HORMONES 2015, 14(3):345-357

Review

Effect of maternal obesity on pregnancy outcomes and long-term metabolic consequences

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INTRODUCTION

Recent years have witnessed a worldwide increase in the prevalence of pre-pregnancy maternal obesity. A survey carried out in the USA between 2003 and 2006 reported that 32% of women aged 20-44 years were classified as obese (WHO 2009).[1] The rise in obesity among pregnant women goes hand in hand with the upward trend of obesity in the general population. In addition, the percentage of women gaining excessive weight during pregnancy has also increased.[2,3]

The accumulation of intra-abdominal (visceral) fat, which obesity entails, results in a set of metabolic disorders. Obesity during pregnancy has detrimental effects on women's health because it is associated with increased risk for gestational diabetes mellitus (GDM), hypertension and preeclampsia. Furthermore, the increase of maternal obesity goes in parallel with the increase of birth weight. A study conducted in Denmark showed that mean birth weight increased by 45 g, from 3474 g in 1990 to 3519 g in 1999. Moreover, the percentage of neonates heavier than 4000 g increased from 16.7% in 1990 to 20% in 1999.[4] Similar results were published in the United States, with a mean increase of 116 g in birth weight from 1975 to 2003.[5] Increased birth weight has been mainly attributed to increased neonatal adiposity at birth,[6] which in turn is predictive of increased adiposity in childhood.[7] Maternal pre-gravid obesity is considered as the strongest predictor of childhood obesity[7] and is postulated to create an adverse endometrial environment which predisposes the offspring to obesity, diabetes and cardiovascular disease in later life. Gestational weight gain is also a potential risk factor for childhood obesity.[8] These findings may partially explain the spectacular increase of childhood and adolescent overweight and obesity in our time.[9]

There is large body of literature exploring maternal obesity and its short- and long-term consequences on the offspring.[10-16] Several systematic reviews and meta-analyses confirm the association of pre-pregnancy overweight/obesity with the risk for high birth weight (HBW), large-for-gestational-age (LGA) neonates, macrosomia and subsequent offspring overweight/obesity,[17,18] while others provide limited evidence to support the aforementioned association.[19] Furthermore, there are still important gaps in the literature that need to be assessed such as the pathophysiological mechanisms involving the maternal obesity effects with adverse pregnancy outcomes and future metabolic consequences for the fetus; the development of markers or algorithms for early prediction (from the beginning of pregnancy) of these adverse pregnancy outcomes, such as gestational diabetes and preeclampsia; establishment of criteria and cor-

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Received: 22-05-2014, Accepted: 30-01-2015

responding management for the pregnancy-acquired weight in specific groups at risk (e.g. pregnant women with pre-pregnancy BMI >40). Lastly, there are no interventional randomized controlled studies which associate the effect of maternal pre-pregnancy weight with pregnancy outcomes.

This nonsystematic review investigates the effect of pre-gravid and pregnancy-acquired (excessive gestational weight gain) maternal obesity upon pregnancy outcomes and its long-term consequences on offspring morbidity. An effort has been made to unfold the potential pathophysiological mechanisms underpinning the programming of obesity and of the resulting cardiometabolic disorders in adulthood. Finally, in order to increase the awareness of clinicians about the deleterious role of maternal pregnancy-acquired weight, current knowledge regarding the management of maternal weight during pregnancy is included. Thus, the aim of this review is to draw conclusions useful for clinicians from the published epidemiological and pathophysiologic studies.

Methods

A search strategy was developed for PubMed; the algorithm was the following: (maternal obesity OR pre-pregnancy weight OR gestational weight gain) AND (pregnancy outcomes OR complications OR birth weight OR long-term metabolic effects) AND (Obesity management in pregnancy). No restrictions pertaining to publication language or study design were adopted. Reference lists of relevant articles were hand-searched for potentially eligible studies ("snowball" procedure) so as to maximize the amount of synthesized evidence. Interventional, prospective and retrospective studies, *in vitro* and animal studies, narrative and systematic reviews and meta-analyses were included.

ADIPOSE TISSUE IN PREGNANCY

In the last decade, a plethora of data have indicated that adipose tissue is not just an energy storage depot but rather a metabolically active tissue.[20] The adipokines produced by the adipose tissue, such as leptin, adiponectin, resistin, visfatin, TNF-α, IL-6 and RBP-4 exert paracrine as well as endocrine effects on a variety of target tissues. Adipokines are directly and/or indirectly involved in reproduction, inflammation, immunity, insulin sensitivity and glucose homeostasis, lipid metabolism, blood pressure regulation, as well as appetite and energy balance.[21] In addition, obesity, which denotes excessive accretion of fat, is now recognized as a low-grade chronic inflammatory disease and is associated with increased levels of CRP, TNF-α and IL-6.[21,22] It has also been established that adipose tissue is extensively infiltrated by macrophages in the obese.[21,23] It has been suggested that this inflammation may be the result of obesity-derived hypoxia characterizing adipocytes distant from the capillary network as fat mass expands prior to angiogenesis.[21]

To the chronic inflammatory state of pre-gravid obesity must be added the accumulation of macrophages and pro-inflammatory mediators found in the placenta of obese women.[24] In addition, substantial changes take place in fat distribution during pregnancy. A prospective study conducted by Sidebottom et al examined body weight and subcutaneous body fat by measuring skinfold thickness at the mid-thigh, triceps and subscapular sites before conception, once at each trimester and once at postpartum in 557 healthy women.[25] They found that subcutaneous fat starts to accumulate around the sixth post-conception week and continues to increase through the 36th week of pregnancy. Women gained higher amounts of central body fat in the subscapular area and this fat was reduced to a lesser extent within the first six months postpartum than the peripheral stores of subcutaneous fat at the thigh and triceps. Of note, parity seems to play a significant role in fat distribution. Increasing parity is associated with a decrease in hip and thigh circumferences and an increase in waist circumference, which is a crude surrogate measure of visceral adiposity.[26,27] Finally, a fair number of studies provide evidence that childbearing may be an important contributor to the enlargement of the intra-abdominal fat depot. Pregnancy is thought to be associated with preferential accumulation of adipose tissue in the visceral compartment.[28] Regarding the differences in fat distribution observed between lean and obese pregnant women, it seems that the latter gain more fat in the central body compartment compared to the former, who gain more fat in the lower part of the body.[29]

ADIPOSE TISSUE AND INSULIN RESISTANCE DURING PREGNANCY

Visceral adiposity is associated with obesity-related insulin resistance, cardiovascular disease, lower HDL-cholesterol levels and progression to type 2 diabetes, particularly among women.[28,30] The increase of insulin resistance during gestation is paralleled by the progressive increase of maternal adipose tissue deposition.[26] Pregnancy *per se* is a physiological state of insulin resistance. In fact, increasing insulin resistance in the liver, muscle and adipose tissue during pregnancy is of great importance because it enables the transfer of glucose and other nutrients to the fetus. This is mainly achieved through the placental hormones, such as human placental lactogen and human placental GH, as well as prolactin, cortisol and progesterone, which antagonize insulin. Compensatory hyperinsulinaemia follows insulin resistance increase during pregnancy. Failure of this adaptive mechanism leads to GDM.[31] Obese women are significantly more insulin resistant than lean and overweight women, especially before conception and in early pregnancy (12-14 weeks).[32] Pre-gravid insulin resistance coupled with inadequate insulin secretion during pregnancy results in the increased prevalence of GDM in women who are overweight or obese before conception.[33-36] It is worth noting that GDM is associated with many adverse pregnancy outcomes. Compared to non-obese and non-GDM women, women with GDM face an increased odds ratio (OR) of 2.19 for birth weight >90th percentile. Odds ratios for primary caesarean delivery, preeclampsia, cord C-peptide and newborn percent body fat >90th percentile were similar (OR: 1.25, 1.74, 2.49, 1.98, respectively).[37] Moreover, women who develop GDM have a considerably higher risk of developing type 2 diabetes mellitus within the following fifteen years.[38]

CLINICAL ASSESSMENT OF WEIGHT IN PREGNANCY

Relationship between pre-pregnancy weight and pregnancy outcomes – *Table 1*

As already mentioned, numerous studies have reported an increased risk of GDM among women who are overweight or obese before conception as compared to thin or normal weight women. A meta-analysis of twenty studies showed that the risk for developing GDM is increased 3.6 times in obese and 8.6 times in severely obese women compared to normal weight women.[34] Similarly, obese women are at increased risk for gestational hypertension and preeclampsia.[32] According to a large prospective multi-center study including 16,102 women, obese women were 2.5 and 1.6 times more likely to develop gestational hypertension and preeclampsia, respectively, than women with a BMI of less than 30 kg/m^2 before pregnancy.[35] These results are confirmed by the HAPO study, which demonstrated that higher pre-pregnancy BMI, independent of maternal glycaemia, is associated with greater likelihood of preeclampsia, caesarian delivery and higher neonatal birth weight and body fat.[39] More specifically, according to a meta-analysis summarizing evidence on the relationship between maternal obesity and caesarean delivery, it was shown that caesarean delivery risk is increased by 50% in overweight women and it is encountered twice more often in obese compared with normal weight women.[40]

Increased pre-gravid weight is also related to certain congenital anomalies. Compared with mothers with recommended BMI, obese mothers are at increased risk of pregnancies affected by neural tube defects (OR 1.87), including spina bifida (OR 2.24), cardiovascular abnormalities (OR 1.3) including septal anomalies (OR 1.2), cleft palate (OR 1.23), cleft lip and palate (OR 1.2), anorectal atresia (OR 1.48), hydrocephaly (OR 1.68) and, finally, limb reduction anomalies (OR 1.34).[41]

Both maternal overweight and obesity have been associated with an increased risk of infant mortality in term births due to increased mortality risk in term births and an increased prevalence of preterm births.[42]

In addition, maternal pre-gravid obesity is associated with a significantly increased risk for a low Apgar score (<7 at 5 minutes after birth). A population study including 369,347 women in Denmark reported that the OR for having a neonate with a low Apgar score was 1.3, 1.4 and 1.9 in overweight, obese and severely obese women, respectively, compared with women of normal weight.[33] In the same study, it was shown that the risk for stillbirth (intrauterine death occurring after 22 completed weeks of gestation) was

Table 1. Pre-pregnancy maternal weight and pregnancy outcomes

Name	Outcome	Type of study	Result
Chu SY et al (2007)	GDM	Meta-analysis	3.6-fold and 8.6-fold risk for obese and severely obese, respectively
Weiss JL et al (2004)	Gestational hypertension	Observational study	2.5-fold risk for obese women
Weiss JL et al (2004)	Preeclampsia	Observational study	1.6-fold risk for obese women
HAPO Study (2010)	Caesarean delivery	Observational study	OR: 2.23 for highest vs. lowest BMI categories (OR: 1.5 and 2.0 in overweight and obese, respectively)
Chu SY et al (2007)	Caesarean delivery	Meta-analysis	The unadjusted ORs of a caesarean delivery were 1.46 (95% CI: 1.34-1.60), 2.05 (1.86-2.27) and 2.89 (2.28-3.79) among overweight, obese and severely obese women, respectively, compared with normal weight pregnant women
Scothard KJ et al (2009)	Congenital anomalies	Meta-analysis	Compared with mothers of recommended BMI, obese women were at increased odds of pregnancies affected by neural tube defects (OR: 1.87; 95% CI: 1.62-2.15), spina bifida (OR: 2.24; 1.86-2.69), cardiovascular anomalies (OR: 1.30; 1.12-1.51), septal anomalies (OR: 1.20; 1.09-1.31), cleft palate (OR: 1.23; 1.03-1.47), cleft lip and palate (OR: 1.20; 1.03-1.40), ano-rectal atresia (OR: 1.48; 1.12-1.97), hydrocephaly (OR: 1.68; 1.19-2.36) and limb reduction anomalies (OR: 1.34; 1.03-1.73)
Johansson S et al (2014)	Increased infant mortality	Observational study	Adjusted OR: 1.25 (95% CI: 1.16-1.35), 1.37 (1.22-1.53), 2.11 (1.79-2.49) and 2.44 (1.88-3.17), respectively, for overweight, obesity grade 1, 2 and 3 compared to normal weight
Ovesen P et al (2011)	Low apgar score	Observational study	OR: 1.3, 1.4, 1.9 in overweight, obese and severely obese, respectively
Ovesen P et al (2011)	Stillbirth	Observational study	OR: 1.4, 1.6, 1.9. in overweight, obese and severely obese, respectively
Chu SY et al (2007)	Stillbirth	Meta-analysis	OR: 2.07 in obese women
Gaillard R et al (2013)	LGA	Observational study	OR: 2.97 in obese women
Gaillard R et al (2013)	Childhood obesity	Observational study	OR: 5.02 in obese women
Boney CM et al (2005)	Metabolic syndrome at 11 years of age in the offspring	Observational study	Children born to obese women show an increased estimated HR (1.81) for metabolic syndrome at 11 years of age
Mingrone G et al (2008)	Insulin resistance in the offspring	Observational study	Offspring of obese women were more insulin resistant than the control group
Hochner H et al (2012)	Increased cardiometabolic risk at 32 years of age in the offspring	Observational study	Mpp BMI was positively associated with offspring BMI ($p<0.0001$), WC ($p<0.0001$), SBP ($p=0.003$), DBP ($p=0.017$), insulin ($p=0.007$) and TG ($p=0.02$) and negatively associated with HDL-C ($p=0.03$)
Reynolds RM et al (2013)	Increased risk of hospital admission for a cardiovascular event in the adult offspring	Observational study	0.29-fold risk of hospital admission for a cardiovascular event in the adult offspring of obese women
Reynolds RM et al (2013)	Increased risk of premature death from any cause in the adult offspring	Observational study	0.35-fold risk of premature death from any cause in the adult offspring of obese women

OR: odds ratio; CI: confidence interval; HR: hazard ratio; GDM: gestational diabetes mellitus; BMI: body mass index; LGA: large-for-gestational-age; Mpp: mean pre-pregnancy; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides.

increased by 40%, 60% and 90% in overweight, obese and severely obese women, respectively, compared with women of normal BMI[33]. Similar results were published in a meta-analysis by Chu et al who estimated the OR of stillbirth at 2.07 in obese women compared with normal weight pregnant women.[43] Finally, pre-gravid obesity has been associated with a 3-fold risk of delivering LGA neonates and a 5-fold risk of childhood obesity.[44,17]

Relationship between weight gain during pregnancy and pregnancy outcomes *– Table 2*

Apart from pre-gravid weight status, the role of gestational weight gain is also under meticulous investigation due to its postulated effect on several adverse pregnancy outcomes.

The majority of studies show some degree of association between higher gestational weight gain and caesarean delivery, with the risk of caesarean delivery being more pronounced among overweight and obese women.[45] Excessive weight gain during pregnancy is an independent risk factor for caesarean delivery, even if birth weight is lower than 4 kg. Pregnant women who put on excessive weight have an OR of 1.4 for caesarean delivery.[46]

Of note, both high and low weight gains are associated with increased risk for preterm birth.[45] It has also been found that there is a positive correlation between gestational weight gain and birth weight, especially among underweight and normal weight women. In addition, increased weight gain during pregnancy is considered to be a risk factor for macrosomia.[45] There is large body of literature corroborating the association between increased gestational weight gain and LGA neonates.[45,47] Simas et al demonstrated that normal weight, overweight and obese women who gain excessive weight during pregnancy have an OR for LGA of 1.76, 2.9 and 1.55, respectively.[48] Interestingly, maternal weight gain during pregnancy seems to influence the weight status of the offspring far beyond neonatal life. There is evidence supporting a positive association between increased gestational weight gain and risk of childhood overweight in the offspring.[49,50] According to a large multi-ethnic cohort study, the odds of overweight at the age of 7 was 48% greater for children whose mothers gained more than the weight gain recommendations (the study refers to the Institute of Medicine guidelines of 1990) than for children whose mothers met the weight gain guidelines.[50] Furthermore, it has been demonstrated that gestational weight gain is associated with BMI and risk of obesity in adolescence and early adulthood.[51,52] More specifically, it has been shown that young adults at 21 years of age are at greater risk of becoming overweight or obese if their mothers had gained excessive weight during pregnancy.[52]

Additionally, a cohort study which included 481 obese, glucose-tolerant women demonstrated that increasing gestational weight gain increased the risk of hypertension, caesarean section, induction of labour and macrosomia.[53]

There is also a considerable body of literature examining the relationship between increased gestational weight gain and disorders in glucose metabolism. Saldana et al found that increased weight gain during pregnancy was associated with impaired glucose tolerance among overweight women.[54] Excessive gestational weight gain, particularly in early pregnancy, has been associated with an increased risk of GDM.[55,56] A retrospective cohort study which included 652 women (163 with GDM and 489 controls) also showed that women who develop GDM have higher gestational weight gain through 24 weeks. The same study showed that gestational weight gain is a risk factor for GDM in overweight and obese patients, but not in those who were underweight or of normal weight before pregnancy.[57]

Of note, women who gain excess weight during pregnancy are at greater risk of becoming overweight or obese[58] and of being diagnosed with diabetes mellitus in later life.[59]

Crane et al have shown that in women with a normal pre-pregnancy BMI, excessive weight gain is associated with increased rates of gestational hypertension (OR 1.27), augmentation of labour (OR 1.09) and birth weight ≥4000 g (OR 1.21).[60] Furthermore, in overweight women, increased weight gain is associated with increased rates of gestational hypertension (OR 1.31) and birth weight ≥4000g (OR 1.30).[60] Finally, in obese or morbidly obese women, excessive weight gain is associated with increased prevalence of birth weight ≥4000gr (OR 1.2) and neonatal metabolic abnormality (OR 1.31).[60]

Table 2. Gestational maternal weight gain and pregnancy outcomes

	Outcome	Type of study	Result
Viswanathan M et al (2008)	Caesarean delivery	Meta-analysis	Moderate evidence
Stotland NE et al (2004)	Caesarean delivery	Observational study Retrospective cohort study	OR: 1.40 (95% CI: 1.22-1.59) for women with excessive weight gain
Jensen DM et al (2005)	Gestational hypertension	Meta-analysis	Increasing weight gain in obese women was associated with significantly higher rates of hypertension (OR 4.8; 95% CI: 1.7-13.1), caesarean section (OR: 3.5; 1.6-7.8), induction of labour (OR: 3.7; 1.7-8.0) and large-for-gestational-age infants (OR: 4.7; 2.0-11.0)
Viswanathan M et al (2008)	Preterm birth	Meta-analysis	Strong evidence supported an association between gestational weight gains and preterm birth
Viswanathan M et al (2008)	Macrosomia	Meta-analysis	Strong evidence supported an association between gestational weight gains and macrosomia
Simas TAM et al (2012)	LGA	Meta-analysis	Excessive GWG associated with increased odds of LGA. Adjusted OR: 1.76 (95% CI: 1.38-2.24), 2.99 (1.92-4.65) and 1.55 (1.10-2.19) for normal weight, overweight and for obese women, respectively
Vesco KK et al (2014)	LGA	Interventional study	Intervention participants gained less weight and had a lower proportion of LGA babies (9 vs. 26%; OR: 0.28; 95% CI: 0.09-0.84)
Oken E et al (2007)	Childhood overweight	Observational study	Greater than IOM recommendations weight gain was associated with higher child BMI z-score (0.13 units per 5 kg; 95% CI: 0.08-0.19) Compared with inadequate weight gain, women with adequate or excessive weight gain had children with higher BMI z-scores [0.47 (0.37-0.57) and 0.52 (0.44-0.61), respectively] and OR for overweight children 3.77 (1.38-10.27) and 4.35 (1.69-11.24), respectively
Oken E et al (2008)	Obesity in adolescence	Observational study	Women with excessive weight gain had children with higher BMI z-scores (0.14 units, 95% CI 0.09-0.18) and risk of obesity [OR: 1.42 (1.19-1.70)]
Al Mamun A et al (2009)	Obesity in young adulthood	Observational study	At 21 years of age, offsprings' BMI was on average 0.3 kg/m^2 (95% CI: 0.1-0.4) higher for each 0.1 kg/wk greater GWG after adjustment for potential confounding factors
Saldana TM et al (2006)	IGT-GDM	Observational study	Weight gain during pregnancy was associated with IGT only among overweight women
Henderson MM et al (2010)	IGT-GDM	Observational study	Rates of weight gain from 0.27-0.40 kg/wk and 0.41 kg/wk or more, were associated with increased risks of GDM [OR: 1.43; 95% CI: 0.96-2.14; and 1.74; 1.16-2.60, respectively]
Morisset AS et al (2011)	IGT-GDM	Observational study	First trimester weight gain was a significant and independent predictor of GDM [OR: 1.25; 95% CI 1.10-1.42)
Gibson KS et al (2012)	IGT-GDM	Observational study	Maternal weight gain was higher (P <.001) in the GDM group (14.8 lb) than in the control group (11.2 lb)
Al Mamun A et al (2010)	Overweight/Obesity in later life (for the mothers)	Observational study	Increased OR for women with excess weight gain during pregnancy to become overweight (2.15; 95% CI: 1.64-2.82) or obese (4.49; 3.42-5.89) 21 years after the index pregnancy
Al Mamun A et al (2013)	DM in later life (for the mothers)	Observational study	1.47-fold (1.11-1.94) risk for mothers with excess weight during pregnancy to experience diabetes at 21 years postpartum compared to mothers with adequate weight gain

OR: odds ratio; CI: confidence interval; GWG: gestational weight gain; LGA: large-for-gestational-age; IOM: institute of medicine; BMI: body mass index; IGT: impaired glucose tolerance; GDM: gestational diabetes mellitus; DM: diabetes mellitus.

The influence of maternal obesity on fetal development and its long-term metabolic effects

Fetal growth and development depend on the equilibrium in the interaction of the triad mother - placenta - fetus. Fetal development is not only determined by the fetal genome but is also influenced by the endometrial environment. Apart from placental growth and function and the external environment, the endometrial environment is also formed by maternal related factors. These include maternal metabolism and its changes during pregnancy, maternal dietary habits and anthropometrics as well as the mother's psychological, behavioural and personality characteristics.

All of the abovementioned factors seem to induce persistent alterations of gene expression through epigenetic changes in the fetus, which may lead to several metabolic and neurodevelopmental disorders later in adult life. This adaptive process of the fetus when a stimulus is applied *in utero* is called fetal programming. Thus, obesity during pregnancy creates an abnormal milieu *in utero* and leads to fetal-neonatal obesity, which is considered to be associated with childhood and adult obesity as well as type 2 diabetes and metabolic syndrome in adulthood.

The association between maternal obesity and fetal macrosomia has been established by many studies.[61,17] Overweight or obese women with normal glucose tolerance levels give birth to heavier neonates compared to lean or normal weight women, apparently because of increased adiposity.[6] In line with this finding, Hull et al found that neonates born to normal weight mothers have significantly less total and relative fat and more fat-free mass than neonates born to overweight or obese mothers.[62] Decreased maternal insulin sensitivity, which is the common denominator in obese women and women with GDM, is also related to fetal overgrowth. In particular, decreased maternal insulin sensitivity before conception appears to have the strongest correlation with fetal fat mass at term.[63] Both maternal over-nutrition and maternal glucose intolerance are associated with elevated fetal plasma glucose and insulin concentrations and increased leptin secretion in fetal adipose tissue. Hyperglycaemia, hyperinsulinaemia and hyperleptinaemia act on central neurons in the energy balance regulating system, causing alterations in appetite and adipocyte metabolism and high neonatal adiposity. It is postulated that the early origins of childhood and adulthood obesity lie in these alterations occurring during fetal life.[64] Epigenetic modifications in response to over-nutrition may lead to metabolic imprinting or permanent alterations in genes involved in the regulation of energy homeostasis. Several such genes have been shown to be regulated by DNA methylation and histone modifications, including genes for leptin,[65] SOCS3[66] and glucose transporter.[67] Recently, Bouchard et al[68] found maternal hyperglycaemia to be correlated with placental leptin gene DNA methylation levels. Animal studies have shown that metabolic imprinting caused by the obese intrauterine environment can actually be transmitted across generations (trans-generational cycle of obesity).[69] These findings suggest that the intrauterine environment of diabetic and obese women may impact the epigenome of the offspring.

Indeed, a retrospective cohort study showed that among children whose mothers were obese in the first trimester of pregnancy, the prevalence of obesity at ages two, three and four years was 15.1%, 20.6% and 24.1%, respectively. This was 2.4 to 2.7 times higher than the prevalence of obesity among children of normal weight mothers. The calculated relative risk for childhood obesity resulting from first trimester-associated maternal obesity at two, three and four years of age was 2.0, 2.3 and 2.3, respectively.[70]

It has also been shown that pre-pubertal LGA-born children are more insulin resistant than matched AGA (appropriate for gestational age) controls, although they have a higher mean serum adiponectin level (adiponectin is considered as an insulin-sensitizing adipokine). Moreover, pre-pubertal LGA-born children >97th percentile have a significantly higher mean serum leptin level than AGA (leptin is considered to increase insulin sensitivity).[71,72] On the other hand, Darendeliler et al have found that LGA children have higher insulin and lower adiponectin levels than AGA children in spite of similar BMI.[73] A study enrolling 52 young adult offspring of obese mothers and 15 offspring of normal weight mothers demonstrated that the former are more likely to be obese and develop insulin resistance than the latter.[74] Of note, higher maternal pre-pregnancy BMI has been associated with higher offspring systolic and diastolic blood pressure, insulin and triglyceride levels and lower HDL cholesterol at 32 years of age.[75] Reynolds et

al have recently extended these results by finding a 29% increased risk of hospital admission for a cardiovascular event in the adult offspring of obese mothers compared with the offspring of mothers with normal BMI.[76] Likewise, the former exhibit a 35% increased risk of premature death from any cause, compared with the latter.[76]

Other pathophysiological mechanisms linking maternal obesity to increased cardiometabolic risk in offspring

Both animal and human studies have suggested a number of mechanisms, apart from hyperinsulinaemia and hyperleptinaemia, linking maternal obesity to the increased incidence of obesity and cardiometabolic diseases in offspring. In ewes, maternal obesity upregulates fatty acid and glucose transporters and increases expression of enzymes mediating fatty acid biosynthesis in fetal adipose tissue depots.[77] Human studies using magnetic resonance imaging have shown that maternal BMI predicts infant intrahepatocellular lipid storage, as seen in animal models, which implies that maternal obesity may predispose the offspring to developing nonalcoholic fatty liver, the hepatic manifestation of metabolic syndrome.[78,79] Furthermore, maternal obesity appears to downregulate fetal myogenesis. Skeletal muscle is the principal site for glucose and fatty acid utilization. Thus, maternal obesity might result in decrease of the offspring's skeletal muscle mass and changes of its properties, eventually increasing their risk for the development of type 2 diabetes and obesity.[80,81] Regarding the programming of vascular function and blood pressure, studies in rats highlighted the presence of endothelial dysfunction in the offspring of obese mothers, while studies in rodents demonstrated that the offspring of obese females develop hypertension and increased cardiovascular response to stress due to increased sympathetic activity.[82] In addition, studies in human full-term placentas showed that maternal obesity impacts placental fatty acid uptake and could therefore modify the fetus metabolism and the child's predisposition to develop diseases later in life.[83] Maternal obesity leads to a lipotoxic placental environment that is associated with decreased regulators of angiogenesis and increased markers of inflammation and oxidative stress.[84] This environment via in utero programming may trigger adaptive pathways which ultimately result in increased percentage of body fat and propensity for future obesity in the offspring of obese women.[85]

MANAGEMENT OF WEIGHT DURING PREGNANCY

As underlined earlier in this review, maternal pre-pregnancy BMI and gestational weight gain are two factors of great importance for pregnancy outcome. The increasing prevalence of overweight and obesity among women of childbearing age and the rising percentage of women gaining too much weight during pregnancy necessitated the revision of the Institute of Medicine (IOM) guidelines of 1990. In 2009, the IOM published new guidelines for recommended weight gain during pregnancy according to the maternal pregravid BMI. Thus, IOM recommends a weight gain of 12.5-18 kg for women of BMI <18.5 kg/m^2, 11.5-16 kg for women of BMI 18.5-24.9 kg/m^2, 7.5-11.5 kg for women of BMI 25-29.9 kg/m^2 and 5-9 kg for women of BMI ≥30 kg/m^2 (Table 3). The committee formulated these guidelines taking into consideration not only the welfare of the child but also the health of the mother and aiming at optimal pregnancy outcome. IOM recommendations provide useful guidance for monitoring weight during pregnancy in order to avoid fetal and maternal complications.

A different approach regarding weight gain during pregnancy has been suggested by a Swedish study of 298,648 singleton pregnancies conducted by Cedergren who proposed that the optimal gestational weight gain based on pre-pregnancy BMI was 4-10 kg for BMI less than 20 kg/m^2, 2-10 kg for BMI 20-24.9 kg/m^2, less than 9 kg for BMI 25-29.9 kg/m^2 and less than 6 kg for BMI of 30 kg/m^2 or more.[86]

Table 3. IOM 2009 recommendations for total weight gain during pregnancy, by pre-pregnancy BMI.[53]

Pre-gestational BMI (kg/m^2)	Recommended gestational weight gain (kg)
<18.5	12.5-18
18.5-24.9	11.5-16
25-29.9	7.5-11.5
≥30	5-9

Health professionals should debunk the myth that pregnant women should "eat for two". Nevertheless, a pregnant woman has to increase her dietary energy intake in order to compensate for the increase of BMR and the energy deposited in fetal and maternal tissues as pregnancy progresses. It has been estimated that the energy needs of a normal weight pregnant woman do not significantly change in the first trimester, but increase by 350 kcal per day in the second trimester and by 500 kcal per day in the third trimester.[87]

There is no real difference between what constitutes a healthy diet during pregnancy and a healthy diet at any time in life. Thus, following IOM recommendations, 45-65% of a pregnant woman's energy intake should come from carbohydrates, 20-35% from fat and 10-35% from proteins.[88] A low glycaemic index diet in pregnancy appears to have a significant positive effect on gestational weight gain and maternal glucose intolerance, although it does not reduce the incidence of large-for-gestational-age infants in women at risk for fetal macrosomia (having previously delivered an infant weighing more than 4 kg).[89] However, a low glycaemic index diet intervention in pregnancy was found to have a beneficial effect on neonatal central adiposity.[90] According to the NICE (National Institute for Health and Care Excellence) guidelines, pregnant women should base their meals on starchy foods, eat at least five portions of vegetables and fruits each day and consume fibre-rich foods instead of foods rich in fat and sugar. Notably, it has been shown that extreme sugar intakes among pregnant adolescents may lead to increased accretion of fetal abdominal fat with little net effect, however, on birth weight.[91]

Pregnant women should also be physically active and incorporate at least 30 minutes of moderate-intensity activity into each day. However, women who did not exercise regularly before pregnancy should begin with no more than 15 minutes of continuous activity three times per week, gradually reaching a target of 30 minutes.[92]

Moreover, women with a BMI ≥30 kg/m^2 should be informed about the risks their weight poses to themselves and to their child in the event of pregnancy. Health professionals should help these women reduce their weight before becoming pregnant by providing them with an individualized weight loss programme built around on a balanced nutrient-rich diet along with exercise.[92] Obese pregnant women should be encouraged to adopt a healthy lifestyle built around the principles which were outlined earlier. A dietary intervention study for limiting gestational weight gain among obese women showed that intervention participants gained less weight and had a lower prevalence of LGA neonates.[47] Moreover, dietary interventions are the most effective type of intervention in pregnancy in reducing gestational weight gain and the risks of pre-eclampsia, gestational hypertension and shoulder dystocia**.**[93] Losing weight during pregnancy is not recommended because it may harm the health of the unborn child.[92,94] Restrictive diets may increase blood ketone levels and could adversely affect the neurocognitive development of the fetus.[92]

The IOM committee recommmends a gestational weight gain range of 5-9 kg for all obese women and does not stratify its recommendations by severity of obesity. However, the optimal gestational weight gain for obese women, especially for those of class II (BMI 35-39.9 kg/m^2) and class III (BMI ≥40 kg/m^2) obesity, is a matter of ongoing debate among researchers. Hinkle et al suggest that gestational weight gains below the IOM guidelines for obese women with BMI ≥35 kg/m^2 may reduce the risk of excessive fetal growth without restricting fetal development.[95] Moreover, it has been found that gestational weight gain of 2.2 kg to less than 5 kg for obese class III white women is associated with probabilities of less than 10% for SGA and LGA births and a minimal risk of preterm delivery.[96] These results raise the question of whether more restrictive weight gain limitations could be set for severely obese pregnant women.

STRENGTHS AND LIMITATIONS

The main strength of this review should be considered the effort exerted to relate results of basic and clinical studies regarding the influence of maternal pre-pregnancy and gestational weight gain upon the development of future pathologic entities in the offspring with everyday practice concerning the management of these women during pregnancy in order to decrease the aforementioned pathology risks. Data on dietary management and its effects on maternal weight gain and neonatal outcomes has

also been included. A limitation of this review is failure to provide a systematic review. This is due, in part, to the type of published research literature available and its lack of homogeneity. In particular, there is a paucity of interventional randomized controlled studies examining the impact of maternal pre-pregnancy weight and gestational weight gain upon pregnancy outcomes. Some interventional studies aiming at limiting gestational weight gain and evaluating pregnancy outcomes have been included. Because pre-pregnancy maternal weight was self-reported or obtained by recall in some studies, the risk of bias in them is present. Finally, based on the included studies, it is difficult to distinguish the true causal relationship between maternal obesity and offspring obesity from confounding factors such as maternal age, ethnicity, smoking during pregnancy, educational level, etc. because it is not clear whether some studies had adjusted for the possible presence of these confounders. To eliminate this weakness, there is a need for randomized controlled intervention trials to assess the effects of pre-pregnancy maternal weight as well as of gestational maternal weight gain on maternal metabolism and neonatal outcomes.

CONCLUSIONS

Obesity constitutes one of the most serious health challenges of the 21st century. The prevalence of adverse pregnancy outcomes is increased among women who are overweight or obese before conception and women who gain excessive weight during gestation. Obese mothers give birth to heavier neonates who are more likely to be obese as children and are at greater risk of developing metabolic disorders in later life. For all these reasons, it is very evident that women should have normal weight when entering pregnancy and should keep their gestational weight gain within the recommended range according to the IOM guidelines of 2009. Obesity engenders obesity and the need to put an end to this vicious cycle is imperative. Nutritional counseling for establishment of a healthy and balanced diet, physical exercise and close monitoring of maternal weight preconceptionally and throughout pregnancy can be useful weapons in our battle against the current epidemic of obesity.

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