

# Maternal metabolism and obesity: modifiable determinants of pregnancy outcome

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**BACKGROUND:** Obesity among pregnant women is highly prevalent worldwide and is associated in a linear manner with markedly increased risk of adverse outcome for mother and infant. Obesity in the mother may also independently confer risk of obesity to her child. The role of maternal metabolism in determining these outcomes and the potential for lifestyle modification are largely unknown.

**METHODS:** Relevant studies were identified by searching PubMed, the metaRegister of clinical trials and Google Scholar without limitations. Sensitive search strategies were combined with relevant medical subject headings and text words.

**RESULTS:** Maternal obesity and gestational weight gain have a significant impact on maternal metabolism and offspring development. Insulin resistance, glucose homeostasis, fat oxidation and amino acid synthesis are all disrupted by maternal obesity and contribute to adverse outcomes. Modification of lifestyle is an effective intervention strategy for improvement of maternal metabolism and the prevention of type 2 diabetes and, potentially, gestational diabetes.

**CONCLUSIONS:** Maternal obesity requires the development of effective interventions to improve pregnancy outcome. Strategies that incorporate a detailed understanding of the maternal metabolic environment and its consequences for the health of the mother and the growth of the child are likely to identify the best approach.

**Key words:** pregnancy / metabolism / insulin / randomized controlled trials

## Introduction

Obesity among pregnant women is highly prevalent and is associated with markedly increased risk of adverse outcome for mother and infant. Obesity in the mother may also independently confer risk of obesity to her child. In this review, we present the evidence for short- and long-term consequences of maternal obesity and gestational weight gain (GWG) and define the underlying need for an effective intervention strategy.

The metabolic sequelae of maternal obesity are addressed including a review of fat deposition and location, and by detailing effects on glucose, lipid and protein metabolism, parallels with type 2 diabetes are highlighted. Lifestyle intervention strategies in type 2 diabetes and gestational diabetes are reviewed, and how these may aid in the development of an intervention for obese women is discussed. Finally, we review the relevant intervention studies, most of which are preliminary reports in women with normal and raised BMI, all of which focus on the prevention

of excessive GWG. We also review the relative merits of GWG or measures of maternal insulin resistance as primary outcomes for large-scale randomized controlled trials in obese pregnant women.

## Methods

To generate this review, a thorough literature search was repeatedly made in PubMed, the metaRegister of clinical trials and Google Scholar without limitations for all studies, with the last repeat performed on 30 September 2009. The Medical Subject Heading Terms used were overweight, obesity, fetus, insulin resistance, pregnancy, metabolism, lipids, amino acids, protein, physical activity, diet, diabetes, gestational diabetes, lifestyle, child, adult, body mass index, body weight, weight gain, adipose tissue, controlled clinical trial and epidemiological studies. The procedure was concluded by the perusal of the reference sections of all relevant studies or reviews, a manual search of key journals and abstracts from the major annual meetings in the field of pregnancy and endocrinology and a contact with experts on the subject, in an effort to identify relevant unpublished data. Finally, unpublished studies were also sought in the websites isrctn.org, clinicaltrials.gov, cih.ca, action.org, UK clinical trials gateway and Wellcome Trust.

## Maternal obesity

### The size of the problem

In 2005, the World Health Organisation (WHO) estimated that at least 400 million adults were obese (BMI > 30 kg/m<sup>2</sup>), a figure projected to rise to over 700 million by 2015 (WHO, 2006). Among women aged 20–44, 32% were classified as obese in the USA in a survey carried out between 2003 and 2006 (WHO, 2009). The influences of obesity on reproductive health in women, particularly adverse effects on pregnancy outcome, present a significant burden to healthcare resources (Galtier-Dereure et al., 2000; Chu et al., 2008). Recent statistics from selected OECD (Organisation for Economic Co-operation and Development) countries show that in 2005, of women aged 15–64, 32.4% in the USA and 23.8% in England were obese (OECD, 2009). Among the non-pregnant women aged 12–44 in the USA, the prevalence of obesity has more than doubled since 1976 and that of severe obesity has increased dramatically; between 1979 and 2004 with Class I (30 to <35 kg/m<sup>2</sup>) and II (35 to <40 kg/m<sup>2</sup>) obesity doubling and Class III rising 3-fold (≥40 kg/m<sup>2</sup>) (Institute of Medicine, 2009). Obesity among women in many developing countries is also rising (Misra and Khurana, 2008) and is highly prevalent in the Middle East (Esmailzadeh and Azadbakht, 2006). Few countries have reliable data documenting the incidence of obesity in pregnant women (Guelinckx et al., 2008), but cohort studies in countries such as the UK where obesity is rising show upward trajectories in parallel with those of the whole population (Kanagalingam et al., 2005; Kiran et al., 2005; Heslehurst et al., 2007, Health Survey for England 2006). In the USA, data available from nine states using the Pregnancy Risk Assessment Monitoring System (PRAMS) showed that 20% of Americans are obese at the start of pregnancy, representing a 70% increase over a decade (Kim et al., 2007).

### Pregnancy complications

Prepregnancy BMI is increasingly recognized as a major determinant of pregnancy outcome, with maternal obesity associated in a linear

manner with an increased risk of the majority of pregnancy complications, with the exception of spontaneous preterm labour and gestosis which are decreased. Several recent large cohorts, systematic reviews and meta-analyses have attempted to provide accurate risk estimates for specific complications relative to maternal obesity (O'Brien et al., 2003; Chu et al., 2007a, b, c; Smith et al., 2007; Heslehurst et al., 2008; Metwally et al., 2008; Rasmussen et al., 2008; Khashan and Kenny, 2009; Poobalan et al., 2009; Stothard et al., 2009; Torloni et al. 2009) and the point estimates from the largest and most recent datasets are summarized in Table 1.

### GWG and fat deposition

Irrespective of the degree of adiposity prior to conception, significant GWG occurs to support the functions of growth and development of the fetus (Fig. 1). However, the total amount of weight gained in normal-term pregnancies varies considerably among women and is related to the number of fetuses (singleton pregnancy 10–16.7 kg, twin pregnancy 15–22 kg, triplet pregnancy 20.5–23 kg) and inversely to the prepregnancy BMI (Institute of Medicine, 2009).

Accretion of maternal fat parallels GWG, with significant energy expended on maternal fat deposition to provide a source of energy for maintaining the fetus, and buffer short or medium-term changes in energy supply. The absolute amount of fat deposited ranges from 1.9 to 5.8 kg, potentially reflecting differences in methodology and populations as well as biological variability (Lawrence et al., 1987; Forsum et al., 1988; Goldberg et al., 1993; Sohlstrom and Forsum, 1995; Highman et al., 1998; Kopp-Hoolihan et al., 1999; Okereke et al., 2004). In obese women, this fat is primarily accumulated between 13 and 35 weeks of gestation (Okereke et al., 2004), consistent with previous skin-fold studies in healthy women (Fig. 2) (Taggart et al., 1967). The total amount of gestational fat deposited may however be reduced in obese pregnancy (Soltani and Fraser, 2000). In a prospective series of 405 women, a one unit increase in prepregnancy BMI was associated with a 0.5 kg reduction in post-partum weight retention (Kac et al., 2004). Assuming that GWG primarily reflects fat deposition, this would suggest that obese women gain less fat. Similarly, the use of a multicompartiment model to measure body composition at 14 and 37 weeks of gestation in 200 women demonstrated that mean fat mass gains were 4.8, 3.9 and 2.8 kg associated with weight gains of 12.6, 12.2 and 11.0 kg in underweight, normal-weight and overweight women, respectively (Lederman et al., 1997). However, reduced fat accretion has not been universally found (Butte et al., 2003; Ehrenberg et al., 2003), which potentially reflects differences between populations and severity of obesity.

Irrespective of prepregnancy BMI, gestational-related fat is predominantly accumulated centrally, with a preferential selection for central sites in obese pregnant women (Ehrenberg et al., 2003). This probably represents a combination of subcutaneous truncal fat (Sohlstrom and Forsum, 1995; Ehrenberg et al., 2003) and visceral fat (Kinoshita and Itoh, 2006). It is visceral fat which correlates strongly with metabolic risk factors such as blood pressure, insulin sensitivity and plasma lipids (Despres et al., 1990), and this relationship is maintained in pregnancy (Bartha et al., 2007). Excess central fat is also strongly associated with cardiovascular disease and diabetes in adult life (Lapidus et al., 1984; Larsson et al., 1984; Carey et al., 1996; Alberti et al., 2005; de Koning

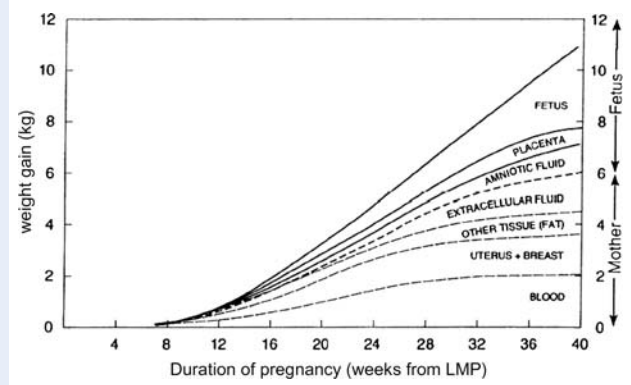
**Table 1** Maternal and neonatal risks of maternal obesity

	Obese women versus normal odds ratio (95% CI)
Congenital anomalies <sup>1</sup>	
All neural tube defects	1.87 (1.62–2.15)
Anencephaly	1.39 (1.03–1.87)
Spina bifida	2.24 (1.86–2.69)
All cardiovascular anomalies	1.30 (1.12–1.51)
All septal anomalies	1.20 (1.09–1.31)
Cleft palate	1.23 (1.03–1.47)
Cleft lip and palate	1.20 (1.03–1.40)
Anorectal atresia	1.48 (1.12–1.97)
Hydrocephaly	1.68 (1.19–2.36)
Limb reduction anomalies	1.34 (1.03–1.73)
Gastroschisis	0.17 (0.10–0.30)
Pregnancy complications	
Miscarriage <sup>2</sup>	1.89 (1.14–3.13)
Recurrent miscarriage <sup>2</sup>	4.68 (1.21–18.13)
Gestational diabetes <sup>3</sup>	3.01 (2.34–3.87)
Pre-eclampsia <sup>4</sup>	2.14 (1.85–2.47)
Venous thromboembolism <sup>5</sup>	2.33 (1.68–3.24)
Stillbirth <sup>6</sup>	2.07 (1.59–2.74)
Labour and delivery	
Spontaneous preterm birth <37 weeks <sup>7</sup>	0.5 (0.4–0.7)
Spontaneous preterm birth <34 weeks <sup>7</sup>	0.4 (0.2–0.8)
Spontaneous preterm birth <32 weeks <sup>7</sup>	0.5 (0.2–1.3)
Induction of labour <sup>8</sup>	1.88 (1.84–1.92)
Use of oxytocin <sup>8</sup>	1.59 (1.36–1.87)
Use of epidural <sup>8</sup>	1.23 (1.19–1.27)
Failure to progress <sup>8</sup>	2.31 (1.87–2.84)
Total Caesarean delivery <sup>9</sup>	2.36 (2.15–2.59)
Elective Caesarean delivery <sup>9</sup>	1.87 (1.64–2.12)
Emergency Caesarean section <sup>9</sup>	2.23 (2.07–2.42)
Instrumental delivery <sup>8</sup>	1.17 (1.13–1.21)
Maternal complications	
Duration of hospital stay (normal 2.4 days) <sup>8</sup>	2.71 (2.62–2.79) days
Maternal haemorrhage <sup>8</sup>	1.24 (1.24–1.28)
Maternal infection <sup>8</sup>	3.34 (2.74–4.06)
Neonatal complications	
Low Apgar score at 5 min <sup>8</sup>	1.57 (1.46–1.68)
Fetal compromise <sup>8</sup>	1.62 (1.54–1.70)
Meconium <sup>8</sup>	1.57 (1.42–1.73)
Shoulder dystocia <sup>8</sup>	1.04 (0.97–1.12)

Continued

**Table 1** Continued

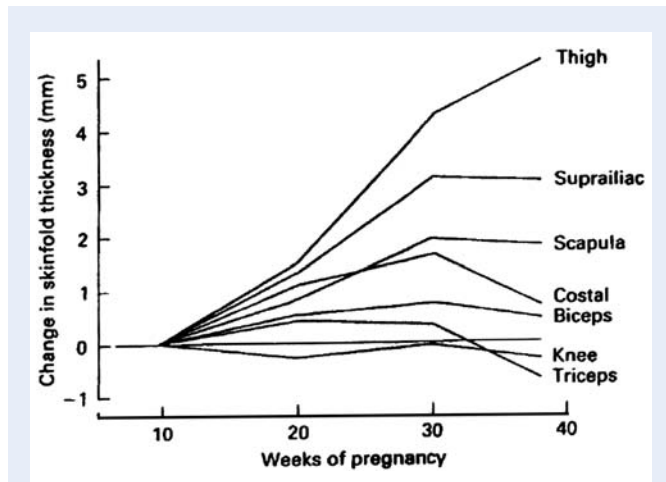
Obese women versus normal odds ratio (95% CI)	
Neonatal intensive care use <sup>8</sup>	1.35 (1.22–1.49)

<sup>1</sup>Stothard *et al.* (2009).<sup>2</sup>Metwally *et al.* (2008).<sup>3</sup>Torloni *et al.* (2009).<sup>4</sup>Sebire *et al.* (2001).<sup>5</sup>Agno *et al.* (2008).<sup>6</sup>Chu *et al.* (2007a, b).<sup>7</sup>Hendler *et al.* (2005a, b).<sup>8</sup>Heslehurst *et al.* (2008).<sup>9</sup>Poobalan *et al.* (2009).**Figure 1** Components of GWG. Reproduced with permission from nutritional support in obstetrics and gynaecology (Pitkin, 1976).

*et al.*, 2007; Vazquez *et al.*, 2007) and in pregnancy with glucose intolerance/gestational diabetes mellitus (GDM) (Zhang *et al.*, 1995; Chu *et al.*, 2007a, b, c; Martin *et al.*, 2009) and gestational hypertension/pre-eclampsia (Sattar *et al.*, 2001). Importantly, although pregnancy influences the site of fat deposition, it does not affect the regional functionality of adipose tissue, explaining the persistence of relationships between central fat and adverse metabolic outcomes (Lindberg *et al.*, 1991). However, as might be anticipated from the increased fat mass, obese pregnant women demonstrate elevated circulating concentrations of leptin and raised levels of inflammatory mediators including IL-6 (Ramsay *et al.*, 2002). Given the well recognized association between an inflammatory state and pre-eclampsia (Redman and Sargent, 2005), these could contribute to the increased risk of this disorder in obese pregnancy. In common with obesity in the non-pregnant state, others have shown that adiponectin is reduced in obese women and this could contribute to insulin resistance (Hendler *et al.*, 2005a, b).

### GWG and pregnancy outcome

Although there is a rationale for linking greater GWG with GDM from the association between fat mass and insulin resistance, the evidence,



**Figure 2** Longitudinal changes in skin-fold thicknesses throughout pregnancy. Reproduced with permission from changes in skin-folds during pregnancy (Taggart et al., 1967).

in contrast to the strong association with prepregnancy BMI, is relatively weak (Viswanathan et al., 2008). This most probably suggests a predominant influence of prepregnancy BMI than weight gain *per se* (Catalano et al., 1993a, b; Nohr et al., 2008) or error induced by the measurement of weight after the inception of treatment. The evidence linking GWG to the hypertensive disorders of pregnancy is also inconclusive because of inconsistent results and methodological flaws (Rasmussen et al., 2009). Similarly although there is a modest association between increased GWG and Caesarean section rates (Rasmussen et al., 2009), the contribution of GWG is modest relative to that of prepregnancy BMI. Furthermore, the relationship between GWG and the risk of large-for-gestational age (LGA) delivery is most pronounced in women with a low BMI, not those with a high BMI.

The most consistent adverse outcome for mothers with large GWG is increased post-partum weight retention which is maintained up to 3 years after the index pregnancy, independent of prepregnancy BMI (Nohr et al., 2008; Rasmussen et al., 2009). This, in turn, is likely to contribute to adverse outcome in the next pregnancy, most convincingly shown in a study of 151 000 Swedish women, in which a gain of 3 kg/m<sup>2</sup> or more was associated with increased risk for pre-eclampsia, gestational hypertension, gestational diabetes, Caesarean delivery, still-birth and LGA birth in the second pregnancy. The associations were linearly related to the gain in weight and were also noted in women who had a healthy prepregnancy BMI for both pregnancies (Villamor and Cnattingius, 2006).

## Maternal metabolism

### Lipid metabolism

Lipid metabolism undergoes major adjustment during pregnancy as, although there is no change in either basal carbohydrate oxidation or non-oxidizable carbohydrate metabolism, there is a significant 50–80% increase in basal fat oxidation during pregnancy and also in response to glucose (Okereke et al., 2004). There is also marked hyperlipidaemia in pregnancy (Knopp et al., 1973; Warth et al., 1975; Alvarez et al., 1996). Specifically, very low-density lipoprotein

(VLDL) triglyceride concentrations increase 3-fold from 14-weeks gestation to term (Fahraeus et al., 1985), with concomitant decreases in the hepatic lipase activity (Alvarez et al., 1996). This increase in the plasma triglyceride concentration may drive the appearance of small dense LDL particles, particularly in late pregnancy (Sattar et al., 1997). Plasma cholesterol levels rise to a lesser degree due to an early decrease in LDL followed by a modest continuous rise in high-density lipoprotein (HDL) (particularly the HDL-2 subfraction) by over 40% after 14-weeks gestation (Fahraeus et al., 1985). HDL cholesterol exhibits a triphasic profile, rising to a peak at 25 weeks, and then declining to 32 weeks with maintenance at this level until term (Desoye et al., 1987). These changes in lipoprotein concentrations are associated with the progressive increases in estradiol, progesterone and human placental lactogen (Desoye et al., 1987), and estrogens are known to enhance VLDL production and decrease the hepatic lipase activity and may play a key role in the accumulation of triglycerides in lipoproteins of higher density than VLDL (Sacks and Walsh, 1994).

In obese pregnant women, this hyperlipidaemia is exaggerated. Total and VLDL triglycerides are increased further and plasma HDL is even lower, whereas, in contrast, LDL is unaltered (Merzouk et al., 1998; Ramsay et al., 2002; Rajasingam et al., 2009). The relative inability of insulin to suppress whole-body lipolysis leads to a marked increase in plasma free fatty acids in obese patients (Sivan et al., 1999), thereby further amplifying the already higher concentrations associated with obesity (Catalano et al., 2002). The increases in fat oxidation are also maintained even in the absence of changes to carbohydrate metabolism, with an inverse correlation between endogenous glucose production and fat oxidation from prepregnancy to early gestation (Okereke et al., 2004). Lastly, the susceptibility of LDL to oxidation, a classic associate of endothelial dysfunction, atherosclerosis and cell toxicity is exacerbated by maternal obesity (Sanchez-Vera et al., 2007). Collectively the pattern of dyslipidaemia observed in obese pregnancy is therefore similar to those observed in non-pregnant obese individuals (Sattar et al., 1998).

This dyslipidaemia may also contribute to obesity-related vascular complications including pre-eclampsia—with maternal hypertriglyceridaemia being a characteristic of women destined to develop pre-eclampsia (Potter and Nestel, 1979; Lorentzen et al., 1994; Sattar et al., 1997; Enquobahrie et al., 2004; Ramsay et al., 2004; Vadachkoria et al., 2006; Rajasingam et al., 2009). The observed changes in triglycerides in pre-eclampsia are accompanied by an almost 3-fold higher VLDL1, a 2-fold increase in VLDL2 concentration (Sattar et al., 1997; Ramsay et al., 2004), marked increases in free fatty acids, and a 3-fold increase in small dense LDL, with a reduction in large buoyant LDL subfractions (Sattar et al., 1997; Hubel et al., 1998; Ramsay et al., 2004; LLurba et al., 2005). It is these small dense LDL particles that are increased in both pre-eclampsia and obesity that are highly atherogenic and capable of promoting foam cell formation and endothelial dysfunction (Griffin et al., 1994), with further impairment of endothelial function by elevated free fatty acids. Collectively this suggests that obese women or women with excessive GWG may have sufficient pre-existing or newly acquired dyslipidaemia to facilitate the acute development of placental bed atherosclerosis and pre-eclampsia. Furthermore, this association, in conjunction with increased inflammation, would provide a potential explanation for the strong epidemiological associations of pre-eclampsia with prepregnancy BMI and



excessive GWG in non-obese women (Sebire *et al.*, 2001; Ramsay *et al.*, 2004; Institute of Medicine, 2009).

### Amino acid metabolism

In pregnancy, the majority of amino acids are utilized for protein synthesis, with a reduction in the amount oxidized by ~10% (Duggleby and Jackson, 2002). Although, counter-intuitively there is no increase in measured protein synthesis in the first trimester, there is an increase in the second and third trimester of 15% and 25% respectively (de Benoist *et al.*, 1985; Jackson, 1987; Thompson and Halliday, 1992; Willommet *et al.*, 1992). These changes are greater than can simply be accounted for by highly active protein synthesis in the fetus and placenta, implying an overall increase in protein synthesis in maternal tissues including the liver, breasts and uterus. The impact of maternal protein turnover on the fetus is striking, with a greater maternal protein synthesis in the second trimester being associated with an increase in birth length and accounts for 26% of the overall variance (Duggleby and Jackson, 2001). The proportion of amino acid metabolism, which is directed towards protein synthesis rather than oxidation, can also modify birthweight, with 34% of the variance of birthweight related to this shift (Duggleby and Jackson, 2002).

At present, the impact of obesity on amino acid metabolism is unknown. However, in non-pregnant obese women, protein synthesis is stimulated less in a hyperinsulinaemic state in comparison with lean women, with no difference in protein oxidation (Chevalier *et al.*, 2005). Obesity is also associated with a greater supply of gluconeogenic amino acids to the liver with preference of their use over glycogen for glucose production (Chevalier *et al.*, 2006). Lastly, visceral lean mass is positively correlated with maternal protein turnover (Duggleby and Jackson, 2001). Collectively, these data would suggest that the anabolic response to pregnancy may be impaired in obese women, raising the possibility that mechanisms may exist to limit fetal growth in a hyperinsulinaemic and glucose-rich environment.

### Glucose metabolism and insulin resistance

In normal pregnancies, dynamic changes in glucose homeostasis and insulin sensitivity accompany the alterations in lipid and protein metabolism. In early pregnancies, maternal fasting glucose decreases by 2 mg/dl very early in gestation (weeks 6–10), with little further decrease by the third trimester (Mills *et al.*, 1998). Basal hepatic glucose production increases with advancing gestation (16–30%), as does total gluconeogenesis to meet the increasing needs of the placenta and fetus (Kalhan *et al.*, 1979, 1997; Catalano *et al.*, 1992; Assel *et al.*, 1993). Post-prandial glucose concentrations are also significantly elevated and the glucose peak is prolonged (Cousins *et al.*, 1980). These increases in glucose production occur despite significant rises in fasting insulin concentrations (Catalano *et al.*, 1992) and are also relative to maternal body weight, such that glucose production per kilogram body weight does not change throughout pregnancy (Kalhan *et al.*, 1997). Commensurate with the increased rate of glucose production, there is an increased contribution of carbohydrate to oxidative metabolism in late pregnancy, with absolute rates of 282 g/day when compared with 210 g/day (Butte *et al.*, 1999).

Facilitating these alterations in glucose homeostasis is marked changes in insulin secretion and sensitivity. During early pregnancies, glucose tolerance is normal or slightly improved and peripheral

(muscle) sensitivity to insulin and hepatic basal glucose production is normal (Catalano *et al.*, 1991, 1992, 1993a, b). This is accompanied by a greater-than-normal sensitivity to the blood glucose-lowering effect of exogenously administered insulin in the first trimester than in the second and third trimesters. Longitudinal studies of glucose tolerance during gestation demonstrate an increased insulin response to oral glucose in the first trimester relative to prepregnancy values (Catalano *et al.*, 1991, 1999), with a subsequent progressive increase in nutrient-stimulated insulin responses despite only a minor deterioration in glucose tolerance, consistent with progressive insulin resistance (Catalano *et al.*, 1991, 1999). Notably, there is also an independent effect of pregnancy on  $\beta$ -cell function independent of the observed changes in insulin; however, the aetiology of this effect is at present unknown, although may include the incretins GIP and GLP-1 (Meier *et al.*, 2005; Cypryk *et al.*, 2007). Overall, the insulin sensitivity of late normal pregnancy is reduced by 50–70% compared with normal, non-pregnant women (Ryan *et al.*, 1985; Catalano *et al.*, 1991, 1992, 1993a, b), with significant increases in basal insulin and the response to glucose with concomitant decreases in insulin clearance (Catalano *et al.*, 1991, 1998a, b; Agardh *et al.*, 1996). Consequently by the third trimester, basal and 24-h mean insulin concentrations may double and the first and second phases of insulin release are 3–3.5-fold greater in late pregnancy (Catalano *et al.*, 1991).

The impact of obesity on these changes is substantial, in particular the decline in fasting glucose in early gestation is reduced, and glucose is not reduced at all in severely obese women (Mills *et al.*, 1998). In late gestation, the normal reduction in peripheral insulin sensitivity of 50% (Catalano *et al.*, 1991) is reduced in obese women as determined by the quantitative insulin sensitivity check index (Endo *et al.*, 2006)—a validated surrogate for the direct measurement of insulin sensitivity using the euglycemic hyperinsulinemic clamp (Kirwan *et al.*, 2001). In addition, there is marked peripheral and hepatic insulin resistance, which manifests as reduced insulin-mediated glucose disposal, a large reduction in insulin-stimulated carbohydrate oxidation and a reduction in insulin suppression of endogenous glucose production, all of which are reversed in the post-partum period (Sivan *et al.*, 1997). Importantly, the overall effects of this impaired insulin resistance are not limited to glucose. In the post-prandial state, this obesity-related insulin resistance exaggerates the normal circulatory increases in metabolic fuels, i.e. glucose, lipids and amino acids. In fact, the fasting, post-prandial and integrated 24 h plasma concentrations of all three macronutrients are affected by enhanced insulin resistance in obese women. Consequently, the impaired glucose uptake exposes the fetus to hyperglycaemia; the inability to suppress whole body lipolysis leads to an increase in free fatty acids available for placental transfer, and the decreased ability of insulin to suppress amino acid turnover causes an elevation in maternal concentrations of branched-chain amino acids, again facilitating transfer of excess nutrients to the fetus. These alternative nutrient pathways may independently contribute to macrosomia, as maternal serum triglycerides and amino acid profiles (serine, threonine, lysine, proline, ornithine and arginine) have been associated with offspring birthweight independent of maternal glucose or prepregnancy BMI (Kalkhoff *et al.*, 1988; Nolan *et al.*, 1995; Di Cianni *et al.*, 2005; Schaefer-Graf *et al.*, 2008).

Although the precise mechanisms regulating insulin sensitivity are uncertain, it would appear that preconceptual fat mass is a major

determinant. Lean women exhibit an inverse correlation between changes in insulin sensitivity and fat mass, which is not seen in obese women (Catalano et al., 1998a, b; Okereke et al., 2004). Obese women do however exhibit a negative relationship between the decrease in insulin sensitivity and accretion of fat mass from pre-pregnancy to late gestation (Okereke et al., 2004). Additionally, although changes in insulin sensitivity related to later pregnancy are primarily mediated at the peripheral level and secondarily at the hepatic level, elevated levels of non-esterified free fatty acids in later pregnancy may also contribute to peripheral and hepatic insulin resistance (Sivan et al., 1998; Homko et al., 2003), with adipose-derived estrogen facilitating further increases in lipids. The peripheral resistance may be mediated by reduced adipose tissue insulin receptor substrate-1 protein levels, which are 43% lower in obese women with gestational diabetes (Catalano et al., 2002). Circulating concentrations of peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) mRNA and protein are also lower than normal (Catalano et al., 2002), and given that PPAR $\gamma$  acts as an important regulator of adipose lipid storage and as a regulator of insulin sensitivity, this may further reduce the insulin suppression of lipolysis in obese pregnancy.

## Longer-term consequences for the child of maternal obesity and altered metabolic state

These profound disturbances in maternal metabolism associated with obesity have obvious and immediate consequences for the growth of the developing fetus, but it is also now widely appreciated that alteration in the maternal nutritional environment may have persistent and effects for the developing child and health in adulthood. The high prevalence of maternal obesity and the emergence of obesity among even very young children have led to the suggestion that the risk of obesity in children could be acquired as a direct consequence of shared 'obesogenic' environment between mother and child *in utero* or in early post-natal life. Consistent with this is the large number of studies demonstrating a positive association of birthweight with BMI during both childhood and adulthood and the risk of overweight/obesity in later life (Fisch et al., 1975; Kramer et al., 1985; Binkin et al., 1988; Seidman et al., 1991; Rasmussen et al., 1998a, b; Hediger et al., 2009; Pietiläinen et al., 2001; Reilly et al., 2005).

### Childhood obesity: the size of the problem

As maternal obesity rates have increased, so has the incidence of childhood obesity (Ogden et al., 2006). In England, 9.6% of boys aged 2–10 were obese in 1995, and 10.3% of girls; by 2004, this had risen to 15.9% and 12.8%, respectively. Very young children are also showing increasing rates of obesity, even in the first 6 months of life (Kim et al., 2006). The question arises as to whether this may represent a persistent influence of maternal obesity *in utero*. Certainly, increases in LGA delivery rates seem to parallel trends in maternal obesity (Surkan et al., 2004). However, although obesity and related maternal metabolic disorders are undoubtedly a cause of macrosomia (Sebire et al., 2001; Ehrenberg et al., 2004), higher birthweight and birthweight centiles can only act as surrogates for increased infant adiposity due to the potential of variable body composition for any given

birthweight (McFarland et al., 1998). Fortunately, recent studies have explored the direct relationship between maternal body composition and offspring adiposity and suggest that offspring body fat is associated with maternal fat, but not with paternal fat mass (Shields et al., 2006). Neonatal fat mass is also related to the maternal glucose concentration (Shields et al., 2006). Consistent with the prepregnancy BMI data, the same group has subsequently found that maternal fat stores are independently associated with percentage fat mass in the neonate (Harvey et al., 2007). In addition, maternal triceps skin-fold thickness (a measure of maternal adiposity) showed a negative association with the percentage of neonatal lean body mass. Collectively, these data support a relationship between maternal and offspring obesity.

### Maternal metabolism and neonatal adiposity

The recent Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study has highlighted the quintessentially important influence of maternal metabolic balance on offspring birthweight, demonstrating a linear relationship between maternal fasting plasma glucose, and oral glucose tolerance test (OGTT) 1- and 2-h glucose with birthweight above the 90th percentile (Metzger et al., 2008). Importantly, infant adiposity as directly measured by the sum of skin-fold thickness, exhibited a similar strong linear relationship with maternal glucose; moreover there was a strong relationship between cord blood C peptide (a surrogate marker for insulin) and neonatal adiposity, providing some of the most comprehensive evidence yet for the Pedersen hypothesis (Pedersen, 1952; HAPO Study Cooperative Research Group, 2009).

Prior to this, Catalano and colleagues had carried out direct measurement of fat mass and found that infants of women with GDM, even with a normal birthweight, had increased body fat compared with offspring of women with normal glucose tolerance (Hashimoto et al., 2002). Subsequent analysis of neonates of overweight and obese mothers has consistently demonstrated increased percentage of body fat and fat mass compared with offspring of normal weight mothers (Sewell et al., 2006; Hull et al., 2008). Maternal weight gain has also been associated with increased fetal fat free mass and fat mass (Catalano and Ehrenberg, 2006). A fatter maternal phenotype in early pregnancy and subsequently at birth for the offspring may contribute to a predetermined insulin resistant state, as fetal insulin resistance assessed by the homeostasis model of insulin resistance using cord blood demonstrated a strong positive correlation with fetal adiposity and was also strongly associated with pregravid BMI, even with adjustment for potential confounders (Catalano et al., 2009). From these studies, it is reasonable to conclude that obese mothers have not only heavier but fatter babies, but is there evidence to suggest that this association is maintained to childhood and beyond?

### Maternal metabolism and obesity; relationships with long-term offspring adiposity

Higher birthweight is undoubtedly associated with a higher BMI in both boys and girls in childhood and in adulthood (Binkin et al., 1988; Curhan et al., 1996a, b; Sorensen et al., 1997; Rasmussen et al., 1998a, b; Parsons et al., 2001; Oken and Gillman, 2003; Ong, 2006).

Most observational studies in mother/child cohorts also provide evidence of an association between maternal obesity and a higher BMI in childhood and adulthood. In 8494 children from low-income families in OH, USA, the risk of obesity at 2–4 years of age was more than doubled by maternal obesity (Whitaker, 2004), and in 2626 children in the National Longitudinal Study of Youth (NLSY) aged 2–14, the risk of childhood obesity was doubled if the mother was overweight and quadrupled if the mother was obese pre-pregnancy (Li *et al.*, 2005). A later report from the same cohort showed an increased risk of both early and late onset obesity in the child (Li *et al.*, 2007). Lastly, in 3022 USA children (1982–1996), maternal pre-pregnancy obesity was identified as an independent factor for increased risk of early overweight and also the development of overweight with age (Salsberry and Reagan, 2005). The same relationship would appear to pertain outside the USA. In the northern Finland, birth cohort offspring of overweight or obese mothers had a higher mean BMI at birth, 1, 14 and 31 years (Laitinen *et al.*, 2001). The UK ALSPAC cohort of children born in the 1990s has shown an association between maternal obesity pre-pregnancy and childhood obesity at age 7 (Reilly *et al.*, 2005), and Swedish conscripts aged 18 years have a higher risk of obesity if their mothers were obese (Koupil and Toivanen, 2008).

These studies have largely defined childhood obesity based on a BMI at or above the 95th centile; however, in children, BMI shows a large variation with age, as does body composition (Cole *et al.*, 2000; World Health Organization, 2000) and is usually calculated using CDC (USA) or international growth charts (Cole *et al.*, 2000; National Center for Health Statistics, 2009). Notably, direct measurement of skin-fold thickness has suggested that these methods can fail to detect as many as 40–50% of children identified as obese (Zimmermann *et al.*, 2004). Direct measurement of childhood adiposity has however confirmed the earlier studies measuring childhood BMI, with 3-year-old children who had been exposed to gestational diabetes having higher skin-fold thickness compared with those who had not (Wright *et al.*, 2009). Similarly, when measurements of maternal and offspring adiposity have been determined in normal pregnancies, these have demonstrated positive relationships between maternal mid-upper arm circumference (an estimate of adiposity) and offspring body composition (Gale *et al.*, 2007). With respect to maternal BMI, these relationships with fat mass in the child are still evident, with maternal obesity associated with increased adiposity in the 5-year-old children (Burdette *et al.*, 2006). Consistent with this maternal overweight/obesity was an independent determinant of fat mass at the age of 7 as assessed by bioelectric impedance analysis (Blair *et al.*, 2007) and at age 24 as assessed by dual-energy X-ray absorptiometry (Mingrone *et al.*, 2008).

## GWG and offspring adiposity

In view of the relationships between GWG and adverse maternal and neonatal outcome, the impact of GWG on childhood BMI or adiposity has also been examined. Some studies, but not all, indicate that weight gain may be a determinant of offspring obesity but the strength of the effect is generally less than that of maternal obesity *per se*. Specifically, Oken *et al.* (2007) have shown that increasing maternal weight gain was associated with increased adiposity at age 3 and at age 9–14 (Oken, 2008). Another large cohort study from the US Collaborative

Perinatal Project has indicated a similar degree of association (Wrotniak *et al.*, 2008). Maternal weight gain and infant BMI relationships have been reported in studies of Portuguese and German children (Moreira *et al.*, 2007; Kleiser *et al.*, 2009), although in the latter, a significant effect was only found if the mother was of normal weight at the start of pregnancy. Similar results have recently been reported from an Australian cohort, with a relationship between maternal weight gain and offspring BMI still detectable in young adulthood (21 years old) (Mamun *et al.*, 2009). However, as previously observed, there was some evidence that the association was stronger among underweight/normal weight mothers (Mamun *et al.*, 2009). This is not a universal finding as others have reported no relationship between maternal weight gain and offspring BMI (Catalano *et al.*, 1995; Koupil and Toivanen, 2008).

## Mechanisms linking parental and offspring adiposity

At present, given the lack of intervention studies in obese pregnant women, it is impossible to determine whether the relationships between maternal obesity or weight gain and offspring obesity are a facet of direct influences on the developing child by maternal obesity, or whether shared genetic and post-natal lifestyle influences predominate. There is good evidence for co-segregation of obesity in families, and shared dietary and physical activity behaviours (Laskarzewski *et al.*, 1980; Simonen *et al.*, 2002). Some of the earliest evidence to suggest a direct association between fetal and neonatal 'overnutritional' status and development of later obesity was derived from offspring of diabetic mothers, notably from the Pima Indians who have a very high incidence of type 2 diabetes (Pettitt *et al.*, 1983, 1987, 1991, 1993; Dabelea *et al.*, 2000a, b). Importantly, the analysis of siblings discordant for *in utero* exposure to maternal diabetes, thereby mitigating against a role for genetic factors, demonstrated that *in utero* exposure to maternal diabetes was associated with a mean increase in BMI of 2.6 kg/m<sup>2</sup> (Dabelea *et al.*, 2000a, b). Others have found a similar relationship between maternal diabetes, either pregestational type 1 and type 2 or GDM and increased childhood BMI (Silverman *et al.*, 1998; Cho *et al.*, 2000; Schaefer-Graf *et al.*, 2005; Malcolm *et al.*, 2006). Notably, the treatment of GDM has been associated with a reduction in the risk of offspring obesity, lending support to the suggestion of a direct influence of the *in utero* environment on later development of obesity (Hillier *et al.*, 2007). More recently, maternal insulin resistance independent of maternal glucose tolerance status has been associated with increased infant weight gain and adiposity over the first year of life, suggesting that insulin regulation of other nutrients, e.g. lipids and amino acids, may also play a role *in utero* (Hamilton *et al.*, 2009).

Many of the studies mentioned above have attempted to control for shared behaviour and potential confounders, and most describe little modification effect, but none can be complete. Accurate estimation of many of these, including diet and physical activity in children, is difficult. Duration of breast feeding is a potential cofounder (Koletzko *et al.*, 2009), and obese women are less likely to initiate breast feeding or may breast feed for a shorter time than leaner women (Oddy *et al.*, 2006). Rapid growth in the immediate post-natal period is another potential confounder as this is also associated with childhood

obesity or increased adiposity (Monteiro and Victora, 2005; Taveras et al., 2009).

Some, but not all, reports that have addressed relationships between BMI of both parents at the time of the index pregnancy and offspring obesity have generally shown a greater effect of maternal than paternal BMI on offspring BMI (Catalano et al., 2009; Lawlor et al., 2007; Reilly et al., 2005; Salsberry and Reagan, 2005; Moschonis et al., 2008) and this could infer an acquired, as opposed to an inherited, relationship. However, one study suggests this to be explicable by inheritance of the variant of the FTO gene associated with obesity (Lawlor et al., 2008). Recently, Li et al. (2009) have shown that early life, as well as later life, weight gain in parents is associated with offspring obesity. Associations with parental early life weight gain were interpreted as being more indicative of a shared genetic component, or establishment of lifestyle pattern, but could equally reflect influences on maternal or paternal germ cell development that could influence later predisposition to obesity. The association with later life weight gain in parents is consistent with an *in utero* influence of maternal obesity on the offspring. Furthermore, and in line with studies of discordant sibling exposure to maternal diabetes, a report of siblings discordant for maternal obesity exposure due to a bariatric surgery demonstrated that offspring born after surgery were less obese (Kral et al., 2006). However, the family 'nutritional' environment may have changed between pregnancies and it is difficult to draw firm conclusions.

## Intervention strategies

The escalation of obesity among women of reproductive age and the complications both short and long term for the mother and child have provided the stimulus for rapid development of an intervention to improve outcomes. To date, none has been validated for clinical use. Undoubtedly, the most successful intervention will be that which prevents the development of obesity before the reproductive years. However, the high rates of obesity among adolescent girls and the upward trends of obesity among pregnant women suggest that this is not immediately attainable. As reviewed above, we have a good understanding of the changes in metabolism accompanying obesity in pregnancy and central to these is the development of insulin resistance and its metabolic sequelae. Since there are strong similarities between the risk profile for type 2 diabetes and the hyperglycaemia, hyperinsulinaemia and dyslipidaemia that characterize maternal obesity, the extensive literature addressing interventions in type 2 diabetes and gestational diabetes may provide guidance.

### Lifestyle modification as a preventative strategy for type 2 diabetes mellitus

Lifestyle intervention is now a critical component of the treatment strategy for diabetes, hypertension, cardiovascular disease and obesity in non-pregnant patients (Authors/Task Force Members, 2007; Graham et al., 2007). Importantly, effective lifestyle intervention strategies can prevent or at least delay the progression to type 2 diabetes in high-risk individuals (summarized in Table II) (Eriksson and Lindgarde, 1991; Pan et al., 1997; Diabetes Prevention Program Research, 2002; Lindstrom et al., 2003; Ramachandran et al., 2006). Notably, the Finnish Diabetes Prevention Study, in addition to the

58% reduction in the incidence of diabetes incidence, also achieved a significant reduction in weight, BMI, waist circumference, fasting plasma glucose, 2 h plasma glucose, serum triglycerides and serum total cholesterol:HDL cholesterol ratio in the intervention group within a year (Lindstrom et al., 2003). In the US Diabetes Prevention Program, attainment of weight loss was achieved by 50% of participants at 24 weeks and 74% had achieved the physical activity targets; importantly this was also accompanied by significant reductions in plasma glucose (Diabetes Prevention Program Research, 2002). These studies raise the exciting possibility that lifestyle modification in a similar form could be applied to pregnancy to prevent the onset of metabolic- and obesity-related complications.

### Safety of exercise in pregnancy

In theory, there are potential risks to the fetus during maternal exercise, including stimulation of uterine contractility (Spinnewijn et al., 1996), decreased uteroplacental flow due to preferential shunting to skeletal muscles (Kennelly et al., 2002), potentially fetal hypoglycaemia secondary to increased glucose used by skeletal muscles and reductions in circulating maternal glucose (Bonet et al., 1992) and hyperthermia from exercise. However, in reality, physical activity has not been associated with adverse obstetric complications beyond 18 weeks gestation (Madsen et al., 2007), and with respect to preterm birth may even be protective (Berkowitz et al., 1983; Hatch et al., 1998; Misra et al., 1998; Evenson et al., 2002). Furthermore, maternal hypoglycaemia, even in type 1 diabetes, has not been consistently associated with adverse neurodevelopment in the offspring, despite maternal plasma  $\beta$ -hydroxybutyrate, an index of ketosis and potentially the necessity for alternative fuel use, being negatively associated with psychomotor and intellectual development (Rizzo et al., 1991, 1995).

Given that physical activity may impact on insulin resistance, thereby reducing circulating glucose levels and decreasing the amount of glucose available for the fetus—there is the potential for an impact on fetal adiposity and birthweight. To date, three different meta-analyses have demonstrated that leisure time physical activity (LTPA) does not influence birthweight (Lokey et al., 1991; Leet and Flick, 2003; Kramer and McDonald, 2006). However, vigorous endurance exercise during the third trimester was potentially associated with a 200–500 g lower birthweight (Clapp and Dickstein, 1984; Bell et al., 1995). Should birthweight be similarly reduced across the whole range? This would be detrimental as the incidence of small-for-gestational age babies would be increased. However, if this reduction in birthweight was restricted to women who are at risk of delivering LGA infants, this would be beneficial and may reduce birth complications and the need for operative delivery. In support of this, moderate or vigorous physical activity for 2 h/week was associated with a reduced risk of delivering a LGA infant [OR 0.3 (95%CI 0.2–0.7)] but was not accompanied by an increase in small-for-gestational age infants (Alderman et al., 1998). At present, however, it is not known whether this iatrogenic growth restriction is associated with any of the classical adverse perinatal and long-term outcomes as those observed for the low birthweight growth restricted infants. Follow-up of the children in the intervention studies where birthweight has been successfully reduced will further inform this, but at present modification of birthweight has been associated with



**Table II Summary of the four lifestyle intervention studies that aimed at preventing type 2 diabetes in non-pregnant subjects with impaired glucose tolerance**

Study	Cohort size	Intervention	Mean BMI (kg/m <sup>2</sup> )	Duration (years)	RRR (%)	ARR (%)	NNT
Malmö	217	Dietary and/or increased physical activity or training	26.6	5	63	18	28
DPS	523	Aim for ≥5% reduction in bodyweight, respectively, through diet and physical activity  <i>Diet:</i> a reduction in dietary fat to <30 proportion of total energy (E%) and saturated fat to <10%E, while increasing fibre to ≥15 g/1000 kcal. Achieved by face-to-face consultation sessions (from 30 min to 1 h) with the study nutritionist at weeks 0, 1–2 and 5–6 and at months 3, 4, 6 and 9, i.e. altogether seven sessions during the first year and every 3 months thereafter  <i>Physical activity:</i> aim of moderate physical activity of ≥30 min/day achieved through progressive, individually tailored circuit type moderate intensity resistance training sessions, exercise competitions, voluntary group walking and hiking	31	3	58	12	22
DPP	2161 <sup>a</sup>	Aim for ≥7% reduction in bodyweight, respectively, through diet and physical activity  <i>Diet:</i> a healthy low-calorie, low-fat diet  <i>Physical activity:</i> moderate intensity, such as brisk walking, for at least 150 min/week	34	3	58	15	21
Da Qing	500	Exercise, diet or exercise + diet	25.8	6	46	27	25
IDDP-I	531	Physical activity target of moderate physical activity of >30 min/day and dietary advice including reduction in total calories, refined carbohydrates and fats, avoidance of sugar and inclusion of fibre-rich foods	25.7	3	28	15	19

RRR, relative risk reduction; ARR, absolute risk reduction/1000 person-years; NNT, numbers needed to treat to prevent one case of diabetes over 12 months; DPS, The Finnish Diabetes Prevention Study; DPP, Diabetes Prevention Program; IDDP-I, Indian Diabetes Prevention Programme.

<sup>a</sup>Combined numbers for placebo and diet and exercise groups.

improvement in significant perinatal and neonatal metabolic sequelae (Crowther et al., 2005; Langer et al., 2005; Landon et al., 2009).

### Lifestyle modification as a strategy for improving glycaemic control in GDM

Given the positive impact of lifestyle modification on type 2 diabetes and potentially birthweight, a similar approach has been applied to GDM. Initial management of affected women now consists of glucose monitoring and lifestyle modification including dietary counselling and a diet that restricts carbohydrates to 35–40% of daily calories (American Diabetes Association, 2003; Reece et al., 2009). This is based on data demonstrating that carbohydrate restriction decreases maternal glucose concentrations and improves maternal and fetal outcomes (Major et al., 1998). Furthermore, in obese women with diabetes, a 30–33% calorie restriction (to ~25 kcal/kg actual weight per day) reduced hyperglycaemia and plasma triglycerides with no increase in ketonuria (Franz et al., 1994). However, despite diet being a core component of management, it is now recognized that dietary advice alone is insufficient for many GDM patients (Moses et al., 2009), and outcomes are improved if it is combined with pharmacological therapy including metformin (Tuffnell et al., 2003; Crowther et al., 2005; Rowan et al., 2008). Although metformin may seem an attractive therapeutic option in obese pregnancy, in one small RCT of 40 women with polycystic ovarian syndrome, it did not reduce the incidence of GDM (Fougner et al., 2008). Furthermore, metformin is not as effective as lifestyle intervention in preventing type 2 diabetes in women with a history of gestational diabetes (Ratner et al., 2008).

Regular physical activity has repeatedly been shown to improve glycaemic control in women with GDM (Avery and Walker, 2001; Brankston et al., 2004; Garcia-Patterson et al., 2001; Jovanovic-Peterson et al., 1989). Primarily due to the physiological pregnancy-related increases in insulin resistance being reduced by moderate intensity daily physical activity (Clapp and Capeless, 1991, Clapp et al., 1992). However, most of these trials studied the effects of a short-term exercise program (i.e. a single bout or only several weeks). Studies on longer-lasting exercise programs, especially those continuing into the third trimester of pregnancy, are currently lacking, and most studies have concerned the treatment, and not the prevention of GDM. However, given the positive impact on type 2 diabetes and GDM, consideration of prophylactic lifestyle modification would be appropriate.

### Lifestyle modification as a strategy for preventing GDM

Epidemiological studies have suggested that physical activity prior to and during pregnancy may significantly reduce the risk of gestational diabetes (Dempsey et al., 2004a, b). Not surprisingly, the highest reduction is seen in women engaged in LTPA during both time periods (RR 0.31, 95% CI: 0.12–0.79) (Dempsey et al., 2004a, b). To date, however, there is a paucity of trial data examining the role of lifestyle modification for the prevention of gestational diabetes (Weissgerber et al., 2006). A pilot study examining controlled energy intake during pregnancy (8350 kJ/day, 200 g/day carbohydrate) combined with exercise at 30%  $\text{VO}_2$  peak demonstrated that this combination was better than mild exercise alone at

controlling blood glucose concentrations, as indicated by a fasting OGTT in late pregnancy (Weissgerber et al., 2006). However, subsequent application of this combined exercise and lifestyle program was only to a small cohort of women at risk of GDM ( $n = 23$ ), and although GDM was prevented, the small numbers prevent any firm conclusion (Weissgerber et al., 2006). Larger, purely physical activity based, studies are currently being undertaken; however, they are still modest in size (Oostdam et al., 2009a, b) and appear limited relative to the non-pregnant diabetes prevention studies, which aimed for a combination of modification of diet, exercise and also attainment of weight loss.

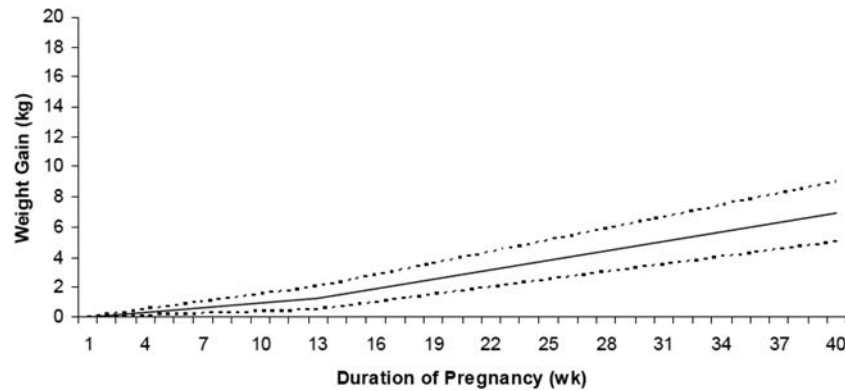
With respect to diet, the aim is to reduce post-prandial glucose levels and thereby fetal growth (Dornhorst and Frost, 2002). Low glycaemic index diets are the most frequently used instrument to achieve this, and reduce post-prandial glucose peaks as well as fasting glucose levels (Thomas and Elliott, 2009). Unfortunately, assessment of a role in the prevention of insulin resistance in pregnancy is limited. Moses et al. (2006) demonstrated that a low GI (glycaemia index) diet ( $n = 32$ ) compared with a high GI diet ( $n = 30$ ) was associated with a reduction in fasting glucose and a reduction in birthweight and incidence of LGA. Fraser established that a high-fibre diet ( $n = 13$ ) when compared with a normal pregnancy diet ( $n = 12$ ) significantly attenuated post-prandial insulin secretion (Fraser et al., 1983). Clapp combined these principles with an exercise program and demonstrated in a randomized controlled trial of 20 women that the combination of a low glycaemic diet and exercise significantly reduced birthweight, ponderal index and maternal fasting blood glucose (Clapp, 2002).

Together, these lifestyle modification trials are still too small to provide definitive conclusions (Tieu et al., 2008), but suggest that diets which are characterized by low GI and high-fibre content combined with exercise would be appropriate for obesity (Thomas et al., 2007).

### Interventions for maternal obesity

Among obese pregnant women, the primary outcome of any intervention study requires careful choice. The majority of those underway or the preliminary studies already published focus on prevention of excessive weight gain as defined by the Institute of Medicine (IOM). Observational studies undoubtedly show that women whose GWG falls within the 1990 IOM guidelines experience a better pregnancy outcome, and the new IOM 2009 guidelines provide new and more evidence-based targets for each category and, for the first time, a specific weight gain range for obese women (5–9 kg) (Rasmussen et al., 2009) (Fig. 3, Table III). However, as described above, excessive GWG is only weakly associated with several of the primary abnormalities linked to obesity including GDM and pre-eclampsia. Despite this, if observational studies are translatable to effects of intervention, prevention of excessive GWG among pregnant women could reduce the risk of LGA, Caesarean section, post-partum weight gain and potentially, childhood obesity.

In contrast, in view of the close association between obesity and insulin resistance as outlined above, and the proposed role that this plays in GDM, pre-eclampsia and macrosomia, maternal insulin resistance may be an alternative primary outcome in intervention studies. Dietary and exercise regimes targeted at gestational diabetes have shown some promise, and although relatively few, previous



**Figure 3** Recommended weight gain by week of pregnancy for obese (BMI  $\geq 30$  kg/m<sup>2</sup>) women (dashed lines represent the range of weight gain) (Institute of Medicine, 2009).

**Table III** New recommendations for total and rate of weight gain during pregnancy by prepregnancy BMI

Pregpregnancy BMI	Total weight gain		Rates of weight gain second and third trimester	
	Range (kg)	Range (lbs)	Mean (range; kg/week)	Mean (range; lbs/week)
Underweight (<18.5 kg/m <sup>2</sup> )	12.5–18	28–40	0.51 (0.44–0.58)	1 (1–1.3)
Normal weight (18.5–24.9 kg/m <sup>2</sup> )	11.5–16	25–35	0.42 (0.35–0.50)	1 (0.8–1)
Overweight (25.0–29.8 kg/m <sup>2</sup> )	7–11.5	15–25	0.28 (0.23–0.33)	0.6 (0.5–0.7)
Obese ( $\geq 30$ kg/m <sup>2</sup> )	5–9	11–20	0.22 (0.17–0.27)	0.5 (0.4–0.6)

Calculations assume a 0.5–2 kg (1.1–4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

interventional strategies in GDM do provide a template for trials in obesity. Notably in practical terms, the lifestyle interventions that are offered to obese women to limit weight gain and to prevent insulin resistance, namely increased physical activity and dietary advice and individual counselling, may differ only slightly.

As described above, physical activity is a modifiable factor which reduces insulin resistance and is likely to reduce GWG. In a recent study from the Project Viva cohort, midpregnancy walking (OR 0.92; 95% CI 0.83–1.01, per 30 min/day) and vigorous physical activity (OR 0.76; 95% CI 0.60–0.97, per 30 min/day) were inversely associated with excessive GWG (Stuebe et al., 2009). Dietary advice, whether it is to reduce insulin resistance or calories, involves avoidance of simple sugars and saturated fats with adherence to a 'healthy diet', but the emphasis will slightly differ with each approach. Dietary energy density is also a modifiable factor which may assist pregnant women to manage weight gain, but this remains to be proven in adequately powered trials (Kramer and Kakuma, 2003; Olafsdottir et al., 2006; Deierlein et al., 2008; Stuebe et al., 2009). Importantly, although dietary glycaemic load has been found not to be associated with GWG (Deierlein et al., 2008), one study suggested that low glycaemic index diet does reduce GWG (Clapp, 2002). Lastly, focusing on prevention of weight gain, if misinterpreted by the pregnant women, has the disadvantage that it may increase the risk of inappropriate fasting or excessive caloric restriction leading to

excessive ketonuria and ketonemia, and the potential to adversely impact upon neurocognitive and motor skill development of the offspring (Stehbens et al., 1977; Rizzo et al., 1991; Rizzo et al., 1995).

Perhaps the greatest challenge for obese women, however, is to achieve these behavioural changes. Understanding barriers to behavioural change using validated instruments in obese pregnant women is a prerequisite in the development of a successful intervention. Obese women are likely to have low self-esteem, and as prepregnancy weight increases, so do psychosocial measures of perceived stress, trait anxiety and depressive symptoms (Laraia et al., 2009). Furthermore, women who gain excess weight in pregnancy relative to the IOM 1990 guidelines are more likely to demonstrate symptoms of depression (Webb et al., 2009). The barriers to physical activity are also substantial, with 85% of women identifying lack of time, tiredness and the inherent physical constraints of pregnancy (Evenson et al., 2008). Socioeconomic factors are also important as pregnant women who are younger, less educated, with a higher BMI, and who have more children are more likely to eat a poor quality and energy dense diet (Rifas-Shiman et al., 2009). Pilot trials of complex interventions are an essential preliminary (Craig et al., 2008), in which psychosocial assessment is an integral part, as well as the objective measurement of dietary and physical activity before and after the intervention, in order to prove efficacy of the intervention prior to embarking on large randomized controlled trials. These feasibility

**Table IV Summary of completed and ongoing lifestyle intervention studies in relation to weight gain and/or obesity**

Authors	Design	Population and sample	Intervention	Outcome
<b>Completed studies</b>				
Gray-Donald <i>et al.</i> (2000)	Prospective intervention study	219 aboriginal Cree women in Quebec, Canada	Intervention: several components, e.g. exercise groups and individual counselling Control: not specified	GWG: no effect  Diet: caffeine intake decreased only PA <sup>1</sup> : no effect
Polley <i>et al.</i> (2002)	Randomized controlled trial	Low-income women (USA) 61 normal BMI, 49 overweight. Control: standard care	Stepped care intervention; healthy eating and exercise advice. Newsletters on diet, physical activity biweekly, telephone contact between visits	Intervention effective in preventing excessive weight gain (IOM, 1990) only in normal weight women. No effect on diet or physical activity
Olson <i>et al.</i> (2004)	Prospective cohort with historical control group	421 normal BMI, 139 overweight rural, primarily white women (USA). Control: historical, care not specified	Healthcare provider monitoring of weight gain; newsletters by mail with return postcards for goal setting; booklet for self-monitoring of weight gain. No visits for dietary or physical activity counselling	Significant effect in preventing excessive weight gain (IOM, 1990) in low-income women only. Diet and physical activity not assessed
Kinnunen <i>et al.</i> (2007)	Selected intervention ( <i>n</i> = 3) and control ( <i>n</i> = 3) maternity clinics	105 (all BMI) primiparous women, control, standard care	Individual counselling on diet and physical activity. Control: standard care. Visits: physical activity-one primary, four boosters; diet-one primary and three boosters	No effect on excessive weight gain (IOM, 1990). Diet; significantly improved fruit and vegetable intake. No effect on physical activity. Intervention group achieved better moderate or physical activity in 3rd trimester; 46% intervention v 30% in control
Claesson <i>et al.</i> (2008)	Prospective interventional study (intervention and comparison cities)	348 obese (BMI > 30) Swedish women. Control; standard care	Motivational sessions with midwife (individual weekly 30 min). Aqua aerobics twice a week	Significant effect on weight gain <7 kg. Diet and PA not assessed
Wolff <i>et al.</i> (2008)	Randomized controlled trial	50 obese (BMI > 30) non-diabetic, non-smoking Danish women. Control, routine antenatal care	10 1 h consultations with dietician to achieve energy reduction according to Danish micronutrient guidelines. Weighed food records	Significant effect on weight gain (6.6 versus 13.3 kg in control). Diet; significant reduction in energy and % of energy as fat. Carbohydrate and protein as %energy increased. Physical activity not assessed
Asbee <i>et al.</i> (2009)	Randomized controlled trial	100 (BMI 25.5) USA women	Initial consultation with dietician. Advised to exercise 3–5 times/week. Information on IOM GWG guidelines. Weighing and advice by healthcare provider at subsequent routine appointments	Effective reduction in weight gain (mean). Routine care group significantly more Caesarean sections. Women with higher BMI less likely to adhere to IOM guidelines. Diet not assessed, physical activity not assessed
Guelinckx <i>et al.</i> , submitted for publication	Randomized controlled trial	195 (BMI > 29 kg/m <sup>2</sup> ) non-diabetic Belgian women. Control group routine antenatal care, passive group given detailed information leaflet and an active group	Three group sessions at 15, 20 and 32 weeks with dietician focusing on healthy eating habits, importance of physical activity and strategies to control eating behaviour	No reduction in GWG in passive or active arm. No impact on birthweight, macrosomia, hypertensive disorders of pregnancy or Caesarean section
Thornton <i>et al.</i> (2009)	Randomized controlled trial	257 non-diabetic obese USA women. Control unmonitored routine antenatal care with prenatal dietary management	A balanced nutritional regimen, with women asked to record in a diary all of the foods eaten during each day	Significant reduction in GWG and post-partum weight. No impact on gestational hypertension
<b>Ongoing studies</b>				
Althuisen <i>et al.</i> (New Life study)	Randomized controlled trial	Healthy nulliparous women (7 months pregnant) <i>n</i> = 300 (the Netherlands)	Tailored advice on physical activity and diet	GWG in relation to IOM guidelines BMI and skin-fold thickness
Brand-Miller (the CHOPP study)	Randomized controlled trial	Pregnant women ( <i>n</i> = 1650, Sydney, Australia)	Low glycemic index diet from 12 to 16 weeks until delivery	LGA delivery; childhood obesity



Chasan-Taber <i>et al.</i> (the B.A.B.Y. study)	Randomized controlled trial	Pregnant sedentary women with GDM in a prior pregnancy ( $n = 364$ , Western Massachusetts, USA)	Tailored advice on physical activity	Incidence of gestational diabetes, physical activity levels and circulating concentrations of glucose, insulin, leptin, TNF- $\alpha$ , resistin, CRP, adiponectin
Dodd <i>et al.</i> (the LIMIT trial)	Randomized controlled trial	Overweight and obese pregnant women ( $n = 2500$ , Australia)	Dietary package and lifestyle advice	GWG
Hauner	Randomized controlled trial	Pregnant and lactating women ( $n = 210$ , Munich, Germany)	n-3 fatty acids from 15 weeks gestation until 4 months post-partum	Body mass of newborn with follow-up until age 5
Ko <i>et al.</i>	Randomized uncontrolled	Pregnant women receiving prenatal care (WA, USA)	Vigorous physical activity	Central adiposity 6–8 weeks post-partum
Krummel <i>et al.</i>	Randomized controlled trial	Obese pregnant women (Cincinnati USA)	Dietary docosahexanoic acid (DHA) supplements from 24 to 28 weeks gestation until term	Maternal insulin sensitivity
Louto <i>et al.</i>	Cluster randomized controlled trial	Women at risk of gestational diabetes (overweight, age 40 years or older, earlier macrosomic child, diabetic first degree relatives) (Finland)	Tailored diet and physical activity counselling, five visits to public health nurse. Monthly group session with physiotherapist	Primary; gestational diabetes, birthweight. Secondary; maternal weight gain, childhood weight at 1 year; requirement for insulin treatment in pregnancy
Ludwig <i>et al.</i>	Randomized controlled trial	Overweight and obese (BMI > 25, <45) pregnant women (Boston, USA)	Low glycaemic load	Birthweight z-score
Parat <i>et al.</i>	Randomized controlled trial	Overweight or obese women (Paris, France)	Counselling on healthy eating and modest exercise	30% reduction in rapid infancy weight gain at 2 years
Fit for 2 study (Oostdam <i>et al.</i> , 2009a, b)	Randomized controlled trial	Dutch women obese (BMI > 30) or overweight with a history of macrosomia or abnormal glucose tolerance in previous pregnancy or first grade relative with type 2 GDM 2 groups of 64 subjects	Intensive exercise program (2 days of week, 60 min each)	Maternal fasting plasma glucose and relative insulin resistance. Primary neonatal outcome birthweight, QUALY
Poston <i>et al.</i> (The UPBEAT Study)	Pilot trial followed by randomized controlled trial	2700 obese pregnant women (UK)	Tailored advice on physical activity and diet. Group sessions	Pilot study; change in dietary and physical activity behaviours, QUALY and barriers to behavioural change. RCT; maternal insulin resistance. Primary neonatal outcome birthweight, QUALY
Shaheta <i>et al.</i>	(1) Observational Study; (2) Randomized controlled trial	(1) All pregnant women delivering in District General Hospital; (2) Women with a BMI > 40	Measurement of waist circumference at booking & 20/40. Metformin plus exercise versus metformin	Macrosomia, pre-eclampsia and GDM
Shen <i>et al.</i>	Randomized controlled trial	All BMI pregnant women (Manitoba, USA)	Community-based lifestyle intervention package (diet and exercise) during and after pregnancy	Excessive GWG
Vintner <i>et al.</i>	Randomized controlled trial	Obese (BMI > 30) pregnant women ( $n = 360$ ; Odense, Denmark)	Individualized counselling on diet and physical activity	Multiple obesity-related adverse pregnancy outcomes

studies also offer insight into the practical issues which underpin success or failure (Kinnunen et al., 2008).

The few published exploratory trials of relevant complex interventions in pregnant women are summarized in Table IV, together with ongoing studies of which we are aware. Of those completed, most have included advice on physical activity and diet, with individual counselling, and all have focused on the promotion of healthy weight gain. As all were exploratory studies, none was adequately powered to address relevant health outcomes or birthweight. When specified, control groups have generally been subjected to routine care. Not all have undertaken objective assessment of diet or physical activity, and none has reported assessment of barriers to behavioural change or changes in quality of life. The two studies to have objectively measured physical activity have shown no effect (Gray-Donald et al., 2000; Polley et al., 2002), and of the four which have assessed diet, one showed a reduction only in caffeine intake (Gray-Donald et al., 2000) and two a change towards the recommended dietary strategy (Kinnunen et al., 2008; Wolff et al., 2008). Effects on GWG have been variable, with three showing a significant reduction (Claesson et al., 2008; Wolff et al., 2008; Asbee et al., 2009), one a reduction among women of normal weight (Polley et al., 2002) and another being effective amongst low-income women only (Polley et al., 2002). Importantly, one report showed a significant improvement in plasma insulin and leptin in the intervention group (Wolff et al., 2008). The intensity of the intervention has also been variable from one study using weekly 30 min interviews and aqua aerobic classes once or twice a week (Claesson et al., 2008) and in another ten 1 h consultations with a dietician (Wolff et al., 2008), but do suggest that more intense and frequent interventions are more likely to be successful. However, interventions that are effective in one population may be inappropriate in another. Variations in healthcare practice, population demographics and access to opportunities for physical activity are all likely to influence success, and in the longer term, there will be need for evidence of health economic benefit for adoption by healthcare providers.

## Conclusions

The maternal obesity 'epidemic' has stimulated the need for the development of effective interventions to improve pregnancy outcome. The rationale for new interventions should incorporate a detailed understanding of the maternal metabolic environment and its consequences for the health of the mother and the child. Several randomized controlled trials are planned or underway, and using slightly different strategies should inform the best approach to effective intervention and evidence for or against adoption of the new IOM GWG guidelines. Importantly, follow-up of childhood body composition in successful studies will provide conclusive evidence for or against the developmental 'programming' of obesity.

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