Focus on Obesity

Impact of maternal obesity on offspring obesity and cardiometabolic disease risk

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Abstract

The prevalence of obesity among pregnant women is increasing. In addition to the short-term complications of obesity during pregnancy in both mother and child, it is now recognised that maternal obesity has long-term adverse outcomes for the health of her offspring in later life. Evidence from both animal and human studies indicates that maternal obesity increases the risk for the offspring in developing obesity and altering body composition in child- and adulthood and, additionally, it also has an impact on the offspring’s cardiometabolic health with dysregulation of metabolism including glucose/insulin homoeostasis, and development of hypertension and vascular dysfunction. Potential mechanisms include effects on the development and function of adipose tissue, pancreas, muscle, liver, the vasculature and the brain. Further studies are required to elucidate the mechanisms underpinning the programming of disease risk in the offspring as a consequence of maternal obesity. The ultimate aim is to identify potential targets, which may be amenable to prevention or early intervention in order to improve the health of this and future generations.

Introduction

The prevalence of obesity (defined as body mass index (BMI) >30 kg/m²) is increasing, even among women of childbearing age. A survey carried out in the USA between 2003 and 2006 reported that 32% of women aged 20–44 years were classified as obese (WHO 2009). In the UK, the rise in obesity among pregnant women parallels the upward trend of obesity in the general population (Kanagalingam et al. 2005, Heslehurst et al. 2007). In addition to the short-term complications of obesity for both mother and child, emerging evidence suggests that maternal obesity has long-term detrimental consequences for offspring health.

One proposal to explain the link between maternal obesity and offspring obesity is the ‘developmental overnutrition hypothesis’. This states that high maternal glucose, free fatty acid and amino acid concentrations result in permanent changes in appetite control, neuroendocrine functioning and/or energy metabolism in the developing foetus, thus leading to risk of adiposity (with accompanying risks of metabolic and cardiovascular disease) in later life (Armitage et al. 2008). There are now a number of animal studies supporting this hypothesis, and there is emerging evidence that a similar phenomenon occurs in humans. Here, we discuss the evidence from animal and human studies that maternal obesity has a permanent impact on offspring obesity and body composition as well as cardiometabolic health. In this developing field, much of the literature reports the phenotypic outcomes in the offspring, and more research is needed to dissect potential underlying mechanisms. Studies using animal models are attempting to separate the effects of maternal obesity per se from ‘overnutrition’, but this is harder to address in humans and is currently limited to those studies including reports of gestational weight gain. Likewise, in human studies, the challenge remains of disentangling the direct effects of maternal obesity on the developing child from the shared genetic and postnatal lifestyle influences.

Timing of exposure

In many early life programming paradigms, the timing of exposure is of critical importance in determining the offspring phenotype (Seckl 2001). In most rodent studies of maternal obesity, females are maintained on...
obesogenic diets (high fat and high carbohydrate or high fat alone) until they are significantly heavier than animals on a control diet and are maintained on the same diet through gestation (about 20–22 days). The offspring are then reared by their own mothers until weaning at around 3–4 weeks of age. Thus, in many studies, offspring have been exposed not only to maternal obesity but also to maternal overnutrition during both pregnancy and lactation, so that the effects of maternal obesity **per se cannot be adequately separated from those of ‘overnutrition’.** While this may reflect the situation that occurs in humans, a number of studies do suggest that there may be particular developmental periods during which maternal obesity/overnutrition may have implications for offspring development. Recent data suggest that maternal obesity impairs oocyte quality in rodents and is associated with impaired development of the early embryo, so that programming effects in the offspring could occur as a consequence of maternal obesity even before fertilisation (Minge et al. 2008). Other studies have employed cross-fostering techniques in order to determine the importance of maternal overnutrition just during pregnancy on the programming of offspring obesity risk (Khan et al. 2005), while others suggest that maternal diet during both pregnancy and lactation is of particular importance in the programming of disease risk in the offspring (Bayol et al. 2008, Howie et al. 2009, Smith et al. 2009b). Finally, while for the purposes of this review, we have focused on animal studies reporting programming effects in the offspring as a consequence of exposure to maternal obesity/high calorie diet during pregnancy alone or during both pregnancy and lactation, the critical importance of nutrition in the early postnatal period has also been demonstrated in a number of animal models. Thus, in rats, offspring exposed to early postnatal overnutrition as a consequence of suckling by mothers on a high-fat diet, as a result of artificial feeding with a high-carbohydrate diet or as a result of rearing in small litters are at increased risk of obesity and cardiometabolic disease (Plagemann et al. 1992, Khan et al. 2005, Srinivasan et al. 2008). Importantly, such effects are also noted in other species including non-human primates, for example overfeeding in the pre-weaning period increases adiposity in female baboons in young adulthood (Lewis et al. 1986).

Thus, data from animal studies suggest that there are various time points during early development, in which maternal obesity and/or maternal/fetal overnutrition may result in programming effects in the offspring. The relevance of these findings to humans remains to be clarified, although data discussed later in this review suggest that the effects of maternal obesity **per se, i.e. the current body composition of the mother, may differ from those of excessive gestational weight gain, i.e. the consequences of the prevailing nutritional milieu during pregnancy, indicating that there are ‘windows’ for programming effects in the offspring.**

### Programming of obesity and body composition

#### Evidence from animal studies for programming of obesity

An increasing number of studies in rodents show that exposure to maternal obesity/overnutrition during both pregnancy and lactation is associated with the development of obesity in the offspring (Guo & Jen 1995, Levin & Govek 1998, Bayol et al. 2007, 2008, Samuelsson et al. 2008, Shankar et al. 2008, Liang et al. 2009, Nivoit et al. 2009, Tamashiro et al. 2009, Yan et al. 2010). This predisposition to obesity is amplified when offspring are themselves exposed to highly palatable or high-fat diets following weaning (Khan et al. 2003, 2004, Taylor et al. 2005, Bayol et al. 2007). In many of these studies, offspring have been studied after exposure to maternal obesity/overnutrition during both pregnancy and lactation, making it difficult to identify the important windows for the developmental programming of obesity. However, one study has shown that the offspring of rats rendered obese as a result of overfeeding before mating, but maintained on a standard diet during pregnancy, became obese in adulthood (Shankar et al. 2008). This suggests that maternal obesity at conception is associated with an increased risk of obesity in the offspring even with normal maternal dietary intake during pregnancy. The programming effects of intrauterine exposure to a high-fat diet in the absence of maternal obesity on offspring obesity risk have been investigated in several studies with variable results. For example, while White et al. (2009) reported that maternal obesity was necessary for the programming effects of a high-fat diet on offspring adiposity in a rat model, another study demonstrated that maternal pre-conceptual obesity had no effect over and above exposure to a high-fat diet during both pregnancy and lactation in terms of programming effects on adiposity (Howie et al. 2009). Likewise, exposure of females to a high calorie or a ‘junk food’ diet just from the start of pregnancy is associated with programming effects on offspring adiposity (Khan et al. 2005, Bayol et al. 2008). Programming effects as a consequence of overnutrition during pregnancy are also seen in animals with different reproductive strategies. In sheep, transient intake of propylene glycol (which is metabolised to glucose) in the last trimester of pregnancy results in lambs with increased weight and ponderal index at birth and more rapid postnatal growth than controls (Smith et al. 2009b).

#### Evidence from animal studies for programmed changes in body composition

In addition to the programming effects of maternal obesity on offspring obesity and fat mass, maternal obesity impacts on body composition. In rats, young offspring of mothers fed a junk food diet either during gestation alone or during both gestation and lactation...
exhibited increased intramuscular lipid content, semitendinosus muscle atrophy, altered expression of genes important in muscle growth and metabolism (Bayol et al. 2005) and reduced muscle force (Bayol et al. 2009). Such changes may be programmed early in development, as reduced myogenesis and increased intramuscular fat have also been reported in skeletal muscle of late gestation foetal sheep exposed to maternal obesity, in association with increased expression of inflammatory markers and altered AMP-activated protein kinase signalling (Zhu et al. 2008, Tong et al. 2009, Yan et al. 2010). These changes may play a role in altered muscle development and impact on later muscle size and strength. Additionally, increased intramuscular fat accumulation and altered gene expression may be important in the pathogenesis of insulin resistance in these models; indeed, offspring of obese mice demonstrate alterations in insulin signalling and mitochondrial complex activity in muscle in early adulthood (Shelley et al. 2009).

What are the potential mechanisms underlying programmed changes in obesity?

Studies have suggested a number of mechanisms that may underpin the programming effects of maternal obesity on offspring obesity risk, including programming of appetite and activity levels, programming of muscle structure and function and altered adipocyte biology.

Programming effects on the brain may be of particular importance in mediating the effects of maternal obesity on offspring appetite and activity. The offspring of mice maintained on a highly palatable diet during both pregnancy and lactation demonstrate hyperphagia before the development of obesity (Samuelsson et al. 2008), and rats exposed to a ‘junk food’ diet during both pregnancy and lactation themselves develop an exaggerated preference for fatty, sugary and salty foods when compared to control animals (Bayol et al. 2007). Such effects may reflect programmed changes in the hypothalamus, which has a pivotal role in the regulation of appetite and food intake (McMillen et al. 2005, Taylor & Poston 2007). However, these studies have involved maternal exposure to high calorie diets during both pregnancy and lactation, since the impact of overfeeding in the early postnatal period in the programming of the hypothalamus is well known (e.g. Davidowa & Plagemann 2000, Li et al. 2002). Detailed cross-fostering studies are therefore needed to determine the relative importance of the different developmental ‘windows’ for the programming of effects in the hypothalamus. Nevertheless, rodent studies using maternal exposure to a high-fat diet from weaning (Gupta et al. 2009) or solely during pregnancy (Chang et al. 2008) and one study in sheep in which glucose infusions were administered directly into foetuses (Muhlhauser et al. 2005) in later gestation have found altered expression of orexigenic peptides in the hypothalamus of foetuses, suggesting that prenatal exposure to increased nutrition may be sufficient to programme alterations in the brain which may impact on appetite control. Additionally, the risk of offspring obesity may be further exacerbated by reduced energy expenditure which has been observed in some, but not all, studies (Khan et al. 2003, Bayol et al. 2007, Samuelsson et al. 2008).

Exposure to maternal obesity may be associated with ‘programmed’ alterations in the expression of genes, which are important in adipocyte differentiation and function and which may be an additional mechanism underpinning the increased risk of obesity and insulin resistance in animal models. Alterations in adipose gene expression may be detected from early development, for example maternal obesity is associated with altered expression of genes in the adipose tissue of foetal sheep, including increased expression of lipoprotein lipase, adiponectin, leptin and the adipogenic factor peroxisome proliferator-activated receptor γ (PPARG; Muhlhauser et al. 2007). Although the exact consequences of these alterations in gene expression remain to be explored, the authors speculate that they may reflect accelerated adipocyte differentiation, with a premature transition from a thermogenic to a lipid storage function (Muhlhauser et al. 2007). These changes may be persistent, since rodent studies suggest that maternal obesity is associated with changes in gene expression in adipose tissue in adulthood, including alterations in the expression of genes such as PPARG, β-adrenoceptors, insulin receptor substrate-1 (IRS1), vascular endothelial growth factor-A (VEGFA) and tumour necrosis factor α (TNF; Caluwaerts et al. 2007, Bayol et al. 2008, Samuelsson et al. 2008, Shankar et al. 2008). Thus, maternal obesity may be associated with programming of altered adipocyte proliferation and differentiation capacity (Bayol et al. 2008), increased expression of inflammatory mediators (Caluwaerts et al. 2007) and altered lipid turnover (Samuelsson et al. 2008, Shankar et al. 2008).

Evidence from human studies

Maternal obesity and offspring obesity and body composition

In humans, increased rates of obesity in mothers are paralleled by an increase in large for gestational age delivery rates (Surkan et al. 2004) and by an increase in obesity rates in children (Ogden et al. 2006). This, and the observation of early onset obesity even among children in the first 6 months of life (Kim et al. 2006), supports a relationship between maternal obesity and offspring obesity. Maternal obesity prior to pregnancy is associated with foetal macrosomia (Jensen et al. 2003), and there are a large number of studies linking increased
birth weight with risk of overweight and obesity in childhood and adulthood (Parsons et al. 1999).

There are now several observational studies supporting an association between maternal obesity with increased risk of obesity in the offspring as neonates (Table 1), childhood (Table 2) and into early adulthood (Table 3). Where obesity in the offspring is assessed by BMI, studies show a clear relationship between increased maternal pre-pregnancy BMI and BMI during pregnancy with obesity in later life in the offspring (Laitinen et al. 2001, Whitaker 2004, Li et al. 2005, Reilly et al. 2005, Salsberry & Reagan 2005, Lawlor et al. 2007, Koupil & Toivanen 2008, Mesman et al. 2009, Reynolds et al. 2009, Stuebe et al. 2009, Tequeanes et al. 2009; Tables 2 and 3). In addition to increased BMI, there are also alterations in body composition of the offspring of obese mothers; maternal obesity is associated with increased fat mass, as assessed by calliper measurements of skinfold thickness or by dual X-ray absorptiometry, in neonates (Sewell et al. 2006, Harvey et al. 2007, Hull et al. 2008, Catalano et al. 2009, McIntyre et al. 2010; Table 1) and in children (Burdette et al. 2006, Blair et al. 2007; Gale et al. 2007; Table 2). Interestingly, offspring body fat does not appear to be associated with paternal fat mass (Shields et al. 2006). There is some evidence that the associations of maternal obesity with foetal growth may plateau at the highest levels of BMI (McIntyre et al. 2010), suggesting that either a maximal influence is present, or alternatively, that maternal obesity can lead to offspring of both high and of low birth weight (Rajasingam et al. 2009), other factors that limit foetal growth may be operating. Intriguingly, the impact of maternal obesity on offspring obesity and body composition is maintained into adulthood, over and above current lifestyle factors with associations reported between maternal obesity and offspring BMI (Laitinen et al. 2001, Koupil & Toivanen 2008, Reynolds et al. 2009, Stuebe et al. 2009, Tequeanes et al. 2009), and fat mass (Mingrone et al. 2009, Reynolds et al. 2009) up to the age of 31 years (Table 3).

Maternal gestational weight gain and offspring obesity and body composition

While, in humans, there are no studies specifically addressing components of the diet in the context of maternal ‘overnutrition’ and offspring outcome, gestational weight gain may reflect the exposure of the developing foetus to the prevailing nutritional environment and thus provide an opportunity to examine the influence of overnutrition as opposed to obesity per se. Interestingly, the impact of maternal obesity on risk of offspring obesity appears to be slightly different from the impact of excessive gestational weight gain. A number of studies have demonstrated a link between maternal gestational weight gain and later obesity in childhood (Oken et al. 2007, Olson et al. 2009) adolescence

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<td>HIGHER PERCENTILE</td>
<td>Body fat by DEXA, Skinfolds at three sites (ankle, subscapular and triceps)</td>
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<td>Observational cohort, Southampton Women's Survey, UK</td>
<td>Body composition by PeaPod airdisplacement plethysmography, Body electrical conductivity</td>
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<td>HIGHER PERCENTILE</td>
<td>Body composition by PeaPod airdisplacement plethysmography, Body electrical conductivity</td>
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<td>Case control, USA</td>
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<td>2 weeks</td>
<td>BMI 25–30 (control) vs BMI &lt; 25</td>
<td>HIGHER PERCENTILE</td>
<td>Body composition by PeaPod airdisplacement plethysmography, Body electrical conductivity</td>
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Table 1 Associations between maternal obesity and offspring obesity as a neonate.
Table 2: Associations between maternal obesity and offspring obesity in childhood.

<table>
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<td>Mesman et al. (2009)</td>
</tr>
<tr>
<td>Retrospective cohort, Low income families, USA</td>
<td>8494</td>
<td>First trimester BMI &gt; 30 kg/m²</td>
<td>2–4 years</td>
<td>BMI ≥ 95th percentile for age and gender</td>
<td>Increased BMI relative risk 2 (1.7–2.3) at 2 years, 2.3 (2.0–2.6) at 3 years, 2.3 (2.0–2.6) at 4 years</td>
<td>Whitaker (2004)</td>
</tr>
<tr>
<td>Retrospective cohort, National Longitudinal Study of Youth (NLSY)</td>
<td>2636</td>
<td>Pre-pregnancy BMI &gt; 30 kg/m²</td>
<td>2–14 years</td>
<td>BMI ≥ 95th percentile for age and gender</td>
<td>Odds ratio for obesity 4.1 (2.6–6.4)</td>
<td>Li et al. (2005)</td>
</tr>
<tr>
<td>Retrospective cohort, USA</td>
<td>3022</td>
<td>Pre-pregnancy BMI &gt; 30 kg/m²</td>
<td>2–7 years</td>
<td>BMI ≥ 95th percentile for age and gender</td>
<td>Odds ratio for obesity 1.37 (1.08–1.73) at 2–3 years, 1.69 (1.22–2.34) at 4–5 years, 2.91 (2.09–4.03) at 6–7 years</td>
<td>Salsberry &amp; Reagan (2005)</td>
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<tr>
<td>Avon Longitudinal Study of Parents and Children (ALSPAC), UK Prospective cohort, Southampton Women’s Survey, UK</td>
<td>8234</td>
<td>Self-reported BMI during pregnancy</td>
<td>7 years</td>
<td>BMI ≥ 95th percentile for age and gender</td>
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<td>Fat mass index (FMI) by DEXA</td>
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<td>Mater-University Brisbane, Australia</td>
<td>3340</td>
<td>Pre-pregnancy BMI</td>
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<td>BMI</td>
<td>Increase in standardised offspring BMI for 1 S.D. increase in maternal BMI 0.362 S.D. (95% CI 0.323, 0.402)</td>
<td>Lawlor et al. (2007)</td>
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Programming of metabolism

In addition to increasing the risk of offspring obesity, maternal obesity also impacts on offspring metabolism. To date, most studies have investigated effects on pancreatic function with attendant effects on glucose/insulin homoeostasis, but studies are beginning to examine the effects of maternal obesity on other components of the ‘metabolic syndrome’ including dyslipidaemia and non-alcoholic fatty liver disease.

Glucose/insulin homoeostasis and pancreatic function

In animal studies, exposure to maternal obesity/over-nutrition during both pregnancy and lactation is associated with the development of metabolic dysfunction in offspring, including hyperinsulinaemia, hyperglycaemia and increased plasma levels of triglycerides, cholesterol and leptin, features that are amplified when offspring are themselves exposed to a high-fat diet (Guo & Jen 1995, Bayol et al. 2008, Samuelsson et al. 2008, Shankar et al. 2008, Liang et al. 2009, Nivoit et al. 2009, Tamashiro et al. 2009, Yan et al. 2010). Additionally, there appears to be an age-related decline in glucose/insulin homoeostasis in many programming models; in mice, offspring of obese mothers were found to be hyperinsulinaemic at 3 months of age (young adulthood), but male offspring

(Oken et al. 2008) and early adulthood (Mamun et al. 2009), while others have shown no effect (Catalano et al. 1995, Koupl & Toivanen 2008). In these studies, the strength of the effect is generally less than that of maternal obesity per se, and there is some evidence that the effect is stronger among underweight/normal-weight women (Mamun et al. 2009). However, a recent study showed that the extremes of gestational weight gain were associated with obesity in the daughters at the age of 18 years (Stuebe et al. 2009) suggesting the importance of good maternal nutrition, even among women who are obese.

Table 3

<table>
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<tr>
<th>Study design</th>
<th>Offspring obesity phenotype</th>
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<td>Offspring overweight or obesity according to BMI per kg/m² = 1.23, 1.45, 1.16</td>
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<tr>
<td>Pelotas Birth cohort, Brazil</td>
<td>BMI</td>
<td>23</td>
<td>Pre-pregnancy BMI calculated from weight at the beginning of pregnancy</td>
<td>BMI, offsprings BMI increased 0.65 and 0.63 kg/m² in men and women respectively</td>
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<td>Birth cohort, Motherwell, UK</td>
<td>BMI, WHR, skinfold thickness</td>
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<td>BMIs WHR, fat mass by DEXA</td>
<td>For each unit of maternal pre-pregnancy BMI, offspring BMI increased 0.65 and 0.63 kg/m² in men and women respectively (P &lt; 0.001)</td>
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Interpretation of many of these studies is limited as pre-pregnancy BMI is often self-reported, and many studies do not have additional measurements of weight during pregnancy. Likewise, most studies do not have detailed measurements of maternal body composition during pregnancy, and so it is not possible to assess the impact of differing body fat distribution on the offspring. Most studies have not considered the potential confounding effect of breastfeeding, which may be important as obese women are less likely to initiate breastfeeding or may feed for a shorter time (Oddy et al. 2006). In addition, most studies have only considered obesity in the mother and have not tested the potential paternal contribution on offspring obesity (Lawlor et al. 2008).
had developed frank diabetes with reduced plasma insulin and decreased pancreatic insulin content by 6 months of age (Samuelsson et al. 2008). It has been proposed that such an age-related decline in pancreatic function may be programmed at an early developmental stage; in sheep, maternal obesity is associated with increased foetal pancreatic weight and a marked increase in the number of insulin-positive cells per unit area of the foetal pancreas, perhaps reflecting enhanced early β-cell maturation (Ford et al. 2009). However, such changes in early pancreatic development may result in premature postnatal β-cell loss and result in a predisposition to the development of obesity and metabolic dysfunction in adulthood (Ford et al. 2009).

Recent studies in humans have started to examine the influence of maternal obesity on offspring glucose/insulin homeostasis. In a small study, offspring of obese mothers (pre-pregnancy BMI 38.4 kg/m²) were more insulin resistant (calculated umbilical cord glucose and insulin concentrations using the homoeostasis model) than offspring of lean mothers (pre-pregnancy BMI 22.0 kg/m²; Catalano et al. 2009), suggesting that the foetus may have increased insulin secretion earlier in pregnancy (Carpenter et al. 1996). Recent evidence from the Hyperglycaemia and Adverse Pregnancy Outcome study including 23 316 participants also reported an association between increased maternal BMI and foetal hyperinsulinaemia (assessed by cord serum C-peptide levels), even after adjustment for maternal glycaemia (McIntyre et al. 2010). In the latter study, BMI in the mothers was measured in the third trimester of pregnancy, a measurement that is less closely correlated with maternal fat mass than BMI measured in early pregnancy (Sewell et al. 2007), and so this may have attenuated the findings.

There is some evidence that the effect of maternal obesity on insulin sensitivity persists into later life with offspring of overweight women (here defined as pre-gravid BMI >27.3 kg/m²) having increased risk of developing the metabolic syndrome by age 11 years (Boney et al. 2005). One study investigated insulin sensitivity using a euglycaemic insulin clamp in 21 lean offspring aged 22 years of ‘obese’ parents compared with 23 lean offspring of normal-weight parents and found no significant differences between groups (Lazarin et al. 2004). However, the mothers were overweight (BMI 27 kg/m²), rather than obese, and the study also included fathers who were obese. A more recent larger study examined 51 offspring in their early 20s of obese mothers (BMI >30 kg/m² before and during pregnancy) and 15 offspring of normal-weight mothers (Mingrone et al. 2008). Insulin sensitivity was calculated from glucose and insulin results during an oral glucose tolerance test using the oral glucose insulin sensitivity index, and insulin secretion and β-cell glucose sensitivity were computed by a mathematical model. Of note, 69% of the obese group offspring were obese and 19% were overweight. The offspring of the obese group were more insulin resistant, but β-cell glucose sensitivity did not differ between groups. In this study, the BMI of the fathers was similar in both groups. Overall, these findings suggest that maternal obesity impacts on offspring glucose homoeostasis, but also raises the potential importance of other nutrients in pregnancy regulated by insulin such as triglycerides, free fatty acids and amino acids which also regulate foetal growth (Schaefer-Graf et al. 2008).

Non-alcoholic fatty liver disease

There is increasing evidence that exposure to an adverse prenatal environment may predispose offspring to developing fatty liver, the hepatic manifestation of the metabolic syndrome (Magee et al. 2008). Offspring of female rats and mice exposed to a high-fat diet before conception and during pregnancy have increased liver triglyceride content (Buckley et al. 2005, Bruce et al. 2009, Elahi et al. 2009). This has been associated with altered hepatic mitochondrial electron transport chain complex activity and with increased expression of genes involved in lipogenesis, oxidative stress and inflammation (Bruce et al. 2009). An effect of maternal high-fat diet on offspring liver triglyceride content has also been shown in non-human primates in which the offspring of females maintained long-term on a high-fat diet had increased liver triglyceride content and evidence of increased hepatic oxidative stress whether or not their mothers had become obese, suggesting that programming of liver fat may be independent of maternal obesity, at least in this model (McCurdy et al. 2009). The impact of maternal obesity in humans on offspring development of non-alcoholic fatty liver disease has not been studied, although preliminary evidence suggests that early feeding habits may impact on development of fatty liver disease in childhood suggesting a potential role for early life experience in development of this condition (Nobili et al. 2009).

Programming of blood pressure and vascular function

A number of rodent studies have demonstrated that the offspring of mothers maintained on a high-fat diet before and during pregnancy and through lactation develop high blood pressure (BP; Khan et al. 2003, 2005, Samuelsson et al. 2008, 2010, Elahi et al. 2009, Liang et al. 2009), which deteriorates further with age (Samuelsson et al. 2008, Liang et al. 2009). Khan et al. (2005) cross-fostered offspring of obese rat mothers onto normal controls and showed that exposure to maternal obesity/high-fat diet during gestation was sufficient to programme hypertension in the offspring. In terms of mechanisms, in rats, the offspring of obese mothers have
endothelial dysfunction (Koukkou et al. 1998, Ghosh et al. 2001, Taylor et al. 2004, Khan et al. 2005) including reduced endothelium-dependent vasodilatation in both small and large vessels (Koukkou et al. 1998, Ghosh et al. 2001, Taylor et al. 2004, Armitage et al. 2005), altered vascular fatty acid content (Ghosh et al. 2001) and increased aortic stiffness with reduced smooth muscle cell number and endothelial cell volume (Armitage et al. 2005). Very recent studies using a rodent model of programming by maternal obesity have demonstrated that the offspring of obese females develop hypertension and increased cardiovascular response to stress before the onset of increased adiposity or hyperleptinaemia, accompanied by evidence of increased sympathetic activity and increased renal norepinephrine concentration and renin expression (Samuelsson et al. 2010), suggesting that programming of autonomic function might be one mechanism underpinning the development of hypertension in this model. However, these findings are not consistent across all studies (Armitage et al. 2005), so that further studies are required to delineate the precise mechanisms of programming of hypertension in the different models.

Despite this animal evidence, there are no data in humans examining the association between maternal obesity and offspring BP. This is probably due to lack of available obese pregnancy-offspring cohorts with measurements of BP in the offspring in adulthood. However, a positive association was reported between gestational weight gain and both offspring obesity and systolic BP at the age of 3 years (Oken et al. 2007). In addition, in a population-based cohort of 2432 individuals aged 21 years, a greater gestational weight gain was associated with greater BMI and with increased systolic BP (0.2 mmHg per 0.1 kg, 95% CI −0.2 to 0.6; Mamun et al. 2009). Although the latter was not statistically significant, the effect size was of similar magnitude as the statistically significant association with BMI. Likewise, although maternal vascular function is altered in pregnancies complicated by obesity with lower endothelium-dependent and endothelium-independent vasodilatation when compared with lean counterparts (Stewart et al. 2007), there are no studies to date examining vascular function in offspring of obese mothers.

Future directions for research
As discussed above, many studies in animal models have shown that exposure to maternal obesity/overnutrition during pregnancy +/− lactation is associated with programming of cardiovascular risk in the offspring. The remarkably similar programming effects observed in the offspring, including programming of obesity and metabolic and vascular dysfunction, from different experimental paradigms and in species with different reproductive strategies suggest that identification of common mechanisms may be possible using data from current animal models and may indeed be relevant to humans.

Nevertheless, extrapolating data from extant animal studies to determine public health policy may be difficult. Studies have employed different diets, for example high-fat, ‘cafeteria’ and ‘junk food’ diets, making it difficult to draw conclusions about the potential role of particular nutrients in the programming of disease risk. Additionally, it is not always clear whether the diets employed were matched for other dietary components such as protein, since low-protein diets are well known to programme offspring metabolism (reviewed in Davenport & Cabrero 2009). Studies are urgently needed to dissect the role of dietary composition in the programming of offspring disease risk. Further studies should also be directed at identifying critical developmental windows of importance in the programming of disease risk to dissect not only the role of maternal obesity versus foetal overnutrition per se but also the relative importance of overnutrition during critical developmental windows within pregnancy and during lactation. Such studies are of paramount importance in informing public health policy in terms of advising women about weight management and diet prior to and during pregnancy.

One area in which there has been much recent interest is the potential role of epigenetic mechanisms in developmental programming. The term ‘epigenetic modifications’ is generally used to describe changes in gene function which are not explained by changes in DNA sequence and which may be mitotically and/or meiotically heritable. Epigenetic modifications that mediate this include DNA methylation, histone modifications and small non-coding RNA, and there is a growing literature demonstrating altered DNA methylation and histone modifications in animal models of intrauterine growth retardation (Waterland & Michels 2007). More recently, the role of epigenetic modifications in mediating the effects of maternal obesity on the offspring has been investigated in several recent studies in primates, which have shown global and genespecific alterations in DNA methylation and histone modifications with maternal exposure to a high-fat diet (Agard-Tillery et al. 2008). In humans, emerging data suggest that severe maternal undernutrition may result in persistent epigenetic changes in the offspring (Heijmans et al. 2008), but the effects of maternal obesity have not been examined.

Other programming targets
While the focus of this review has been the impact of maternal obesity on offspring obesity, body composition and cardiometabolic health, there are also other long-term adverse effects of maternal obesity on offspring health. This has been little explored in humans beyond
How can we prevent the long-term consequences of maternal obesity on offspring outcome?

Given the clear associations of maternal obesity with adverse long-term outcomes for the offspring, it would appear that interventions that result in maternal weight loss should be beneficial to the offspring and have a potentially great impact on public health. A follow-up study of 111 children from 49 obese mothers who had lost $36 \pm 1.8\%$ body weight sustained for $12 \pm 0.8$ years with bariatric surgery (weight loss surgery) showed that the children had lower birth weight associated with reduced prevalence of macromamia. At follow-up at the age of 2.5–26 years, the children were leaner, and had improved metabolic profiles with greater insulin sensitivity and improved lipid profile (Smith et al. 2009a). However, there remain many questions, including when is the best time for women to lose weight when planning pregnancy, and how should they manage their weight when pregnant? A recent systematic review noted that there is minimal evidence to support any specific dietary or lifestyle intervention strategy (Dodd et al. 2008), and results of randomised controlled trials are eagerly awaited.

Conclusions

Thus, a growing body of evidence from both animal and human studies suggests that maternal obesity has an impact on offspring health, which has profound implications for public health policy. Of particular concern is the increased risk of obesity and metabolic sequelae in the offspring of obese mothers reported in both animal and human studies, which has the potential to result in an ‘intergenerational cycle’ affecting obesity and cardiovascular disease risk across a number of generations (Drake & Walker 2004, Drake & Liu 2010). Further studies are urgently needed in order to delineate the mechanisms underpinning these programming effects and identify suitable interventions to reduce the risks of these complications in the offspring.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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