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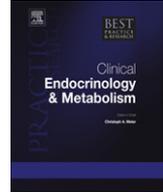
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# Best Practice & Research Clinical Endocrinology & Metabolism

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## The maternal and fetal impacts of obesity and gestational diabetes on pregnancy outcome

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Gestational diabetes mellitus  
Adverse pregnancy outcome  
Gestational weight gain  
Bariatric surgery

Obesity has reached pandemic proportions and is of growing concern worldwide. Adverse health outcomes associated with a raised body mass index present the greatest challenge currently facing clinicians across all disciplines.

Obesity is a chronic illness which is associated with metabolic disease, nutritional deficiency, musculoskeletal complications and cancer. These obesity-related health issues extend to pregnancy where they are responsible for producing a variety of medical and obstetric complications resulting in an increased incidence of maternal and fetal adverse outcomes.

Management of diet, gestational diabetes and gestational and inter-gestational weight may improve outcomes in women who are obese during pregnancy. Specific recommendations for the management of obesity in pregnancy have recently been published.

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### Obesity... why worry?

There is no doubt that obesity (defined as body mass index (BMI)  $> 30 \text{ kg/m}^2$ ) is an increasing problem and presents one of the greatest challenges to the practicing clinician, across all disciplines. The incidence of obesity, a modifiable risk factor for metabolic and cardiovascular disease, has increased to pandemic proportions over the past 20 years. In 2005, the World Health Organization

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(WHO) estimated that approximately 1.7 billion adults worldwide were overweight (BMI > 25 kg/m<sup>2</sup>) and 400 million obese with a projected increase to 700 million by 2015.<sup>1,2</sup> Alarming, 10% of the world's children, under the age of 15 years are obese. In the United States the rate of childhood obesity has stabilized at 17% since 1999, having tripled in the period prior to this from 1980.<sup>3</sup> The problem of obesity has more recently become apparent in the developing world where its incidence has also tripled over the past 20 years. Figures from developed countries estimate that between 24 and 35% of the general adult population are obese, with a further 40% overweight.<sup>1,4</sup> It is interesting that adults of normal BMI are now in the minority, and that the prevalence of obesity in adult women is greater than that in men.

Concern relating to the obesity pandemic is far greater than a cosmetic consideration. This paradoxical condition of chronic, overfed malnutrition is associated with a plethora of medical complications. The association between obesity and the metabolic syndrome/type 2 diabetes mellitus is well established.<sup>5</sup> We also know that the incidence of malignancy, musculoskeletal disorders and chronic respiratory disease are raised in obesity, and as a consequence of associated medical complications death by the age of 50 is increased two to threefold in those who are obese in middle age.<sup>6</sup>

### Raised BMI and pregnancy

The increasing prevalence of obesity amongst females of reproductive age is of particular concern with epidemiological data describing an overall incidence of 32.4% in the United States. In women of reproductive age, the prevalence of grade I (BMI 30–34.9 kg/m<sup>2</sup>) and grade II (BMI 35–39.9 kg/m<sup>2</sup>) obesity has doubled since 1979 and that of grade III (BMI > 40 kg/m<sup>2</sup>) obesity has increased threefold over the same period.<sup>1</sup> Data from the Pregnancy Risk Assessment Monitoring System (PRAMS database) shows a pre-pregnancy incidence of obesity in the United States of 20%, which represents an overall increase of 70% over a ten-year period.<sup>7</sup>

At the time of presentation for a booking obstetric visit, 21% of Irish women are obese and 37% overweight (Fig. 1).<sup>8</sup> In 2005, the prevalence of obesity in pregnant women in the United Kingdom at their booking visit was between 16 and 19%.<sup>9</sup> The impact of obesity on pregnancy outcome and parturition is now considered a primary obstetric issue. Numerous studies have shown that a raised pre-pregnancy BMI is associated with a linear increase in adverse maternal and fetal outcomes. Adverse pregnancy outcome in obese mothers is attributed predominantly to impaired glucose

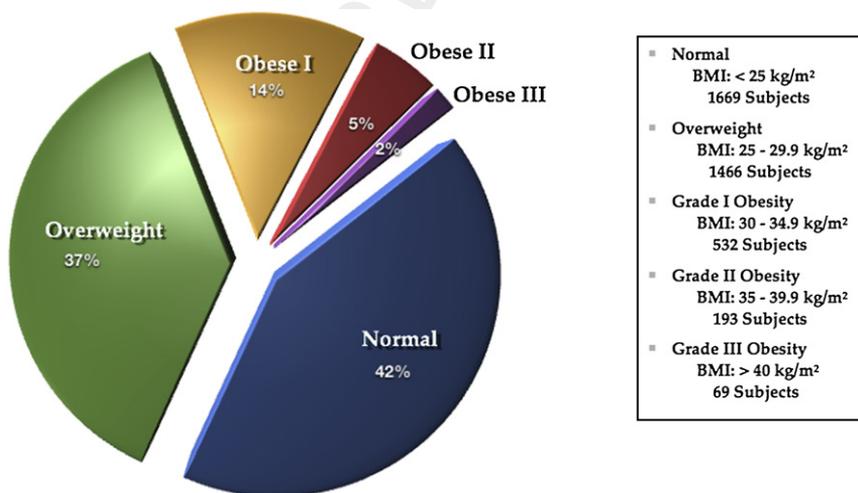


Fig. 1. Body mass index (BMI) measurements in an Irish obstetric population. Measurement of weight and height was taken at booking obstetric visit, prior to 28 weeks gestation. Data from ATLANTIC-DIP prospective observational study.

homeostasis and unhealthy metabolic status, a mechanism which may also account for the poor outcomes seen in obese and overweight mothers described as “glucose tolerant” when current criteria for the diagnosis of gestational diabetes are used.<sup>10–12</sup>

In this review, we will examine the prevalence, risks and potential mechanisms of short-term and long-term outcomes observed in relation to raised pre-pregnancy BMI and gestational weight gain. We will also discuss the effect of pre-pregnancy care, weight loss and bariatric surgery on these outcomes.

### Adverse pregnancy outcome

A raised maternal BMI is associated with greater frequency of complications of pregnancy for both mother and fetus during gestation, parturition and in the immediate postpartum period (Table 1). The majority of studies investigating maternal and neonatal outcomes in obesity have included obese mothers who have gestational diabetes but studies from Ireland and Denmark confirm that obesity is an independent risk factor for adverse pregnancy outcome in glucose tolerant women.<sup>12–15</sup>

#### Adverse maternal outcomes

When compared with women with a normal BMI, obese mothers have a greater risk of medical diseases during pregnancy.<sup>16</sup> The risk of mothers entering pregnancy with established type 2 diabetes mellitus increases linearly with increasing BMI.<sup>17</sup> Raised pre-pregnancy BMI also produces an additional threefold risk of developing gestational diabetes (GDM).<sup>18,19</sup> Hypertensive disease of pregnancy, including pre-eclamptic toxæmia (PET) occurs in obesity with a frequency two to four times that of mothers with healthy BMI.<sup>20</sup> The association between PET and raised BMI occurs independently of gestational diabetes, and demonstrates a linear rise in risk with increasing BMI, from a doubling of risk in overweight mothers to a fourfold increase in those categorized as grade III obesity.<sup>8,13</sup> Mechanical complications associated with pregnancy such as pelvic pain and lower back pain are reported more frequently in overweight and obese women during pregnancy.<sup>21</sup> Not only do these women have to bear the burden of the expanding gravid uterus, but also the increased tissue mass of obesity, which of itself

**Table 1**

Meta-analysis (Heslehurst et al.; Stothard et al.) summary for adverse maternal and fetal pregnancy outcomes in obese and overweight women. Figures expressed as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). Number of studies analyzed expressed as  $n = x$ .

Outcome	Overweight versus Healthy BMI aOR (95% CI)	Obese versus Healthy BMI aOR (95% CI)
<i>Delivery</i>		
Total Caesarean	1.483 (1.390–1.581); $n = 14$	2.005 (1.872–2.148); $n = 16$
Elective Caesarean	§	1.240 (0.899–1.710); $n = 3$
Emergency Caesarean	§	1.629 (1.396–1.893); $n = 6$
Failure to Progress	§	2.306 (1.871–2.842); $n = 4$
<i>Birthweight</i>		
SGA	0.933 (0.89–0.978); $n = 14$	0.841 (0.782–0.905); $n = 19$
LGA	1.308 (1.215–1.407); $n = 8$	2.357 (2.293–2.422); $n = 15$
<i>Maternal Outcome</i>		
Haemorrhage	1.420 (1.095–1.842); $n = 3$	1.202 (1.163–1.243); $n = 4$
Infection	§	3.335 (2.738–4.062); $n = 6$
<i>Fetal Outcome</i>		
Neonatal ITU Admission	1.121 (0.979–1.283); $n = 3$	1.377 (1.157–1.639); $n = 4$
Fetal Compromise	2.062 (1.439–2.955); $n = 4$	1.623 (1.545–1.705); $n = 5$
Meconium	§	1.570 (1.422–1.732); $n = 5$
<i>Congenital Abnormality</i>		
Neural Tube Defect	1.20 (1.04–1.38); $n = 8$	1.87 (1.62–2.15); $n = 9$
Cardiovascular Anomaly	1.17 (1.03–1.34); $n = 6$	1.30 (1.12–1.51); $n = 7$
Orofacial Cleft	1.00 (0.87–1.15); $n = 3$	1.20 (1.09–1.40); $n = 3$
Anorectal Atresia	1.19 (0.91–1.71); $n = 1$	1.48 (1.12–1.97); $n = 1$

also expands throughout gestation. The combination of these factors contributes to reduced mobility in the overweight and obese cohort during pregnancy and consequently to the risk of developing venous thromboembolism (VTE). Overall, there is a fivefold increase of antenatal venous thrombosis and a doubling of the risk of pulmonary thromboembolism antenatally in women with a BMI  $\geq 30$  kg/m<sup>2</sup> when compared to those with BMI  $< 25$  kg/m<sup>2</sup>.<sup>22</sup> Reduced mobility, because of the mechanical complication of pregnancy, increases this risk dramatically. One large case control study described an adjusted odds ratio (aOR) of 62.3 for antenatal venous thromboembolism (VTE) and 40.1 for post-natal VTE in women with BMI  $> 25$  kg/m<sup>2</sup> who were immobilized during pregnancy when compared to women of normal BMI who remained mobile throughout.<sup>23</sup> The impact of obesity on the peripartum period is also important, with a high rate of intrapartum complications. While maternal obesity is not currently an indication for labour induction, obese women are more likely to have induction of labour when compared to their normal BMI counterparts. Labour induction in obesity requires higher oxytocin and prostaglandin doses, failure of progression is more common and the requirement for delivery intervention increases.<sup>24</sup> Trends from the published literature consistently show higher caesarean section rates with increasing BMI.<sup>13,18,25,26</sup> In our population of glucose tolerant women, the aOR for elective caesarean section was 1.7 in overweight mothers and 4.4 in women with grade III obesity when compared to mothers with normal BMI. A similar trend was seen for emergency caesarean section, the aOR rising from 1.4 to 3.5 across the range of BMI categories from overweight to grade III obesity. This progression to emergency caesarean section may be partially explained by the fewer successful instrumental deliveries observed in mothers with raised BMI (aOR 0.66).<sup>8,13</sup> In those proceeding to delivery by caesarean section, obesity carries a risk of failed regional anaesthesia, inadequate analgesia, difficulty with intravenous access and requirement for general anaesthesia, which is in turn complicated by obesity-related difficulty with intubation.<sup>25,27</sup> Operative wounds following caesarean sections are also more likely to get infected and break down, leading to specific recommendations for subcutaneous suturing and antibiotic prophylaxis. Puerperal infections of the respiratory and urinary tract are also more likely with raised BMI.<sup>25</sup> There is also compelling evidence demonstrating increased risk of antepartum and postpartum haemorrhage in obese mothers, which can be reduced with active management of the third stage of labour.<sup>26</sup> A particularly worrying report describes maternal obesity as the greatest risk factor for maternal mortality in the developed world, the recent United Kingdom Confidential Enquiry into Maternal And Child Health (CEMACH) show 50% of maternal deaths occurring in obese women and 15% in women classified as grade III obesity.<sup>28</sup>

#### *Adverse fetal and neonatal outcomes*

The risks to the fetus associated with raised maternal BMI have been demonstrated in numerous obstetric populations and analyzed in a recent meta-analysis (Table 1).<sup>16</sup> There is a consistent association between raised pre-pregnancy maternal BMI and fetal macrosomia, regardless of the definition used (birthweight  $> 4.5$  kg,  $>90$ th percentile or  $>2SD$  above the mean gestational age adjusted birthweight for the reference population). Additionally, obesity during pregnancy carries the greatest risk for birth of infants large for gestational age (LGA).<sup>29</sup> Fetal macrosomia and LGA are surrogate risk factors for adverse pregnancy outcomes such as shoulder dystocia and fetal birth injury.<sup>16,18,30</sup> Immediate neonatal complications such as hypoglycaemia, hyperbilirubinaemia and respiratory distress syndrome are also associated with raised maternal BMI.<sup>16</sup>

Infants born to overweight and obese mothers require admission to the neonatal intensive care unit more frequently than offspring of normal weight mothers, predominantly due to a higher incidence of preterm birth, meconium aspiration and shoulder dystocia.<sup>12,16,31</sup> Congenital abnormalities are also described more commonly in infants of obese mothers, including neural tube defects, orofacial abnormalities, cardiac defects, limb reduction defects and intestinal tract anomalies such as anorectal atresia and omphalocele.<sup>8,13,32</sup> The most commonly occurring congenital anomalies are neural tube defects (aOR 1.87 obese; 1.2 overweight) followed by cardiovascular anomaly (aOR 1.30 obese; 1.17 overweight). Within these groups spina bifida (aOR 2.2 obese) and cardiac septal anomalies (aOR 1.20) were the most frequent.<sup>32</sup> Not surprisingly there is also an increased risk of stillbirth and perinatal death.<sup>33</sup>

## Long-term outcomes for mother and offspring

### *Postpartum and long-term maternal outcome*

Obesity associated morbidities extend into the immediate postpartum period and beyond. Many obese women can expect numerous obstetric and medical challenges which affect not only their own health, but also the health of their offspring for the future. Breastfeeding is initiated and maintained with significantly poorer success both as a consequence of maternal attitude and mechanical difficulty with infant positioning.<sup>34,35</sup> In future pregnancies, maternal obesity is a risk factor for unsuccessful vaginal birth after caesarean (VBAC). Grade III maternal obesity carries the additional risks of neonatal injury and uterine rupture following trial of labour.<sup>36</sup>

The risk of developing type 2 diabetes in mothers with previous GDM is seven times that following normoglycaemic pregnancy. This risk appears to be highest in the immediate five years following pregnancy.<sup>37,38</sup> Independent of GDM, pre-pregnancy maternal BMI within the overweight and obese range is a risk factor for type 2 diabetes, one study showing an aOR of 2.0 and 2.6 respectively over a period of 10 years.<sup>39</sup> We selected a cohort from the ATLANTIC-DIP prospective observational study of pregnancy outcome in Ireland who during gestation had normal glucose tolerance, impaired glucose tolerance (IGT) or GDM and performed a 75 g oral glucose tolerance test 12 weeks postpartum. Within this cohort, 15.1% of women with abnormal glucose homeostasis (IGT/GDM) during pregnancy had persistence of dysglycaemia, compared with fewer than 1% of women who had a normoglycaemic pregnancy. Those who had GDM were at greatest risk of postpartum disorders of glucose metabolism; 10.6% demonstrated IGT or impaired fasting glucose (IFG) and 6.4% type 2 diabetes.<sup>40</sup> Further research is needed to investigate whether or not women who have persistence of abnormal glucose handling postpartum are in fact dysglycaemic prior to conception. This possibility further highlights the need for education, weight optimization and management of maternal metabolic status prior to conception.

### *Childhood obesity*

The concept that obesity begets obesity is very apparent in the offspring of obese or overweight mothers. The published data correlates childhood obesity directly with maternal rather than paternal BMI.<sup>41</sup> We have previously addressed studies examining neonatal birthweight in relation to maternal BMI which demonstrate a positive correlation. Offspring of obese mothers whose birthweight is appropriate for gestational age have a higher proportion of body fat when compared to offspring born to lean mothers.<sup>18,42</sup> Even more concerning is the finding that children born to obese mothers demonstrate insulin resistance (HOMA-IR) calculated from fetal cord blood. Does this poor neonatal profile translate into a long-term effect?

The current body of evidence would overwhelmingly suggest that this is indeed the case. Higher birthweight is associated with raised BMI throughout childhood and into adulthood. Studies in the United States, the United Kingdom, Sweden and Finland have all demonstrated a doubling of the risk of childhood obesity in both boys and girls born to overweight mothers and this risk is raised fourfold in those born to obese mothers.<sup>43,44</sup> These studies have also shown the long-term effects of maternal obesity on offspring is apparent across a broad age range, from 2 to 18 years.<sup>44</sup>

The accuracy of defining raised a BMI in childhood (>95th percentile for the age-matched child) often provokes controversy, as there is variance within different age-groups, particularly during adolescence. Adiposity, assessed by anthropometric measures or dual emission X-ray absorptiometry (DXA), may more reliably measure childhood obesity.<sup>18,42</sup> These techniques demonstrate higher adiposity in children up to the age of 7 years and also in adults between 18 and 24 years who were born to mothers with raised BMI, and/or exposed to gestational diabetes *in utero*.<sup>45–48</sup>

The association between raised maternal BMI and LGA birthweight or raised neonatal adiposity implies a direct effect on the developing fetus of an adverse uterine environment during pregnancy. It is difficult however to determine whether in the long term, raised BMI and adiposity in the offspring of obese mothers occur directly due to adverse uteroplacental priming of the fetus during the obese pregnancy (*versus* inherited genetic influences), or as a result of the indirect environmental influence of an “over-fed” home.

## Mechanisms of adverse pregnancy outcome in obesity

The mechanisms underlying the adverse pregnancy outcomes in obesity, while poorly understood, are probably initiated by abnormal adipose tissue distribution secondary to excessive weight gain in women who are already obese prior to conception. This in turn, contributes to metabolic and immunologic dysfunction at a time of natural physiological aberrancy. Clinically, obesity is an umbrella term used to describe a broad conglomeration of mechanical, metabolic and inflammatory disease. The adverse pregnancy outcomes of obesity should be viewed as a domino effect, whereby poor maternal metabolic health contributes to an adverse utero-placental environment, and culminates in a plethora of complications which arise as a consequence of each other. When examining the contribution of increased maternal BMI and GDM to adverse pregnancy outcome, few studies have separated these two factors, but those that have show that raised BMI remains a risk factor for adverse maternal and fetal outcome in women who remain normoglycaemic during pregnancy.<sup>8,12,13</sup>

### Gestational weight gain

Over the duration of a normal, healthy pregnancy maternal weight gain of approximately 12 kg has, in the past, been accepted as normal.<sup>49</sup> Acceptable gestational weight gain is now more appropriately calculated according to pre-pregnancy BMI.<sup>50</sup> Evidence from smaller cohorts suggests that management of gestational weight gain, within these guidelines, can limit adverse metabolic status during pregnancy and larger studies are ongoing (Fig. 2; Table 2). The gravid uterus accounts for half of gestational weight gain, with expansion of extracellular fluid and maternal fat deposition accounting for the remainder. From early pregnancy onwards, irrespective of pre-pregnancy adiposity or BMI, fat deposition increases. Normal gestational adipose tissue gain, approximately 4 kg, is a mechanism of physiological preconditioning, in anticipation of fetoplacental and maternal demands associated with later gestation and lactation.<sup>44,51</sup> In women of healthy pre-pregnancy BMI, early gestational adipose tissue gains are laid down in the subcutaneous compartments of the breast, trunk and upper thigh, and during later pregnancy a small quantity of fat is stored as visceral adipose tissue.<sup>52,53</sup>

Although there is conflict in published data, greater gain in gestational adiposity probably occurs in mothers who are overweight or obese prior to conception. Excess gestational fat in obese mothers is stored predominantly in the visceral compartment rather than in the subcutaneous compartments.<sup>53,54</sup> In the non-pregnant state, regional preference for visceral adiposity contributes to insulin resistance and metabolic complications of obesity.<sup>55</sup> The predisposition for gestational storage of excess visceral fat in obese and overweight mothers is likely to play a role in the pathogenesis of the homeostatic imbalance which characterizes the obese pregnancy, as visceral adiposity during pregnancy is associated with a higher risk of GDM and gestational hypertension/PET.<sup>44,56</sup>

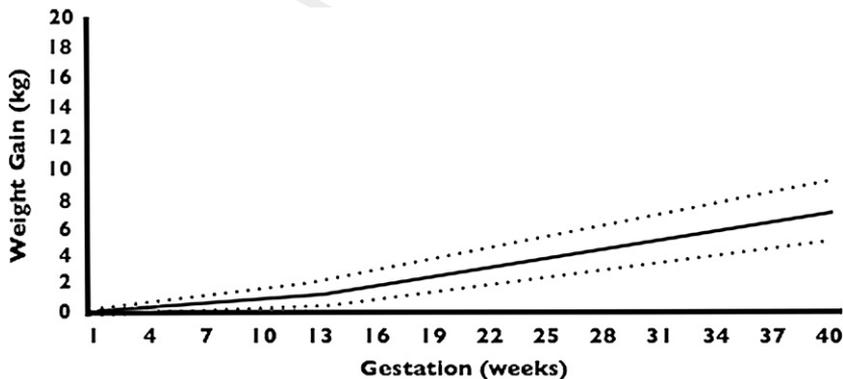


Fig. 2. Institute of Medicine recommendations for gestational weight gain in women who are obese ( $\geq 30 \text{ kg/m}^2$ ) pre-pregnancy.

**Table 2**

Recommended weight gain during pregnancy according to pre-gestational BMI.

Pre-Gestational BMI (kg/m <sup>2</sup> )	Total Weight Gain Range (kg)	Weight Gain in 2nd and 3rd Trimesters (Mean: kg/week)
Underweight (<18.5)	12.5–18.0	0.51
Healthy BMI (18.5–24.9)	11.5–16.0	0.42
Overweight (25.0–29.9)	7–11.5	0.28
Obese (≥30)	5–9	0.22

The effect of gestational weight gain for women with normal pre-pregnancy BMI, as a contributor to adverse outcomes, including GDM and pre-eclampsia, remains to be proven. Pre-pregnancy raised BMI is a more reliable predictor of poor pregnancy outcome and adverse effects of gestational weight gain in this setting. Visceral gains in adiposity probably reflect adverse fetal and maternal pregnancy outcomes rather than absolute increase in BMI *per se*. The influence of pre-gestational BMI as a factor of gestational weight gain on pregnancy outcomes is shown in a Swedish study of 151,000 women, which demonstrated that gestational BMI increases >3 kg/m<sup>2</sup> in primiparous women were associated with weight retention in the puerperium, independent of pre-pregnancy BMI, and that weight retention was associated with adverse maternal and neonatal outcomes in the second pregnancy of these women.<sup>57</sup>

#### Maternal metabolism during pregnancy

During healthy pregnancy, maternal metabolism and glucose homeostasis are in a state of dynamic change depending on the trimester. Early pregnancy induces an increase in insulin sensitivity and significant reductions in fasting glucose concentrations. With advancing gestation, fasting and post-prandial glucose concentrations increase and the post-prandial peak of glucose is prolonged. By the third trimester of normal pregnancy, insulin sensitivity has fallen to 50–70% that of pre-pregnancy values. Consequently, the insulin response to oral carbohydrate is elevated and basal insulin production increases, producing an overall 2–3-fold rise in mean insulin concentrations over any 24 h period.<sup>58,59</sup> The naturally insulin resistant state of late pregnancy provides an adaptive mechanism, supplying sufficient fuel to support the placenta and fetal development. A state of normal insulin sensitivity is restored in the immediate puerperium.

Normal, healthy pregnancy also produces a natural state of increased lipid turnover. Basal oxidation of fatty acids increases by approximately 70% during pregnancy and results in relative hyperlipidaemia, when compared with the pre-pregnant state. Serum concentrations of very low density lipoprotein (VLDL) and triglyceride increase threefold in the second and third trimesters. This is accompanied by an initial small reduction in the calculated low density lipoprotein (LDL) which is followed by a continuous rise, throughout the later trimesters. High density lipoprotein (HDL) steadily increases through to the 24th week of pregnancy, declines thereafter until the 32nd week and remains unchanged at this concentration until the postpartum period.<sup>44</sup>

Obesity induces a state of insulin resistance, independent of pregnancy. During gestation, insulin resistance in overweight and obese women is further exaggerated and often falls to 40% that of normal pre-pregnancy values. This profound insulin resistance produces a pathological response, resulting in maternal hyperinsulinaemia, hyperglycaemia and gestational diabetes mellitus.<sup>58–60</sup> Exaggerated hyperlipidaemia also occurs during obese pregnancy. VLDL concentrations are increased compared with normal pregnancy and the appearance and oxidation of small LDL particles is characteristic. Abnormal lipid metabolism during pregnancy in obese mothers indicates endothelial dysfunction which is likely to contribute to vascular complications, including pre-eclampsia.<sup>44,61</sup>

#### Gestational diabetes mellitus and impaired glucose tolerance

Gestational diabetes (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, occurs in 7% of all pregnancies in the United States.<sup>62,63</sup> Raised maternal BMI is an established risk factor for gestational diabetes. This is not surprising, given the association

between raised BMI and both type 2 diabetes and the metabolic syndrome. Compared with lean women, obese mothers carry a fourfold increased risk of developing GDM. Obesity of grade III and above raises this risk to ninefold.<sup>26,64</sup> Clearly, there is a linear association between the incidence of gestational diabetes and BMI. It is estimated that in the absence of obesity, the prevalence of gestational diabetes would fall by approximately 50%.

While many studies have described gestational diabetes as an independent risk factor for adverse maternal and fetal outcome it has not often been investigated independently of raised BMI. Poor maternal and fetal outcomes are not exclusively seen in obese and overweight women with gestational diabetes or impaired glucose tolerance, but also in pregnant women with raised BMI, who have satisfied current criteria for normoglycaemia following a 75 g oral glucose tolerance test (OGTT).<sup>12,13</sup> Obesity, dysregulated metabolism and insulin resistance are inextricably linked in both the pregnant and non-pregnant states. The association of raised BMI with adverse pregnancy outcome is at least partially linked to hyperinsulinaemia, abnormal lipid turnover and an adverse maternal metabolic milieu. The greater prevalence of poor gestational outcomes in pregnant women of apparently “normal” glucose tolerance, who have a BMI raised above the normal reference range, has resulted in recent recommendations advising a lowering in the current diagnostic thresholds for gestational diabetes mellitus and impaired glucose tolerance during pregnancy (Table 3).<sup>11,65</sup>

The Pedersen Hypothesis proposes fetal hyperglycaemia and overnutrition as a mechanism underlying adverse fetal outcome in the setting of poorly controlled maternal diabetes mellitus. Excessive transfer of carbohydrate across the placenta would induce relative fetal hyperglycaemia and compensatory fetal hyperinsulinaemia. Fetal hyperinsulinaemia is now known to produce a twofold effect to cause macrosomia; the metabolic effects of insulin on its putative receptor increases fat and glycogen deposition, and additionally excess insulin acts on the insulin-like growth factor (IGF) receptors to directly stimulate fetal growth. In addition to macrosomia, compensatory fetal hyperinsulinaemia increases the risk of neonatal hypoglycaemia.<sup>30</sup>

### Chronic inflammation

Activation of various pro-inflammatory elements of the immune system is reflected by raised serum markers of inflammation in the obese population. Numerous studies show increased circulating pro-inflammatory cytokines.<sup>5,66–68</sup> Additionally, the non-specific marker of inflammation, C-reactive protein (CRP) is raised and the anti-inflammatory adipokine, adiponectin, reduced. These serum markers of inflammation are associated with a poor metabolic profile, type 2 diabetes and gestational diabetes.<sup>15,69,70</sup> Chronic inflammation in obesity probably occurs secondary to excessive deposition of visceral fat rather than subcutaneous fat which is greater during pregnancy in women who are obese prior to conception.<sup>71</sup>

**Table 3**

Updated recommendations, based on HAPO study findings, for the diagnosis of gestational and type 2 diabetes during pregnancy (see reference<sup>11</sup> for details).

Diagnostic Criteria	
Screening – Booking Obstetric Visit	Fasting Plasma Glucose < 7.0 mmol/L HbA1c > 6.5%
Diagnostic Test	75 g OGTT @ 24–28 weeks gestation
Thresholds	> 5.1 mmol/L
Fasting Plasma Glucose	> 10.0 mmol/L
1 Hour Plasma Glucose	> 8.5 mmol/L
2 Hour Plasma Glucose	
GDM Diagnosis	Single value above recommended threshold
Impaired Fasting Glucose	Diagnosis eliminated
Identification of Overt Diabetes	HbA1c ≥ 6.5% at any time in pregnancy. Fasting Plasma Glucose ≥ 7.0 mmol/L at booking visit Random Plasma Glucose ≥ 11.1 mmol/L at any time during pregnancy if reconfirmed by fasting plasma glucose or HbA1C

423 The aetiology of chronic inflammation in obesity remains poorly understood. A raised macrophage  
424 population of pro-inflammatory potential (M1 polarized) is observed in both omental and subcuta-  
425 neous adipose tissue. The proportion of pro-inflammatory adipose tissue macrophages (ATM) in both  
426 subcutaneous tissue and omentum tissue correlates with insulin resistance. These macrophages  
427 surround and engulf elements of apoptotic adipocytes and consequently contain high quantities of  
428 intracellular fat.<sup>72,73</sup>

429 During pregnancy, serum markers of inflammation are raised in overweight and obese women.<sup>74</sup>  
430 Placental tissue examined postpartum from obese mothers also has a higher macrophage pop-  
431 ulation and greater concentrations of pro-inflammatory cytokines.<sup>75</sup> Therefore, the chronic inflam-  
432 matory process associated with obesity extends to the placenta during pregnancy, with recently  
433 described direct, adverse fetal effects.<sup>76</sup>

434 Many of the adverse pregnancy outcomes linked with maternal obesity have independent associ-  
435 ations with chronic inflammation. The relationship between insulin resistance, abnormal glucose  
436 homeostasis and chronic inflammation is well established. Compensatory increases in endogenous  
437 cortisol release as a stress response to inflammation produces insulin resistance via the glucocorticoid  
438 receptor. Direct inflammatory activation will block the insulin signaling pathway resulting in insulin  
439 resistance and abnormal glucose homeostasis.<sup>77,78</sup> PET, VTE, preterm labour and respiratory distress  
440 syndrome are all associated with raised markers of inflammation both in maternal serum and placental  
441 tissue, independently of BMI.<sup>74</sup>

442 The contribution of chronic inflammation to the pathogenesis of obesity-related adverse pregnancy  
443 outcome is a developing area of research interest, and presents an exciting therapeutic target area.  
444 Pregnancy always presents the additional challenge of protecting both mother and fetus from the  
445 adverse effects both the disorder and the therapy.

#### 446 *Lipid turnover*

447  
448  
449 Lipid turnover and circulating concentrations of lipoproteins are altered to the detriment of the  
450 maternal metabolic profile during obese pregnancy. Dysregulated lipid turnover and abnormal fatty  
451 acid flux can act independently in contributing to the chronic pro-inflammatory profile of obesity.<sup>72</sup>  
452 Elements of the intracellular inflammatory signalling pathway are stimulated directly by raised  
453 intracellular concentrations of saturated fatty acids. Upstream along this pathway, abnormal circula-  
454 ting concentrations of saturated fatty acids also bind and activate immune pattern recognition  
455 receptors (toll-like receptors), for which bacterial lipopolysaccharide (LPS) is the usual ligand (see  
456 Herrera chapter).<sup>77,79,80</sup>

#### 457 458 *Vitamin D and folate*

459  
460 Serum concentrations of vitamin D are lower in obese and overweight individuals, when compared  
461 with their lean counterparts. The prevalence of vitamin D deficiency (52–72 nmol/L) is estimated at  
462 twice that of the geographically matched population. It follows, therefore, that obese mothers are at  
463 greater risk of vitamin D deficiency when compared to pregnant women of normal BMI. Cord blood  
464 from babies born to obese mothers also has a lower mean vitamin D concentration compared to those  
465 born of women with normal BMI.<sup>81–83</sup>

466 Several mechanisms of vitamin D deficiency in obesity are proposed. Dietary deficiency of vitamin D  
467 is common and while the diet in obesity is of high calorific value, it has relatively poor nutritional  
468 benefit.<sup>5,81</sup> Ironically, obesity may be viewed as a state of overfed malnutrition as a consequence of  
469 poor dietary and lifestyle habits. Dietary deficiency of obese or “formerly obese” individuals may occur  
470 following gastric bypass or gastric sleeve resection bariatric surgery.<sup>84,85</sup> Vitamin D conversion to 25-  
471 hydroxy-vitamin D in the skin is also reduced in obese individuals due to decreased skin exposure to  
472 the sun. Vitamin D is a fat soluble vitamin which preferentially deposits in adipose tissue. Once  
473 deposited in adipocytes however, it is sequestered and by virtue of a chronic state of irreversible  
474 storage and zero bioavailability this fraction becomes functionally useless.<sup>81</sup>

475 Vitamin D deficiency in pregnancy has been associated with pre-eclampsia, insulin resistance and  
476 gestational diabetes mellitus, although cause and effect has not been established. During pregnancy,

the developing fetus is dependent on maternal skin exposure for activation of vitamin D and therefore, maternal vitamin D deficiency extends to the fetus. There is consequently significant scientific evidence to support the requirement for maternal vitamin D sufficiency in pregnancy for normal development of the fetal brain and skeleton (see chapter by McElduff).<sup>86</sup>

Dietary folate deficiency is also common in women of BMI  $\geq 27$  kg/m<sup>2</sup>. Folate deficiency in the general pregnant population is associated with an increased risk for fetal neural tube defect, and this risk is reduced by the use of pre-conceptual folate. Therefore, it is hardly surprising that the prevalence of neonatal neural tube defects is raised in obesity, given the likelihood of folate deficiency.<sup>87,88</sup>

### Management of obesity in pregnancy and between pregnancies

The impact of maternal obesity and gestational diabetes extends to the need for greater monitoring and specialist input during the management of pregnancy and labour. The Royal College of Obstetricians and Gynaecologists (RCOG) and the United Kingdom Centre for Maternal and Child Enquiries (CMACE) have published a joint guideline on management of women with obesity in pregnancy.<sup>89,90</sup> A further guideline is currently in progress by the National Institute for Clinical Excellence (NICE). These guidelines place raised maternal BMI as the greatest single risk factor contributing to maternal death and adverse maternal outcome of pregnancy.

Ideally, management of obesity in pregnancy starts with pre-pregnancy care and weight loss. Education and awareness is essential for all women of child-bearing age regarding the risk of adverse outcome associated with obesity in pregnancy. Availability of weight management services to provide advice on weight optimization prior to conception is recommended. While the provision of these services is often limited by lack of funding and resources, recent obesity awareness media campaigns emphasize obesity-related health risks, which may help to improve our ability to address pre-pregnancy weight management in the future, particularly in nulliparous women considering their first pregnancy. Education of already expectant mothers at booking obstetric visit and immediately post-natally should emphasize the need to optimize weight prior to further pregnancy. Following calculation of BMI at booking visit, those  $\geq 27$  kg/m<sup>2</sup> will enter into an education programme emphasizing the risks of obesity in pregnancy.<sup>90</sup>

Management of obesity in pregnancy predominantly involves risk factor modification and planning of delivery, in an effort to improve maternal and fetal outcomes. Weight loss during pregnancy is not recommended but preventing excessive gestational weight gain may have benefit in terms of reducing primary adverse outcomes such as GDM.<sup>84</sup> Dietary advice and lifestyle modification during pregnancy is aimed at stressing the importance of healthy diet. The major challenge in preventing excessive gestational weight gain is that of over-education of the mother, leading to inappropriate caloric restriction. While prevention of inappropriate gestational weight gain is desirable, this must be balanced with the provision of sufficient bioavailable calories to nourish the fetus and avoid keto-naemia with potential negative neurocognitive fetal impact. Numerous small studies have examined the introduction of low glycaemic index (GI) and high fibre diets with moderate exercise in pregnancy to minimize weight gain and prevent GDM in “at risk” individuals. The results have consistently been promising, showing reductions in the rates of LGA birth and gestational diabetes.<sup>91–93</sup> However, data is available only in cohorts of fewer than 50 patients and sufficient data to recommend introduction of these measures on a larger scale is lacking.<sup>44</sup>

Vitamin supplementation in overweight and obese pregnancy merits special consideration. In an effort to reduce the risk of neural tube defects and skeletal abnormality, supplementation with higher doses of folate (5 mg) and vitamin D (10  $\mu$ g) should be undertaken pre-pregnancy or in early pregnancy in women of BMI  $\geq 27$  kg/m<sup>2</sup>.<sup>90</sup> Recommendations in some European countries extend vitamin D supplementation to the postpartum period, suggesting that supplementation should be commenced in children for the first year of life. Rapid growth and development at this age promotes susceptibility to bone deformities associated with rickets. Children of obese mothers may have insufficient stores of vitamin D, to meet their needs, but the choice of appropriate pharmaceutical preparations of vitamin D for use in this age group is limited (see chapter by McElduff).<sup>94</sup>

531 The practical obstetric challenges of obese pregnancy must be addressed as early as possible.  
532 Preparation for the possibility of complicated delivery, caesarean section and difficulties associated  
533 with regional anaesthesia can be achieved by early consultation between obstetrician and anaesthetist.  
534 Thromboprophylaxis with low molecular weight heparin (LMWH) is recommended in the antenatal  
535 period for all women of BMI  $\geq 40$  kg/m<sup>2</sup> and in women of BMI  $\geq 30$  kg/m<sup>2</sup> who have two or more  
536 additional risk factors for thromboembolism. Early postpartum mobilization is also essential, and  
537 postnatal heparin should continue for six weeks postpartum.<sup>90</sup>

538 It is currently recommended that all women with a BMI greater than 30 kg/m<sup>2</sup> be screened for  
539 gestational diabetes mellitus between 24 and 28 weeks gestation by performing a 75 g oral glucose  
540 tolerance test (OGTT).<sup>89</sup> There is increasing evidence to extend this recommendation to pregnant  
541 women of BMI less than 30 kg/m<sup>2</sup>.<sup>13</sup> Close liaison with the diabetes service is needed to adequately  
542 manage gestational diabetes. Dietary intervention, regular capillary glucose monitoring and intro-  
543 duction of insulin therapy to maintain adequate glycaemic control will minimize complications such as  
544 macrosomia and shoulder dystocia.<sup>95</sup> Metformin may provide an alternative to insulin therapy for  
545 intensifying glycaemic control in pregnancy. Studies in which this agent has been used show satis-  
546 factory safety data and suggest additional benefit in women with polycystic ovarian syndrome  
547 (PCOS).<sup>96,97</sup> In obese women with gestational diabetes, further screening with OGTT should be  
548 undertaken 6 weeks postpartum. A normal OGTT in the postpartum period however is not completely  
549 reassuring as the risk of developing type 2 diabetes in the 5 years following a pregnancy complicated by  
550 GDM is almost 8 times that of euglycaemic pregnancy. Therefore, screening for cardiometabolic risk  
551 factors and type 2 diabetes should be undertaken on a yearly basis in addition to ongoing weight  
552 management and dietary advice.<sup>90</sup>

553 Regular blood pressure monitoring is undertaken in all pregnancy. Surveillance and monitoring for  
554 pre-eclampsia is now recommended in pregnant women of BMI  $\geq 35$  kg/m<sup>2</sup> with one additional risk  
555 Q2 factor (Table 4) in line with Pre-eclampsia Community Guidelines (PRECOG). Additionally, NICE clas-  
556 sifies obesity as a moderate risk factor for pre-eclampsia and recommends instituting aspirin therapy  
557 (75 mg daily) at 12 weeks gestation and continuing this to the birth of the baby.<sup>90</sup>

558 Management of labour is particularly challenging in obese women during pregnancy. Current  
559 recommendations state that all mothers of BMI  $\geq 35$  kg/m<sup>2</sup> should give birth in a consultant led obstetric  
560 unit with appropriate neonatal services. Home birth is not an option in this cohort due to an unac-  
561 ceptable risk of emergency caesarean section and postpartum haemorrhage (PPH) for the mother and  
562 the increased likelihood that neonatal special care or intensive care admission is required. Upon  
563 presentation of the obese mother in labour, the midwifery and obstetric team should liaise with the  
564 anaesthetic, paediatric and if necessary the diabetes teams. Active management of the third stage of  
565 labour is recommended in these women to minimize the risk of PPH. Those proceeding to caesarean  
566 section should have suturing of the subcutaneous space and prophylactic antibiotic therapy, in light of  
567 a higher incidence of wound breakdown and infection.<sup>90</sup>

### 569 **Interventional strategies for weight management**

570  
571 Regardless of culture, race, sex or gestational status, instituting successful weight management and  
572 weight loss programmes, presents a huge challenge and is met with variable results. Engaging patient  
573 adherence in undertaking major dietary and lifestyle changes is very difficult and while initial short-  
574 term benefit is seen, the published longer term results show an approximate 45% drop out rate in the  
575 first year, weight regain in the majority of patients after six months and in all patients after five years.<sup>5</sup>  
576 Pharmaceutical “weight loss” therapy, added to dietary and lifestyle change, has largely been poorly  
577 effective, offering an excess weight loss of less than 3 kg when compared to diet and exercise alone. The  
578 majority of these agents have in the past been amphetamine-derived and associated with unaccept-  
579 able, sometimes fatal, side-effects resulting in their withdrawal.<sup>98</sup>

580 Two questions must be addressed. How then can we achieve pre-pregnancy or inter-pregnancy  
581 weight loss in obese and overweight women? Can we reverse the risks associated with adverse  
582 outcome in pregnancy associated with obesity in achieving weight loss?

583 Achieving pre-pregnancy and inter-pregnancy weight optimization will best be achieved by  
584 a proper education programme. Lifestyle intervention in the developed world has previously been

585 achieved with apparently good success after education of potential and expectant mothers  
586 regarding the maternal and fetal risks of smoking during pregnancy.<sup>99</sup> Appropriate education in  
587 this regard reduced the percentage prevalence of smoking during pregnancy in the United States  
588 by 16% between 1990 and 2002. However, smoking cessation during pregnancy, while difficult, is  
589 a short-term intervention and postpartum relapse of smoking is high.<sup>100</sup> Weight optimization  
590 requires lifelong alteration of multiple lifestyle and dietary habits to prevent future regain of  
591 weight. The commitment required for success is therefore often difficult to meet. Furthermore,  
592 significant psychosocial barriers also often exist to instituting behavioural and lifestyle modification  
593 in obese subjects. Essentially, effective management is difficult to achieve in the primary care,  
594 should promote referral to a multidisciplinary clinical environment involving physician, bariatric  
595 surgeon, dietitian, specialist nurse, physiotherapist and psychologist.<sup>5</sup> The promise of pharmaco-  
596 logical agents in weight management must also be met with caution. Currently, orlistat,  
597 a pancreatic lipase inhibitor, is the only pharmaceutical agent available for treatment of obesity in  
598 Europe. At best, with optimal combination of diet and exercise, this agent produces a mean weight  
599 loss of approximately 4–5 kg and in fact some studies have shown weight gain following its  
600 initiation.<sup>101</sup> Newer agents under development include various gastrointestinal neuroendocrine  
601 peptide derivatives and GLP-1 agonists, currently used in the treatment of type 2 diabetes.<sup>98</sup> In  
602 phase II clinical trials, GLP-1 agonists produce moderate degrees of weight loss when used at doses  
603 higher than currently used in diabetes therapy and imaging studies suggest a weight loss prefer-  
604 ence for visceral adipose tissue. The use of GLP-1 agonists as weight management agents provides  
605 the additional benefit of improved metabolic status and makes them an attractive future choice for  
606 this indication.<sup>102</sup> However, the authors advise two points of caution when presenting the option to  
607 initiate pharmacotherapy for weight management in obesity. “Diet drugs” may be erroneously  
608 viewed by the patient as an “easy option” for weight loss or as an alternative rather than an  
609 adjunct to lifestyle and dietary modification. Scientific data points not only to the harmful effects of  
610 high calorific intake, but also to those of the constituent elements of an unhealthy diet in  
611 contributing to the adverse milieu of obesity.<sup>68,79,80</sup> Therefore, the onus is on the prescriber to  
612 ensure that patient is fully aware of ongoing requirement for dietary weight management in  
613 addition to the possible facilitatory effects of pharmacotherapy, and consequently to ensure that  
614 patient expectations from pharmacotherapy are not unrealistic. Secondly, the effects of weight  
615 management drugs on the developing fetus are unknown and in the interests of safety these  
616 agents should only be prescribed in non-pregnant women of reproductive age with appropriate  
617 contraceptive advice.

618 The most effective way in achieving weight loss in obese subjects is bariatric surgery.<sup>103</sup> The three  
619 methods of surgery in current, mainstream practice are the adjustable laparoscopic gastric band (LAP  
620 banding), gastric sleeve resection and gastric bypass surgery. In non-pregnant subjects with grade II  
621 obesity and above, gastric bypass surgery is associated with sustained weight loss of 26% body  
622 weight and an improvement in metabolic parameters of hyperglycaemia, hypertriglyceridaemia and  
623 hypertension.<sup>103–105</sup> Patients with more moderate degrees of obesity, BMI range between 30 and  
624 40 kg/m<sup>2</sup> also show significant weight loss and metabolic benefit from LAP banding.<sup>106</sup> Few studies  
625 have investigated the effects of weight loss following bariatric surgery on adverse pregnancy  
626 outcome. Recent evidence has shown a benefit in fetal outcomes following maternal inter-gestational  
627 weight management surgery, with lower birthweight, less fetal macrosomia and improved neonatal  
628 metabolic status.<sup>107</sup> However, concern has been raised regarding the appropriate time period  
629 between bariatric surgery and future pregnancy, particularly in light of post-surgical nutritional  
630 deficiencies.<sup>85</sup> Raised neonatal birthweight has also been associated with early gestational weight  
631 loss, a matter of concern should a woman conceive in the initial 18 months following bariatric  
632 surgery.<sup>84</sup>

## 633 Summary

634 In light of the overwhelming body of evidence available, which unquestionably points towards  
635 the adverse pregnancy outcomes of obesity and dysglycaemia in pregnancy, we have a responsibility,  
636 as physicians, to address the issue with all obese and overweight women of reproductive age. A  
637  
638

639 culture of ‘political correctness’ promoting obesity as an acceptable lifestyle characteristic which is of  
640 cosmetic concern only, should be appropriately balanced by education and information reinforcing  
641 obesity as a chronic illness carrying unacceptable risks of morbidity and mortality, particularly in the  
642 setting of maternal obesity. The authors recommend that the first step in educating the general  
643 populace in this regard involves encouraging government departments of health to launch media  
644 and public awareness campaigns, similar to that undertaken to inform individuals of the hazards of  
645 cigarette smoking. Like all modifiable risk factors of disease, the best approach to obesity in preg-  
646 nancy is its avoidance.

647 At risk women of BMI  $\geq 30$  kg/m<sup>2</sup> (or  $\geq 27$  kg/m<sup>2</sup> with manifest metabolic disease, hypertension,  
648 hyperlipidaemia or any degree of clinically apparent abnormal glucose handling) must be introduced to  
649 the clinical importance of weight management prior to gestation and cautiously advised against  
650 pregnancy until weight optimization has occurred. This is particularly relevant in those seeking fertility  
651 treatment. Screening for metabolic complications of raised BMI should be performed at least yearly by  
652 measuring blood pressure and fasting blood levels of lipids and glucose. Women who have had  
653 previous gestational diabetes mellitus must be entered into a regular screening programme, testing  
654 blood glucose at 6 weeks, 3 and 6 months postpartum and following this with yearly screening for  
655 at least five years. Careful planning of pregnancy accompanied by aggressive glycaemic and metabolic  
656 management prior to pregnancy is advised in those with a manifest adverse metabolic milieu. Met-  
657 formin provides weight neutral metabolic and glycaemic control and has an acceptable safety profile  
658 during pregnancy. Therefore this is the author’s first choice of anti-hyperglycaemic agent, if required  
659 for type 2 diabetes prior to conception. It is the author’s opinion that treatment with GLP-1 agonists  
660 may offer a good option for glycaemic and metabolic control while also aiding weight loss in women of  
661 reproductive age, but these agents must be substituted once pregnancy is being planned and should  
662 only be given in the setting of active contraception.

663 The challenge of weight loss involves a long-term patient commitment to a properly designed  
664 programme of dietary intervention, lifestyle changes and exercise. A health service-led, structured  
665 weight management treatment algorithm is an ideal guide for primary care physicians, further  
666 instruction on the time of appropriate referral to the specialist weight management team. If primary  
667 care resources are insufficient to provide a structured weight management option, “at risk” women  
668 should be referred at the earliest opportunity to specialist care. Treatment within specialist should  
669 primarily centre on patient engagement to the weight loss programme and reproductive health  
670 education. Currently, no suitable pharmacotherapy for weight management is available. However,  
671 a trial of orlistat as a facilitatory agent, in the setting of a patient already losing weight is reasonable.  
672 Bariatric surgery may a reasonable option for women  $\geq 40$  kg/m<sup>2</sup>, or in women of BMI  $\geq 35$  kg/m<sup>2</sup>  
673 with metabolic risk factors, meeting the pre-surgical weight loss requirements. However, the authors  
674 would caution against becoming pregnant in the initial 18 months following bariatric surgery.  
675 Women should be commenced on vitamin D and calcium supplementation following bariatric  
676 surgery.

### 679 Clinical Practice Points

- 682 • Lifestyle and dietary advice to optimize weight for all women pre-conceptually
- 683 • Early identification of pregnant women with high BMI ( $\geq 27$  kg/m<sup>2</sup>) as high risk
- 684 • Early screening for gestational diabetes mellitus in pregnant women with high BMI
- 685 • Appropriate supplementation with Vitamin D and high dose folate in obese pregnancy to  
686 avoid adverse fetal outcome
- 687 • Careful obstetric planning of delivery and labour in women of BMI  $\geq 30$  kg/m<sup>2</sup>
- 688 • Postpartum screening for adverse metabolic outcome in “at risk” women at 6 weeks, 12  
689 weeks and yearly thereafter
- 690 • Appropriate contraceptive advice if using pharmacotherapy for obesity
- 691 • Post-bariatric surgery, women should wait 18 months prior to conception

## Research Points

- Larger studies required to evaluate pregnancy outcomes in women following bariatric surgery
- Larger studies to investigate effects of gestational weight gain
- Larger studies to compare pre-gestational insulin resistance with incidence of GDM and postpartum persistence of dysglycaemia
- Randomized, controlled, interventional trials are required to: evaluate the effectiveness of weight control programmes pre-gestationally and during pregnancy, and to assess benefit in terms of neonatal and maternal outcomes
- Scientific studies to further investigate the contribution of immunological dysfunction and chronic inflammation to an adverse maternal metabolic profile during pregnancy

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