Focus on Obesity

Obesity, pregnancy, inflammation, and vascular function

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Abstract

Maternal obesity is associated with increased morbidity and mortality for both mother and offspring. The mechanisms underlying the increased risk associated with maternal obesity are not well understood. In non-pregnant populations, many of the complications of obesity are thought to be mediated in part by inflammation and its sequelae. Recent studies suggest that a heightened inflammatory response may also be involved in mediating adverse clinical outcomes during pregnancy. This review summarizes our current knowledge about adipose tissue biology, and its role as an endocrine and inflammatory organ. The evidence for inflammation as a key mediator of adverse pregnancy outcome is also presented, focusing on the role of inflammation in adipose tissue, systemic inflammation, the placenta, and vascular endothelium.

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Clinical impact of maternal obesity on pregnancy

Human obesity is an increasingly common condition among both sexes, with an estimated prevalence of 4–28% among European men and 6–37% among European women (Berghofer *et al*. 2008). The prevalence of obesity is also increasing in women of reproductive age, and currently it is estimated that more than one in five pregnant women are obese (Heslehurst *et al*. 2007, 2009). Maternal obesity is associated with increased morbidity and mortality for both mother and offspring. Antenatal risks include gestational diabetes and hypertensive disorders including pre-eclampsia and thromboembolic complications (Sebire *et al*. 2001, Bhattacharya *et al*. 2007, Denison *et al*. 2008). Peripartum, women are more likely to face induction of labor, operative delivery, and postpartum hemorrhage (Sebire *et al*. 2001, Denison *et al*. 2008). High pregravid body mass index (BMI) and excessive gestational weight gain are also important predictors of short-term postpartum morbidity and higher postpartum weight retention (Gunderson *et al*. 2001), with the latter being associated with increased risks during future pregnancies and of lifelong obesity for women (Oken *et al*. 2008). Offspring of obese mothers tend to be large for gestational age at birth and are at a higher risk of late

fetal death, congenital anomaly, and admission to the neonatal unit. Maternal obesity also increases the lifetime risk of obesity in offspring and a tendency to develop metabolic syndrome in childhood and adolescence (Boney *et al*. 2005), thus perpetuating the cycle of obesity and its adverse consequences into the next generation. The mechanisms underlying the increased risk associated with maternal obesity are not well understood. However, many of the complications of obesity in non-pregnant populations are thought to be mediated in part by inflammation and its sequelae. Recent studies suggest that a heightened inflammatory response, both locally (adipose tissue, placenta, and vascular endothelium) and systemically (circulating plasma concentrations), may also be involved in mediating adverse clinical outcomes during pregnancy. This article reviews the evidence which links maternal obesity, local and systemic inflammation, and adverse pregnancy outcomes.

Adipose tissue biology

Obesity involves a massive expansion of adipose tissue, with a disproportionately smaller expansion of other tissue types within the body. Over the last decade, there has been a paradigm shift in the understanding of the nature of adipose tissue. It is now known that fat is not just a storage organ, but it is a highly active tissue metabolically, comprising one of the largest endocrine organs in the body. In obesity, expansion of adipose tissue mass is associated with increasing inflammation of

adipose tissue, and there is emerging evidence that this inflammation is causally linked both to insulin resistance and to other obesity-related morbidities such as cardiovascular disease. To date, much of the evidence in this area comes from the studies on non-pregnant individuals, with much less information on adipose tissue biology in pregnant women. In this section, we will attempt to review current understanding of adipose tissue ontogeny and function, how it becomes disordered in obesity, and the possible impact both of pregnancy on adipose tissue biology and of adipose tissue expansion and inflammation on pregnancy disorders.

Mature adipose tissue consists of adipocytes and stromal vascular cells, with the latter including vascular endothelial cells, fibroblasts, and cells of the hemato-poietic lineage. Immature adipose tissue first appears in the fetus between 14 and 16 weeks of gestation. The stages in adipose development are as follows: i) emergence of undifferentiated loose connective tissue clusters, ii) mesenchymal condensation associated with angiogenesis, iii) differentiation of mesenchymal cells into preadipocytes within a vascular matrix, iv) emergence of primitive fat lobules characterized by the appearance of fat vacuoles appearing in the cytoplasm of the mesenchymal cells, and v) appearance of definitive fat lobules: fat lobules well separated from each other by dense septae of perilobular mesenchymal tissue (Poissonnet *et al.* 1983). In terms of location, adipose tissue becomes first noticeable in the fetus at the head and neck, followed by the trunk, and finally in the upper and lower limbs (Poissonnet *et al.* 1984). By 28 weeks of gestation, fat tissue is present in the fetus in the six principal fat deposit areas: the face (buccal and ocular pads, cheek, and chin), the neck, the thorax (anterior and posterior chest wall, and mammary area), the abdomen (abdominal wall and perirenal), the upper limb (shoulder, forearm, arm, and hand), and the lower limb (gluteus, thigh, leg, and foot), and the number of fat lobules in adipose tissue is likely complete, with further adipose tissue expansion being mostly due to an increase in the size of fat lobules (Poissonnet *et al.* 1984). However, the development of obesity during childhood can further increase the number of adipocytes, with greater adipocyte number in obese individuals compared with lean individuals being obvious as early as 1 year (Knittle *et al.* 1979). In contrast, once adulthood is reached, adipose cell number likely remains constant, with obesity due to an expansion of adipose cell size, except possibly in extreme obesity (Spalding *et al.* 2008). Importantly, different types and sites of adipose tissue have different functions. All mammals contain white adipose tissue (WAT) and brown adipose tissue, with specific functions of lipid storage and thermogenesis respectively, with possible transdifferentiation between the two (Cinti 2009). Additionally, in many animals including humans, visceral adipose tissue, which surrounds internal organs, is more important than subcutaneous adipose tissue in the development of the metabolic syndrome (Despres & Lemieux 2006).

Adipose tissue as an endocrine organ

The concept that adipose tissue has actions far beyond the mere storage of triglycerides began in 1993 with the demonstration that the adipocytes in mouse adipose tissue generate tumor necrosis factor α (TNF), and with obese animals having greater adipose-specific TNF expression and greater circulating levels of TNF (Hotamisligil *et al.* 1993). A strong relationship between adipose tissue TNF production and insulin resistance was also identified, with cause and effect being confirmed by experiments showing that TNF antagonism reduced peripheral insulin resistance in this mouse model (Hotamisligil *et al.* 1993). The following year, leptin, the product of the *ob* gene (deletion of which causes profound obesity), was identified as a major secretory product of adipose tissue, and the model of adipose tissue as an endocrine organ became firmly established (Zhang *et al.* 1994). TNF and leptin are examples of 'adipokines', peptides released by adipose tissue, and which can signal to distant tissues (Hotamisligil *et al.* 1993). In humans, WAT produces over 50 'adipokines', including TNF which contributes to the low-grade inflammation found in obesity, leptin which has effects on food intake, and a host of other agents with a variety of effects (Lago *et al.* 2007, Maury & Brichard 2010). Table 1 lists some of the major adipokines and their functions. In parallel with these proinflammatory events, WAT also produces anti-inflammatory cytokines such as adiponectin (which, paradoxically, tends to be lower in obese individuals) and interleukin (IL)10 and IL1R1 (IL-1Rα; production of which is proportional to body weight). These inflammatory markers, although originating in fat, circulate and are measurable in serum.

In obesity, there is an upregulation of chemokine and receptor synthesis in both visceral and subcutaneous adipose tissues (Huber *et al.* 2008), albeit with a greater increase in visceral adipose tissue (Fain *et al.* 2004), and this is likely a mechanism by which visceral adipose tissue is more strongly associated with the metabolic syndrome than the subcutaneous adipose tissue (Demerath *et al.* 2008). Cytokines secreted by visceral adipose tissue are 'sensed' directly by the liver due to venous drainage from this adipose depot via the portal system. Thus, visceral adipose tissue is plausibly capable of influencing hepatic glucose homeostasis and insulin sensitivity (Tordjman *et al.* 2009). Figure 1 summarizes the potential interactions between adipose tissue and distant organs.

Inflammatory gene expression in fat is closely positively correlated with both liver fat content and systemic arterial dysfunction (the latter assessed using

Table 1 Key adipokines expressed and secreted by adipose tissue and their functions.

Adipokine	Changes in obesity	Functional effects
'Proinflammatory' cytokines		
Tumor necrosis factor α (TNF)	↑ Circulating (Cartier *et al.* 2008)	Activity is predominantly paracrine
	↔ Circulating levels	Stimulates lipolysis
	↔ mRNA expression, but ↑ release by cultured adipose (Kern *et al.* 2001)	Increases insulin resistance via interference with IRS1 downstream signalling
		Impairs preadipocyte differentiation
		Downregulates anti-inflammatory pathways
Chemokine (C-C motif) ligand 2 (CCL2; also known as MCP-1)	↑ Expression in WAT (Bruun *et al.* 2005, Di Gregorio *et al.* 2005)	Promotes monocyte recruitment into WAT
Interleukin (IL)6	↑ Circulating levels correlate with visceral adiposity (Sabio *et al.* 2008, Maury & Brichard 2010)	Secretion by adipose tissue leads to hepatic insulin resistance in upregulation of SOCS3
IL8	↑ Circulating (Straczkowski *et al.* 2002)	Potent chemoattractant
IL1B	↑ Expression (Juge-Aubry *et al.* 2003)	Impairs insulin signaling by downregulation of IRS1
		Cytotoxic effects on pancreatic islet cells
Anti-inflammatory cytokines		
IL10	↓ Circulating (Esposito *et al.* 2003)	Broad anti-inflammatory activity
	↑ Circulating (Juge-Aubry *et al.* 2005)	Decreases cytokine production by monocytes
		Decreases monocyte activation
IL1R1 (IL-1Rα)	↑ Circulating (Meier *et al.* 2002)	Antagonizes IL1
Hormones		
Leptin	↑ Circulating (Heinonen *et al.* 2005)	Acts centrally on appetite centers in the brain
		Stimulates fatty acid oxidation in the liver and skeletal muscle
		Induces secretion of IL1R1
Adiponectin	↓ Circulating (Arita *et al.* 1999, Maury & Brichard 2010)	Stimulates fatty acid oxidation via ADIPOR1
		Activates PPARG via ADIPOR2
		Reduces hepatic gluconeogenesis
		Antagonizes some actions of TNF
		Induces secretion of IL10
Visfatin	↑ Expression in visceral adipose	Regulates β-cell function in pancreas
	↓ In subcutaneous adipose (Rasouli & Kern 2008)	Role unclear in humans
Resistin	↑ Expression in mice (Steppan & Lazar 2002)	Increases secretion in murine model of diet-induced obesity
	↔ In humans (Janke *et al.* 2002)	Role unclear in humans
Apelin	↑ Circulating (Heinonen *et al.* 2005)	Central action on feeding behavior
		Infusion restores glucose tolerance in mice
		Role unclear in humans
Adipokines involved in vitamin A metabolism		
Retinol-binding protein (RBP)4	↑ Expression/circulating (Rasouli & Kern 2008, Maury & Brichard 2010)	Increases insulin resistance in animal studies (Yang *et al.* 2005)
		Role unclear in humans
Other factors		
Plasminogen activator inhibitor (PAI)1	↑ Secretion (Maury & Brichard 2010)	Oversecretion leads to decreased fibrinolysis and excessive thrombosis
Angiotensinogen	↑ Circulating (Maury & Brichard 2010)	Increases fat mass and hypertension in transgenic mice
Prostaglandins	↓ Release of PGE$_2$ by cultured adipose tissue (Fain *et al.* 2004, Hétu & Riendeau 2007)	Inhibits adipocyte lipolysis

ultrasound), and inversely correlated with whole body insulin sensitivity and omental lipogenic factors (Makkonen *et al.* 2007, Apovian *et al.* 2008, Poulain-Godefroy *et al.* 2008). A recent study in a rodent model has demonstrated that i.v. infusion of each of TNF and CCL2 (also known as monocyte chemoattractant protein-1, MCP-1; Tateya *et al.* 2010) induced features of the metabolic syndrome, and blockade of TNF with drugs such as infliximab has been reported to improve insulin sensitivity in a murine model (Araujo *et al.* 2007). Together, these studies suggest that adipokines may have a more causal relationship with the metabolic syndrome that has been recognized previously. In addition to cytokines, the enzyme 11β-hydroxysteroid dehydrogenase type 1, which is involved in intra-adipose regulation of local bioavailability of active corticosteroid, is also significantly increased in adipose tissue in obese/overweight individuals compared with non-obese individuals (Paulsen *et al.* 2007, Wake *et al.* 2007, Morton & Seckl 2008). This key enzyme is likely to modulate local inflammatory responses within adipose tissue.
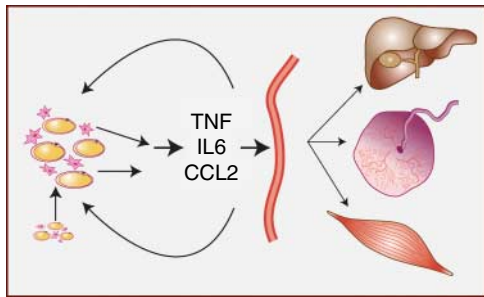
Figure 1 Adipose tissue is a source of inflammatory mediators with local and systemic effects. Adipocytes and cells of the stromal vascular fraction can secrete inflammatory cytokines such as TNF, IL6, and CCL2 (MCP-1). These have local autocrine and paracrine effects, but may also contribute to elevated circulating levels in obesity, with systemic effects including modulation of hepatic and skeletal muscle insulin signaling, and potential effects on placenta.
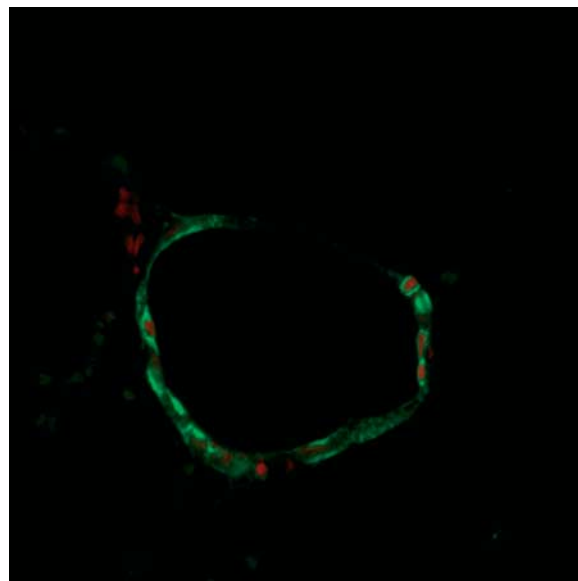
Inflammation in adipose tissue

Although the association between obesity, low-grade inflammation, and insulin resistance is propagated in part by adipokines generated by adipocytes and cells of the stromal vascular fraction as described above, an influx of inflammatory cells into adipose tissue is also implicated (Xu *et al*. 2003, Hotamisligil 2006). Originally, it was thought that cells of the innate immune system were the major players in this event, but increasing evidence implicates T cells and possibly other leukocytes (Lumeng *et al*. 2009). However, the predominant leukocytes in adipose tissue are macrophages, which are present in the stromal vascular fraction and their density is in direct proportion to the levels of obesity (Weisberg *et al*. 2003). Indeed, there is a significant functional overlap between adipose tissue and macrophage biology, with both (under the correct conditions) being phagocytic; producing transcription factors, cytokines, inflammatory molecules, fatty acid transporters, and scavenger receptors; and with some evidence that preadipocytes can be 'converted' to macrophages (Charriere *et al*. 2003, Wellen & Hotamisligil 2003).

Adipose tissue macrophages (ATMs) are found in both lean and obese individuals, and have been identified in 'crown-like structures' (SM Barr, JE Norman, BR Walker & NM Morton, 2009, unpublished observations; Fig. 2) surrounding the necrotic adipocytes. However, their functional activity is proportional to the degree of obesity (Lumeng *et al*. 2007), and may reflect the need for additional scavenger activity due to additional adipocyte death as a result of disordered hypertrophy (Zeyda & Stulnig 2007). ATMs have a distinct phenotype, being typical of neither M1 nor M2. In lean individuals, ATMs more closely resemble the M2 'alternatively activated' phenotype, secreting anti-inflammatory cytokines such as IL10 and IL1 decoy receptor, and also secreting arginase which blocks inducible nitric oxide

synthase (NOS2, also known as iNOS) activity; however they are capable of significant proinflammatory cytokine production (Zeyda *et al*. 2007) on stimulation with interferon-γ. In contrast, in obese individuals, there is a shift toward the M1 'classically activated' phenotype, secreting proinflammatory cytokines TNF, IL6, and IL12, and generating reactive oxygen species such as nitric oxide via activation of NOS2 (Lumeng *et al*. 2007).

T_H2 cytokines are the likely drivers toward the M2 phenotype of ATMs in lean individuals (Lumeng *et al*. 2007). With the development of obesity, there is both a change in macrophage phenotype toward M1 and an increase in macrophage density (probably as a result of invasion of new macrophages from the bloodstream rather than local proliferation of macrophages (Weisberg *et al*. 2003)). These invading and activated macrophages then interact with adipocytes to initiate vicious cycle of macrophage recruitment, production of inflammatory cytokines, and impairment of adipocyte function (Wellen & Hotamisligil 2003). As with adipokine production, the increase in macrophage density in adipose tissue is greater in visceral deposits than in subcutaneous deposits (Harman-Boehm *et al*. 2007). Additionally, increased macrophage invasion into the adipose tissue is associated with insulin resistance, an important component of the metabolic syndrome (Xu *et al*. 2003). A feedback loop likely exists, since treatment with an insulin-sensitizing agent (rosiglitazone) in a mouse model of obesity reduces markers of macrophage density (Xu *et al*. 2003). The adverse metabolic effects of ATM invasion are not limited to insulin resistance: endothelial dysfunction in obesity is also related to ATM number and activity (Apovian *et al*. 2008).

Figure 2 Macrophages can be identified in adipose tissue surrounding dead adipocytes in 'crown-like' structures. Obesity is associated with macrophage infiltration into adipose tissue, plausibly in response to disordered adipocyte hypertrophy and necrosis.

The change in ATM phenotype in obesity is likely to be driven by the action of T_H1 cytokines, with emerging data suggesting that T cells in adipose tissue play a major role in regulating ATM phenotype and function (Lumeng *et al*. 2009). As with ATM biology, much of the information on T cell function in adipose tissue comes from mouse studies. In lean mice, CD3+T cells account for just under 15% of the stromal vascular cell fraction in adipose tissue (Nishimura *et al*. 2009). Obesity in mice is associated with a greater adipose tissue density of CD8+T cells (largely effector T cells) and a lower density of CD4+T cells and Treg cells (Feuerer *et al*. 2009, Nishimura *et al*. 2009, Winer *et al*. 2009). Temporally, CD8+ cell invasion precedes that of reduced CD4+ and reduced Treg cell density in adipose tissue following diet-induced obesity, and both changes are followed by an increase in macrophage density (Nishimura *et al*. 2009). These data, together with data from CD8+-depleted mice and/or mice in which CD8+ cell activity was blocked, show that CD8+ cells are necessary for both initiation and maintenance of ATM invasion, particularly M1 macrophages. Importantly, CD8+ activity and decreased Treg cell density also appear to be crucial in the pathogenesis of the insulin resistance that accompanies obesity (Feuerer *et al*. 2009, Nishimura *et al*. 2009, Winer *et al*. 2009).

Thus, T cells appear to be major regulators in controlling ATM number and function in mouse and in human obesity (Kintscher *et al*. 2008). However, the question of what initiates adipose tissue inflammation remains incompletely answered. Although necessary, CD8+ cells alone are not sufficient to initiate macrophage invasion, differentiation, and activation in adipose tissue: interactions between CD8+T cells and adipose tissue are required (Nishimura *et al*. 2009). The factor(s) triggering the type of interaction between T cells and adipose tissue that will initiate macrophage recruitment and phenotypic change are unknown, but free fatty acid-induced physical stress or oxidative damage to the endothelium (Wellen & Hotamisligil 2003) (possibly mediated via Toll-like receptors) (Schaeffler *et al*. 2009), hypoxia, and adipocyte death have all been proposed (Lumeng *et al*. 2009) as the initiating factors.

Whether macrophages and T cells are the only important leukocytes in adipose tissue inflammation is unclear. For example, the activity of mast cells in adipose tissue may also be relevant – obesity is associated with increasing mast cell density in WAT in both humans and rodents (Liu *et al*. 2009), and reducing mast cell numbers in a mouse model of diet-induced obesity reduces body weight and insulin resistance, probably via decreased adipocyte apoptosis and angiogenesis (Liu *et al*. 2009). The possible efficacy of mast cell-stabilizing agents as therapies to prevent/treat obesity is demonstrated by the association between BMI and serum tryptase (a mast cell product) levels after adjustment for gender (Liu *et al*. 2009).

Maternal studies

Fewer studies have looked at the link between obesity and inflammation during pregnancy. In a study of 47 women, serum levels of leptin, CRP, and IL6 were higher in obese women compared with gestation-, smoking-, and parity-matched lean women (Ramsay *et al*. 2002). These findings were confirmed in a subsequent study by the same group, which also showed higher serum ICAM-1 levels and lower plasminogen activator inhibitor (PAI)1:PAI2 ratios in obese women compared with non-obese pregnant women (Stewart *et al*. 2007). This increase in circulating proinflammatory cytokines relates in part to production by maternal peripheral blood mononuclear cells, which show greater *TNF* and *IL6* mRNA production and expression of differentiation and activation markers (CD14 and CD68; Challier *et al*. 2008).

In contrast to the evidence on macrophage invasion and other inflammatory events in adipose tissue in non-pregnant obese individuals, there have (to our knowledge) been no quantitative studies on these events in pregnant women, although we have identified macrophages and crown-like structures in visceral and subcutaneous adipose tissues from obese pregnant women (SM Barr, JE Norman, BR Walker & NM Morton, 2009, unpublished observations; Fig. 2). This finding is supported by a recent study in baboons in which maternal obesity was accompanied by macrophage infiltration into adipose tissue (Farley *et al*. 2009).

In pregnancy, as in the non-pregnant state, obesity and particularly abdominal obesity are associated with glucose intolerance and insulin resistance (Ramsay *et al*. 2002, Martin *et al*. 2009), with the result that gestational diabetes is commoner in obese pregnant women. The biochemistry of these events is less well studied in pregnancy. TNF has been shown to be a predictor of insulin resistance in non-obese pregnant women in late gestation (Kirwan *et al*. 2002), although secretion of TNF from adipose tissue was not different when pregnant women with normal glucose tolerance were compared to lean women with gestational diabetes (Kirwan *et al*. 2002). However, defects in the insulin signaling cascade have been described in pregnant obese women of normal glucose tolerance in both adipose tissue and skeletal muscle (Colomiere *et al*. 2009). Given that both glucose intolerance (Metzger *et al*. 2008) and insulin resistance (seen in women with polycystic ovarian syndrome; Boomsma *et al*. 2006) are associated with adverse pregnancy outcome, and given their link with obesity in pregnancy, it seems likely that both glucose intolerance (Metzger *et al*. 2008) and insulin resistance partially mediate the effects of obesity on adverse pregnancy outcome (described above). The increased inflammation found in pregnant and non-pregnant individuals is also plausibly linked to the increased rates of

pre-eclampsia in obese individuals, given that around 30% of the effect of increased BMI risk on pre-eclampsia is related to inflammation and triglyceride levels (Bodnar *et al.* 2005).

Placental biology

Inflammation and inflammatory cytokines have a pivotal role in placental function throughout pregnancy. Virtually, all known cytokines are capable of being synthesized and released by cytotrophoblast, syncytio-trophoblast, and resident placental macrophages or Hofbauer cells (Bowen *et al.* 2002) with their release being developmentally regulated (Hauguel-de Mouzon & Guerre-Millo 2006). For example, in early pregnancy, coordinated release of IL10 (Pang *et al.* 2008) and IL11 (Paiva *et al.* 2007) regulates trophoblast differentiation and invasion (for review see Guzeloglu-Kayisli *et al.* (2009)), and is therefore involved in the establishment of pregnancy. The physiological role of cytokines in later pregnancy is less well established; however, IL6 and TNF are thought to be involved in the regulation of fetal growth via modulation of expression and activity of the system A, but not L-amino acid transporter (Jones *et al.* 2009).

Over the last decade, significant advances in our understanding of placental biology have established that placental function is dynamic and influenced by maternal health, and has an important regulatory role in maternal well-being during pregnancy. For example, in women with type 1 diabetes, there is upregulation of placental glycosylation and acylation pathways and a trend toward increased placental weight (Nelson *et al.* 2009, Radaelli *et al.* 2009). Moreover, the progressive development of insulin resistance during pregnancy is due in part to placentally derived cytokines (Rusterholz *et al.* 2007) such as TNF (Kirwan *et al.* 2002) and leptin (Hauguel-de Mouzon & Guerre-Millo 2006). Studies have also demonstrated major changes in the placental gene expression profile of inflammatory genes in women who have developed gestational diabetes mellitus (GDM; Radaelli *et al.* 2009). Given that maternal obesity is accompanied by significant dysregulation of normal physiology, it is therefore plausible that placental structure and function may be altered as a consequence of maternal obesity, and equally, that the placenta may modulate maternal physiology by release of inflammatory cytokines. Table 2 compares the gene expression changes found in placenta from women with GDM with gene expression changes which have been described in placenta from obese women.

The placenta as an inflammatory organ

There has been a recent trend toward increasing placental weight (Swanson & Bewtra 2008), paralleling the significant rise in maternal BMI; however, further studies are needed to confirm whether the rise in maternal obesity is responsible for the increase in placental weight. Hypo- or hypercoiling of the umbilical cord, associated with fetal demise and vascular thrombosis (Sebire 2007), is also more common in pregnancies complicated by obesity, gestational

Table 2 Changes in gene expression levels in placenta from women with gestational diabetes mellitus (GDM) and obese women compared to non-obese healthy pregnant women.

Gene	Changes in GDM placenta	Changes in obesity placenta
Proinflammatory cytokines		
TNF	↑ (Radaelli *et al.* 2003)	↑ (Varastehpour *et al.* 2006)
	↔ (Kleiblova *et al.* 2010)	↑ (Challier *et al.* 2008)[a]
IL6	↔ (Kleiblova *et al.* 2010)	↑ (Challier *et al.* 2008)[a]
IL1	–	↑ (Challier *et al.* 2008)[a]
IL8	↔ (Kleiblova *et al.* 2010)	–
CCL2	–	–
IFNG	↓ (Radaelli *et al.* 2003)	–
Hormones		
Leptin	↑ (Lepercq *et al.* 1998)	↑ (Varastehpour *et al.* 2006)
	↔ (Kleiblova *et al.* 2010)	–
Leptin receptor	↑ (Radaelli *et al.* 2003)	–
Adiponectin	–	–
Adiponectin receptor 1	↔ (Kleiblova *et al.* 2010)	–
Adiponectin receptor 2	↔ (Kleiblova *et al.* 2010)	–
Resistin	↔ (Kleiblova *et al.* 2010)	–
Visfatin	↔ (Telejko *et al.* 2009)	–
Other factors		
MIF	↓ (Radaelli *et al.* 2003)	–
ESR1	↔ (Kleiblova *et al.* 2010)	–
ESR2	↔ (Kleiblova *et al.* 2010)	–
PLA2G2A	↑ (Varastehpour *et al.* 2006)	–
PLA2G5	↑ (Varastehpour *et al.* 2006)	–

↔, no relative change in gene expression levels; –, change not determined.
[a]Changes in gene expression levels in macrophage population isolated from placenta.

diabetes, and pre-eclampsia (de Laat *et al.* 2005). Although these pregnancy complications are all associated with increased inflammation, a causal link between inflammation and cord coiling abnormalities is yet to be established.

At the microscopic level, there are (to our knowledge) no detailed studies examining the effect of maternal obesity on placental structure. However, given that placentae from gestational diabetics have a characteristic morphology (placental immaturity and edema, chorangiosis, and vascular anomalies; Madazli *et al.* 2008), it is plausible that obesity may also affect placental structure. Supportive of this is a study by Challier *et al.* (2008) which demonstrates a two- to three-fold increase in placental macrophages in obese women compared with non-obese women. The macrophage population was characterized by increased expression of the proinflammatory cytokines IL1, TNF, and IL6, and marked phenotypic heterogeneity with complex subsets of CD14+, CD68+, and CD11b+ (mac-1) cells. A similar placental phenotype has recently been reported in a baboon model of obesity (Farley *et al.* 2009). It is also possible that maternal obesity may affect the number and function of other immune cell populations (Weisberg *et al.* 2003, Maroof *et al.* 2005, Macia *et al.* 2006) at the maternal–fetal interface including natural killer cells and dendritic cells. Alterations in these cell populations could have lifelong implications for the fetal acquired immune system and disease susceptibility in later life (Challier *et al.* 2008). Figure 3 summarizes the potential role of inflammation in the placenta and the interactions between maternal and fetal tissues.

Maternal obesity may also affect placental transport and substrate availability. Varastehpour *et al.* (2006) demonstrated a significant increase in the expression of the phospholipase A2 (PLA2) genes *PLA2G2A* and *PLA2G5* (the main placenta phospholipases), leptin, and TNF in placentae from obese neonates (body fat >16%) compared with lean neonates (body fat <8%; Varastehpour *et al.* 2006). By demonstrating that leptin and TNF induced a time-dependent activation of PLA2G2A and PLA2G5, they suggested that this inflammatory loop may be one mechanism by which excess fat accumulates in obese neonates. Alternatively, Elchalal *et al.* (2005) demonstrated that insulin and fatty acids enhance the expression of adipophilin, which is associated with cellular lipid droplets and implicated in cellular fatty acid uptake and storage of neutral lipids, in term human trophoblasts (Elchalal *et al.* 2005). In maternal obesity, higher circulating levels of insulin (Challier *et al.* 2008, Catalano *et al.* 2009) might therefore upregulate the expression of fatty acid transporters, thereby increasing the availability of fatty acids to both the placenta and the fetus.

Amino acid transport may also be affected by maternal obesity. As described previously, physiological
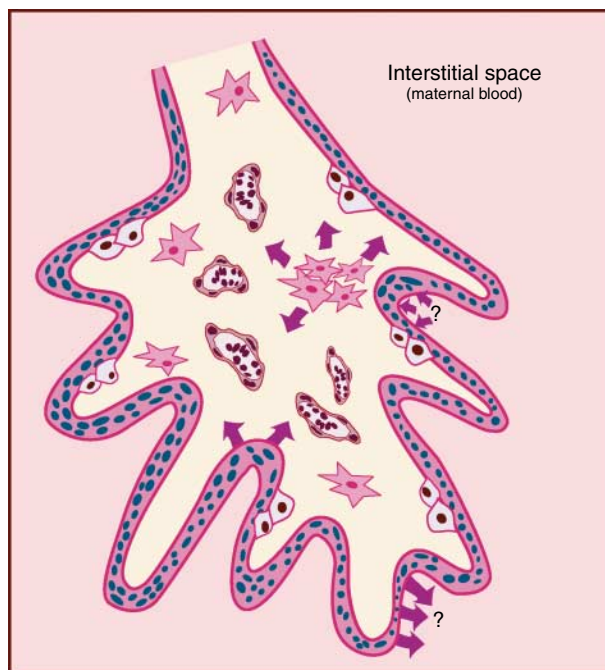
Figure 3 Inflammatory events within the placenta of obese pregnant women. Increased levels of placental macrophages (Hofbauer cells) in conjunction with the cytotrophoblast and syncytiotrophoblast cells are thought to contribute to a heightened inflammatory state within the placenta through the secretion of proinflammatory cytokines such as IL1, TNF, and IL6 (as shown by arrows). An interplay between the trophoblast and immune cells may exist which could further contribute to the heightened inflammatory state of the placenta. It is unclear exactly which proinflammatory cytokines pass through the placenta barrier. However, transfer of proinflammatory cytokines from the maternal circulation across to the placenta could potentially add to the increased local inflammatory state within the placenta. Similarly, proinflammatory cytokines from the placenta may be released into the maternal circulation and contribute to the systemic increase in inflammatory mediators, which is observed in maternal obesity.

concentrations of the proinflammatory cytokines IL6 and TNF stimulate the activity of amino acid transporter system A (Jones *et al.* 2009). In maternal obesity, increased levels of IL6 and TNF in the placenta could systemically stimulate the system A transporter further, thus increasing amino acid transport to the fetus. Other inflammatory markers that have been demonstrated to differ in placentae from obese animals compared with non-obese animals are carboxypeptidase E (Singh *et al.* 2006) and resistin (Zhou *et al.* 2006). Adipokines also modulate placental function. For example, leptin has been shown to regulate placental angiogenesis (Islami *et al.* 2003), protein synthesis (Perez-Perez *et al.* 2009), and growth, and cause immunomodulation (Fietta 2005). Thus, it is possible that the increase in local and/or circulating levels of leptin in maternal obesity may modulate placental inflammation and function (Islami *et al.* 2003, Fietta 2005, Perez-Perez *et al.* 2009).

Thus far, the evidence presented suggests that the placenta is a passive bystander in the hostile inflammatory environment of maternal obesity. However, this explanation may be too simplistic. A recent study by Roberts *et al.* (2009) has demonstrated that although nitrative stress was increased in placentae from obese women compared with non-obese women, this was accompanied by a decrease in oxidative stress. They proposed that the shift in balance between nitrative and oxidative stress may act as a protective mechanism for the placenta with the formation of peroxynitrite consuming reactive oxygen species and reducing oxidative stress. A similar protective mechanism appears to be present in women with gestational diabetes with antioxidant gene expression being increased in placentae from women with gestational diabetes compared with controls (Lappas *et al.* 2005). Furthermore, when placental explants from women with gestational diabetes were subjected to oxidative stress, expression and release of inflammatory cytokines were reduced compared to explants from normal pregnant women (Lappas *et al.* 2010). Finally, Colomiere *et al.* (2009) demonstrated post-receptor defects in the insulin signaling pathway in placentae from obese women compared to non-obese women with significant decreases in expression of mRNA for IR-β, PI3K p85α, and SLC2A4 (GLUT-4; Colomiere *et al.* 2009). Together, these studies raise the intriguing possibility that the placenta may be able to 'sense' the maternal environment and adapt to protect not only itself but also potentially the fetus from the hostile inflammatory, oxidative, hyperinsulinemic milieu present in maternal obesity.

Vascular and fibrinolytic function

In the non-pregnant state, obesity has profound and complex effects on vascular and fibrinolytic function (Stapleton *et al.* 2008). Clinically, this is reflected by an increased risk of hypertension, atherosclerosis, and ischemic heart disease, and having a myocardial infarction or a cerebrovascular accident. Thus far, most studies investigating the link between obesity and vascular and fibrinolytic function have been undertaken in non-pregnant individuals as opposed to pregnant individuals. In this section, we will review the current evidence linking obesity and inflammation to vascular and fibrinolytic dysfunction in non-pregnant individuals, the effect of pregnancy on vascular and fibrinolytic function, and finally, the combined effect of pregnancy and obesity on these variables.

In obese individuals, local and systemic vascular and endothelial function is significantly impaired. Blood vessel structure is altered in obesity with an increase in vessel diameter, basement membrane thickness, vascular permeability, and vessel stiffness (Zebekakis *et al.* 2005). With disease progression, microvascular vessel walls start to atrophy, vessel diameter narrows, and progressive microvascular rarefaction develops (Frisbee 2005, Stepp & Belin De Chantemele 2007), increasing the risk of local tissue ischemia. Adipose tissue, which surrounds blood vessels (perivascular adipose tissue), also indirectly affects vascular structure and tone via release of vasoactive inflammatory mediators including adipokines, angiotensin, and endothelin-1 (Zhang & Zhang 2009). At a functional level, the vasodilatory response to endothelium-dependent vasodilators such as acetylcholine is attenuated (Steinberg *et al.* 1996), whereas the response to endothelium-independent vasodilators, such as sodium nitroprusside, remains intact (Van Guilder *et al.* 2006). Flow-mediated dilation, which induces release of endothelium-dependent relaxing factors increasing blood vessel diameter, is also impaired (Sturm *et al.* 2009). Vasomotor responses are further blunted by an increase in sensitivity to vasoconstrictive agonists including prostanoids, endothelin-1, and a hyperactivity of the sympathetic nervous system (Esler *et al.* 2001, Agapitov *et al.* 2002, Traupe *et al.* 2002, Frisbee 2006).

Obesity is also associated with a prothrombotic state with plasma concentrations of prothrombotic factors including von Willebrand factor, fibrinogen, and factor VII being higher in obese controls compared with lean controls (Faber *et al.* 2009). Excess adipose tissue contributes directly to the prothrombotic state by i) impairing platelet function via low-grade inflammation and increase in circulating leptin, ii) impairing fibrinolysis by production of plasminogen activator inhibitor-1 and possibly thrombin-activatable fibrinolysis inhibitor, iii) impairing coagulation by release of tissue factor, and iv) affecting hepatic synthesis of the coagulation factors fibrinogen, factor VII, factor VIII, and tissue factor, by releasing free fatty acids and proinflammatory cytokines (IL1B, TNF, and IL6) into the portal circulation and by inducing hepatic insulin resistance (Faber *et al.* 2009).

In order to sustain the developing fetus, extensive cardiovascular adaptation occurs during pregnancy (Robb *et al.* 2009a, 2009b). Increased production of endothelium-derived vasodilators is accompanied by enhancement of endothelial function and reactivity (Anumba *et al.* 1999) and an increase in flow-mediated dilation of the brachial artery (Dorup *et al.* 1999). This is accompanied by a progressive increase in pulse wave velocity and augmentation index over the third trimester (Robb *et al.* 2009b). These changes occur despite the increase in systemic inflammation (Sacks *et al.* 1998, 2004), insulin resistance, and hyperlipidemia that occur during normal pregnancy (Sattar & Greer 2002). Pregnancy is also accompanied by significant alterations in the fibrinolytic and coagulation system with increased plasma concentrations of t-PA, coagulation factors, and inhibitors of fibrinolysis (Hellgren 2003, Robb *et al.* 2009a) and impaired endogenous fibrinolysis (Robb *et al.* 2009a).
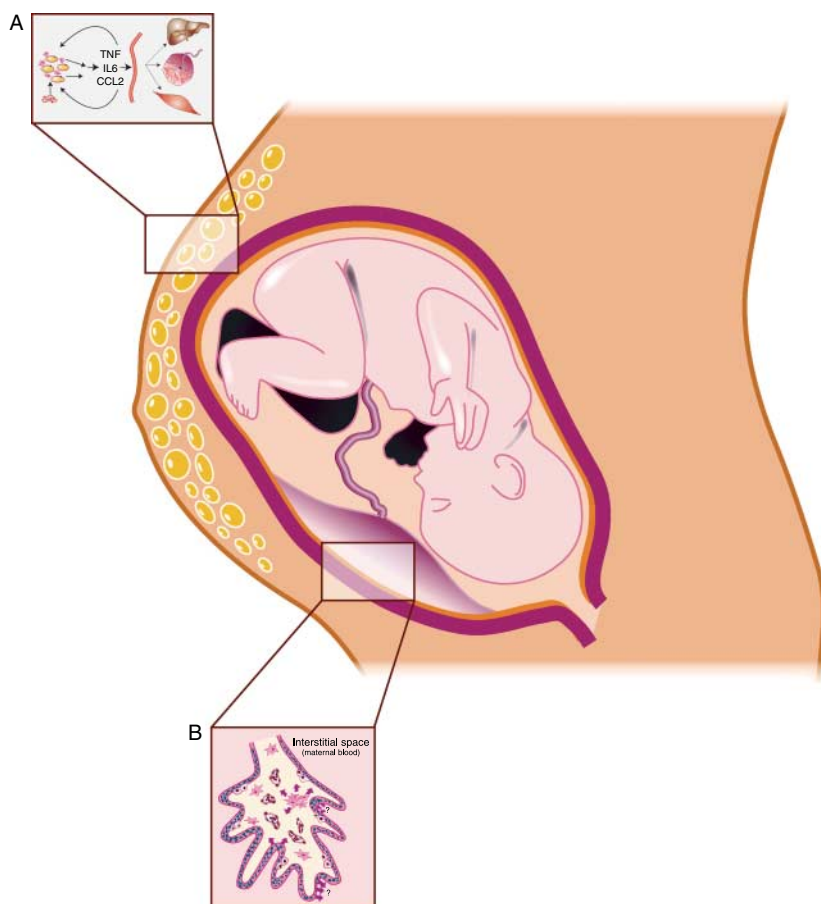
Figure 4 Maternal obesity and heightened inflammatory response. There are several potential sources of inflammatory mediators, including adipose tissue (A), placenta (B) and vascular endothelium, which may contribute to the local and systemic adverse effects.

Vascular and fibrinolytic function and inflammation

Obese women enter pregnancy with chronic preexisting endothelial activation. Although endothelium-dependent function increases during pregnancy in obese and lean women, it remains lower in obese women compared with lean women at all stages of pregnancy (Ramsay *et al*. 2002, Stewart *et al*. 2007). Moreover, by 4 months *post partum*, endothelial function declines to first trimester levels in obese women, whereas improved endothelium-dependent function persists in lean women (Stewart *et al*. 2007). Endothelium-dependent vasodilation is also impaired in myometrial arteries from women with an elevated BMI at booking compared with those with a BMI within the normal range (Myers *et al*. 2006). The mechanisms underlying impaired endothelial function in obese women are not well understood. However, it is likely that both systemic (Ramsay *et al*. 2002, Stewart *et al*. 2007) and local inflammation within the vasculature are likely to be involved in mediating impaired endothelial function (Walsh 2007). Maternal obesity is also associated with an increased risk of thromboembolism. However (to our knowledge), there are no studies that have compared endogenous fibrinolysis in obese women compared to lean women during pregnancy, nor established whether there are any differences in clotting factors between these groups.

Summary

Maternal obesity is associated with an increase in maternal and neonatal morbidity and mortality. However, the mechanisms underlying this association remain poorly understood. It is likely that excessive local and systemic inflammation play a key role in the pathophysiology of the adverse outcomes (Fig. 4). Further studies are urgently required to investigate the biology of adipose tissue in obese pregnant women, its links to insulin resistance, circulating inflammatory cytokines, placental, endothelial and fibrinolytic function, and adverse pregnancy outcome. Such studies will inform rational therapies for testing to reduce pregnancy-related mortality and morbidity among both the mother and the neonate.

Declaration of interest

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