [1]. Approximately 60% of obese pregnant women gain more weight than recommended during pregnancy [4,9]. This in turn is associated with higher postpartum weight retention and plausibly long-term risk of obesity-associated diseases including T2DM and metabolic syndrome. Furthermore, maternal EGWG is an independent predictor for childhood obesity in affected offspring.

Maternal motivation for a healthy newborn represents a unique opportunity to implement lifestyle modifications and medical interventions to control EGWG among obese gravidas [82]. Indeed, achieving a reduction on EGWG would improve maternal immediate and long-term outcomes. Obesity is directly associated with increased risks for GDM and preeclampsia and reductions in the rate of EGWG may mitigate the onset of these complications. Appropriate gestational weight gain may reduce the need for operative delivery and incidence of birth injuries. Limited postpartum weight retention may lead to greater control over weight management in the future and would decrease pre-pregnancy BMI in subsequent pregnancies. It is plausible that weight gain within the current recommendations may decrease long-term maternal cardio metabolic risks. Finally, the development of feasible and acceptable interventions designed to facilitate limited weight gain in pregnancy may result in decreased costs of health services in the long-term.

Adequate gestational weight gain among obese gravidas would likewise improve neonatal immediate and long-term outcomes. Weight gain within the IOM recommendations would reduce the rates of LGA, macrosomia and may even decrease the incidence of perinatal death. Newborns may also benefit from a better and more sustained lactation period. In the long-term, prevention of EGWG would decrease the rates of childhood obesity and obesity-related diseases later in life.

Non-pharmacologic interventions such as diet and exercise are currently first-line strategies in the management of obesity and prevention of EGWG. However, the evidence supporting clinical effects of these interventions is scarce and in many ways conflicting. There is an urgent need of novel pharmacologic and non-pharmacologic interventions to mitigate the effects of EGWG among obese and gestational diabetic women in addition to diet and exercise. Recent reports have analyzed Metformin for weight management purposes in pregnancy and postpartum [83–85]. Metformin has a high safety profile and is widely used in the management of PCOS and GDM, and recent reports suggest that it may delay the onset of T2DM in women who had GDM [86]. In the Metformin in Gestational Diabetes (MiG) study, which compared the effect of metformin versus insulin in women with gestational diabetes [83], weight gain in pregnancy was lower in the metformin group (difference of 1.6 kg, P = 0.001). By age two, offspring of the participants randomized to metformin had greater subcutaneous fat, but overall body fat was the same as in children whose mothers were treated with insulin alone, suggesting that the “metformin offspring” have smaller deposits of visceral,
metabolically active fat [84]. However, even recent interventional trials involving metformin report challenges such as medication adverse effects and adherence [85]. Further research is required to examine the role of this and other pharmacologic interventions in preventing EGWG, whether their effects persist into later life, and whether children exposed to metformin will be more insulin sensitive. In the meantime, adequate patient counseling about the importance to adhere to the current IOM recommendations along with lifestyle modifications to prevent EGWG is paramount.

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