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REVIEW

The impact of maternal obesity on inflammatory processes and consequences for later offspring health outcomes

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Obesity is a global epidemic, affecting both developed and developing countries. The related metabolic consequences that arise from being overweight or obese are a paramount global health concern, and represent a significant burden on healthcare systems. Furthermore, being overweight or obese during pregnancy increases the risk of offspring developing obesity and other related metabolic complications in later life, which can therefore perpetuate a transgenerational cycle of obesity. Obesity is associated with a chronic state of low-grade metabolic inflammation. However, the role of maternal obesity-mediated alterations in inflammatory processes as a mechanism underpinning developmental programming in offspring is less understood. Further, the use of anti-inflammatory agents as an intervention strategy to ameliorate or reverse the impact of adverse developmental programming in the setting of maternal obesity has not been well studied. This review will discuss the impact of maternal obesity on key inflammatory pathways, impact on pregnancy and offspring outcomes, potential mechanisms and avenues for intervention.

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Introduction

Obesity continues to be a global health concern. Although the increasing obesity rates in developed countries has slowed in the past 10 years, obesity rates in developing countries continue to increase, as much as tripling in some developing countries over the past 30 years.[1,2] This is largely attributed to a growing shift to a western lifestyle, including reduced physical activity and widespread availability of cheap and calorically dense food (typically high in sugar, salt and saturated fat).[2,3] Obesity is a major risk factor for a number of adverse health conditions [including type 2 diabetes (T2DM), hypertension, hypercholesterolemia, asthma, arthritis, some cancers and general poor health] and therefore represents a significant burden on the healthcare system.[4]

Rates of overweight and obesity in women of reproductive age can be as high as 64% depending on the population studied.[5] Being overweight or obese during pregnancy not only increases the risk of a number of obstetric and fetal complications,[6,7] but predisposes these children to obesity and metabolic syndrome.[8–11] Maternal obesity not only has immediate consequences, but has the potential to perpetuate a transgenerational cycle of obesity.[11]

There are a number of physiological differences between normal-weight and obese pregnancies. In normal-weight pregnancies, given fetal nutrient requirements, it is typical for a woman to undergo a reduction in insulin sensitivity, increased protein synthesis, and increased lipogenesis and fat accretion.[12] Women who are obese while pregnant are more likely to become more insulin resistant earlier in pregnancy (and more likely to develop gestational diabetes)[12] and have exaggerated increases in inflammatory cytokines, glucose, lipids and amino acids.[13,14] Therefore, the developing fetus may be exposed to a combination of inflammatory cytokines and excess nutrition *in utero*, with lasting consequences in postnatal life.

Obesity in the non-pregnant state is associated with a state of chronic low-grade inflammation.[15] However, the role of maternal obesity-mediated changes in inflammatory processes as a mechanism underpinning developmental programming in offspring is not well defined. The use of anti-inflammatory agents as an intervention strategy to ameliorate or reverse the impact of adverse developmental programming in the setting of maternal obesity has not been well studied. This review will discuss the impact of maternal obesity on key inflammatory pathways, impact on pregnancy and offspring outcomes, potential mechanisms and avenues for intervention.

Obesity results in metabolic inflammation

Once traditionally considered an inert depot for energy storage, the white adipose tissue is now recognized as a highly metabolically active endocrine organ.[16] In the lean state, the adipose tissue maintains a state of homeostasis. Excess energy is stored as lipids in adipocytes, there is adequate vascularization to the tissue and a predominance of M2 alternatively activated macrophages which preferentially secrete the anti-inflammatory cytokine interleukin (IL)-10.[17] In general, as an individual becomes obese, the adipose tissue undergoes a number of key structural and functional alterations which can negatively impact whole-body metabolism. Adipocytes become enlarged and undergo hypertrophy (and/or hyperplasia) to cope with

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increased energy storage demands.[18] If the adipose tissue's capacity to store lipid is exceeded, lipids may be ectopically stored in other tissues including the skeletal muscle and liver, which can promote local insulin resistance (IR) in these tissues.[19] As the adipose tissue expands, vascularization of the tissue may become inadequate and hypoxia can occur.[20] There is an increased secretion of pro-inflammatory cytokines including tumor necrosis factor-α (TNFα), IL-6, IL-1β and monocyte chemoattractant protein-1 (MCP1), which cause an infiltration of M1 classically activated macrophages and further exacerbate inflammation.[21,22] The secretion of a number of adipose tissue-derived cytokines are also dysregulated. Circulating leptin (suppresses food intake and promotes energy expenditure) concentrations are increased,[23] while adiponectin (an insulin sensitizing hormone) concentrations are reduced.[24] In obesity, the complex interplay of these molecular alterations promote metabolic inflammation and IR in the adipose tissue, which also contributes to whole-body metabolic derangements.

However, these impairments may not necessarily occur in all obese individuals, as a significant proportion of obese individuals may be considered metabolically healthy.[25] This concept is under current debate, as metabolically healthy obese individuals are still at an increased risk of metabolic syndrome[26] and mortality[27] compared to non-obese healthy individuals, suggesting that metabolically healthy obesity is a transient state, before the progression to metabolic dysfunction.

Key cytokines involved in metabolic inflammation

The following section discusses some of the key cytokines involved in obesity-induced metabolic inflammation and their impact on insulin sensitivity in the non-pregnant state. Further research is required to understand how these cytokines become dysregulated in both the mother and her offspring as a result of maternal obesity.

TNFα

Hotamisligil *et al.*[28] was first to demonstrate that TNFα expression and secretion from adipose tissue was higher in obese compared with lean mice. Further, *in vivo* neutralization of TNFα increased insulin-stimulated glucose utilization in obese-diabetic rats. They also confirmed elevated TNFα expression in the adipose tissue of obese humans, which strongly correlated with the degree of hyperinsulinemia.[29] TNFα has since been shown as a major regulator of lipid metabolism, acting through multiple mechanisms, including increasing free fatty acid production, inducing lipolysis, inhibiting enzyme activity and regulating cholesterol metabolism.[30] In both high fat diet (HFD)-induced and genetic (*ob*/*ob*) models of obesity, TNFα knockout improves insulin sensitivity.[31] However, *ob*/*ob* mice with knockout of TNFα receptors were still technically insulin resistant, implying that TNFα is not the only factor responsible for obesity-induced IR.

IL-1β

Chronic treatment of human and murine adipocytes with IL-1β inhibits insulin-induced phosphorylation of insulin receptor subunits and Akt, thus reducing insulin-stimulated glucose uptake and lipogenesis.[32] IL-1β treatment also reduces lipid content in adipocytes, which may be due to a reduction in peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT-enhancer-binding protein α (C/EBPα), two key regulators of adipogenesis.[32] HFD-induced obesity in mice lacking the IL-1 receptor I (IL-1RI) show improved glucose tolerance compared with their wildtype counterparts and are partially protected from developing IR.[33] Despite having no difference in M1 or M2 macrophage number, macrophages from IL-1RI knockout mice were less immunogenic, with reduced secretion of IL-6 and TNFα. Adipose tissue from obese IL-1RI knockout mice also had a less inflammatory phenotype compared with obese wildtype mice. Furthermore, in wildtype but not IL-1RI mice, there was synergism between TNFα and IL-1β to induce macrophage and adipose tissue inflammation.

IL-6

IL-6 has a pleiotropic hormone-like role, with functions dependent on the tissue, physiological state, and whether it is elevated acutely or chronically.[34] An estimated 15–35% of circulating IL-6 originates from adipose tissue.[35] Adipose tissue secretion of IL-6 can be 15-fold higher in insulin resistant individuals.[36] Treating adipocytes[36] or hepatocytes[37] with IL-6 impairs insulin signaling. In contrast, upon exercise, the muscle secretes a large amount of IL-6, which can act on the liver (to maintain glucose homeostasis) and the adipose tissue (to promote lipolysis).[38] However, in large population studies (American Nurses' Health Study), elevated IL-6 is a predictive indicator for later diabetes risk.[39] In a smaller study of morbidly obese patients who underwent gastric surgery, reduced circulating IL-6 was significantly correlated with a reduction in IR.[40] However, IL-6 knockout mice develop hypertrophic obesity, IR, hepatic inflammation and lipid accumulation.[41]

IL-10

In contrast to the pro-inflammatory cytokines, IL-10 has an anti-inflammatory or counter-regulatory role. IL-10 has been postulated to be protective against the development of T2DM and the metabolic syndrome in humans.[42] In lipopolysaccharide-stimulated macrophages, IL-10 prevented the production of the cytokines TNFα and IL-6.[43] Lumeng *et al.*[17] have shown a number of beneficial effects of IL-10. IL-10 is highly expressed on M2 macrophages, with adipose tissue macrophages from obese mice having reduced IL-10 expression. Moreover, treatment of adipocytes with IL-10 resulted in rapid phosphorylation of Akt (which promotes glucose uptake) and also reduced adipocyte secretion of MCP1. In addition, pre-treatment of adipocytes with IL-10 prevented

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TNFα-induced downregulation of glucose transporter type 4 (GLUT4) and the insulin receptor and downregulation of insulin-stimulated glucose uptake.

Maternal obesity and metabolic inflammation

Pregnancy itself is associated with heightened systemic and adipose tissue inflammation.[44,45] However, in pregnancies complicated by obesity, the state of low-grade inflammation is greater in magnitude than observed in normal-weight pregnancies.[14,46–48] Maternal obesity is associated with increased risk of pre-eclampsia and gestational diabetes mellitus, conditions in which inflammation is also inherently involved.[49] Breastfeeding is generally considered to be protective against offspring obesity.[50] However, breast milk composition is highly variable, and emerging research has revealed relationships between maternal obesity and increased pro-inflammatory factors in breast milk.[51] Therefore, in multiple aspects, inflammation may represent a key mechanism mediating the adverse outcomes arising from maternal obesity.

Maternal obesity is also associated with dysregulation of a number of other circulating factors and hormones, which can contribute to developmental programming in offspring. In obesity, lipolysis and circulating free fatty acids are increased, potentially contributing to impaired insulin signaling through several mechanisms as recently reviewed by Morignya *et al.*[52] These include accelerating ectopic lipid deposition, altering adipose tissue adipokine secretion and/or further promoting adipose tissue inflammation.[52] Glucocorticoids may also act as a programming factor, as plasma glucocorticoids are increased in obese dams and offspring at postnatal days 2 and 110.[53] Concentrations of ghrelin, an appetite stimulating hormone, are reduced in human obesity.[54] Neonatal overnutrition in mice (by reducing litter size to increase milk consumption) programs obesity in offspring, concomitant with reductions in circulating ghrelin and potential ghrelin resistance.[55] In addition, in human cohorts early life feeding choices, such early introduction of solids and breastfeeding, can impact obesity risk in offspring.[50,56]

There is a long period of time required for the manifestation of metabolic disease in humans. Few human studies have been able to investigate the impact of maternal obesity-induced metabolic inflammation on long-term offspring adiposity and metabolic outcomes, with many studies only able to report associations between maternal inflammation and neonatal and early life outcomes. In a study of 18 mother–offspring pairs, Radaelli *et al.*[57] reported a significant correlation between maternal IL-6 concentrations at term and neonatal fat mass; however there was no correlation between cord blood IL-6 and neonatal fat mass. This suggested maternal inflammation may drive the increased risk of adiposity in offspring. McCloskey *et al.*[58] reported a significant correlation between maternal pre-pregnancy body mass index (BMI) and maternal C-reactive protein (CRP) during the 28th week of gestation. Maternal pre-pregnancy BMI was significantly correlated with cord blood CRP and adiposity in newborns, suggesting that maternal pre-pregnancy obesity influences offspring adiposity, with inflammation likely a mediating factor. A longitudinal study in 1116 mothers–offspring pairs examined CRP as a biomarker of low-grade inflammation in maternal plasma during mid-pregnancy.[59] Pre-pregnancy BMI was significantly associated with maternal CRP concentrations during mid-pregnancy. CRP concentrations were also associated with increased total and truncal fat mass in offspring aged 7–10 years, independent of maternal pre-pregnancy BMI and other confounding factors. Taken together, these studies demonstrate that maternal inflammation during pregnancy is linked to increased adiposity in offspring.

Several studies have also reported no association between maternal inflammation and offspring outcomes. A study in 71 pregnant women found that maternal IL-6 and IL-8 concentrations were significantly correlated with maternal adiposity at 28 weeks of gestation.[60] However, maternal TNFα, IL-1β, IL-6 and IL-8 concentrations were not associated with fetal body composition at 28 and 37 weeks of gestation (assessed by ultrasound) or with birth weight. A recent study reported a significant correlation between maternal BMI and cord blood TNFα concentrations, however there was no correlation with offspring body weight at 9 months of age.[61] A study of 439 mother-offspring pairs reported no significant relationship of maternal CRP, TNFα, IL-1β or IL-6 measured during the third trimester of pregnancy and features of the metabolic syndrome in offspring at 20 years of age.[62] However, this study was conducted in healthy, mostly normal-weight women and they adjusted for maternal pre-pregnancy BMI. In the absence of the physiological changes related to obesity, these findings may not necessarily be applicable to maternal obesity.

Animal models have been invaluable in elucidating the mechanisms underlying metabolic inflammation and developmental programming. Rodent models demonstrate that maternal immune activation during pregnancy results in enhanced immunogenic potential in offspring.[63,64] Treatment of non-obese pregnant rats with endotoxin (mimicking infection or classic inflammation) results in obesity and IR in adult male offspring.[65] Therefore, it is plausible that low-grade inflammation resulting from maternal obesity could have a similar impact on offspring. In a model of HFD-induced obesity, pregnant dams had increased circulating TNFα concentrations, increased adipose tissue gene expression of TNFα and MCP1 and increased adipose tissue macrophage infiltration on day 17 of pregnancy.[66] Fetuses had significantly higher insulin and glucose concentrations, accompanied by increased subcutaneous adipose tissue expression of TNFα and CD68 (macrophage marker) and reduced expression of the glucose transporter GLUT4. These findings suggest that offspring exposed to maternal obesity may have impaired insulin sensitivity via inflammatory mechanisms in the adipose tissue. Interestingly, Alfaradhi *et al.*[67] have recently shown that maternal obesity programs adipose tissue inflammation in

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young mice without obesity, with altered expression of miRNAs as a potential mechanism.

Potential inflammatory mechanisms of developmental programming

The state of low-grade systemic and adipose tissue inflammation induced by maternal obesity is linked to a number of consequences that may contribute to developmental programming. Maternal adipose tissue inflammation can not only influence maternal insulin sensitivity, but it is also associated with aberrant secretion of adipose tissue-derived hormones. Animal and human evidence demonstrates that maternal obesity is associated with increased placental inflammation,[68,69] which may contribute to abnormal placental function and/or nutrient transport. Therefore, the fetus may develop in an inflammatory environment which has the potential to impact development and lifelong health of the offspring. Adverse placental function may impact fetal nutrient supply and therefore development. Understanding the mechanisms underpinning developmental programming is key to identifying effective intervention strategies. However, the mechanisms are likely multifactorial in nature, with a range of mechanisms likely involved.

Dysregulation of adipose tissue-derived hormones

Obesity causes dysregulated secretion of hormones from the adipose tissue, which impact inflammatory processes and metabolic health. The two most well-defined adipose tissue-derived hormones are leptin and adiponectin.

Leptin is a hormone primarily secreted by adipocytes, which is released into the circulation, and acts on the brain to regulate long-term energy balance by suppressing food intake and increasing energy expenditure.[70] Leptin also acts as a pro-inflammatory factor. Treating macrophages with leptin causes a significant upregulation of inflammatory cytokines including TNFα, IL-12 and IL-6.[71] Treating human placental explants with leptin results in significantly increased secretion of TNFα, IL-1β and IL-6.[72] Elevated plasma and cerebral spinal fluid leptin concentrations are associated with a higher body fat percentage and BMI,[73] indicating a central resistance to leptin in obesity.

In rodent models of maternal obesity, mothers and adult offspring commonly display hyperleptinemia.[74] Oben *et al.*[75] demonstrated that obese dams had increased circulating leptin concentrations compared with lean dams, and therefore leptin may mediate programmed alterations to appetite regulation. The use of drugs or specific bioactive food components with anti-inflammatory properties, especially in the hypothalamus, may help to overcome leptin resistance.[76]

Adiponectin is an adipose tissue-derived insulin sensitizing and anti-inflammatory protein. In contrast to leptin, adiponectin mRNA expression[77] and circulating concentrations[78] are inversely correlated to body fat, whereas reduced adiponectin is correlated with obesity, hyperlipidemia and IR.[24] Adiponectin's insulin sensitizing activity is linked to its ability to increase fatty acid oxidation and inhibit hepatic gluconeogenesis.[79] Adiponectin polarizes adipose tissue macrophages toward an M2 activated state, promoting the production of anti-inflammatory cytokines such as IL-10.[80]

In models of maternal obesity, circulating concentrations of adiponectin are also reduced.[81] Aye *et al.*[82] assessed the effects of adiponectin infusion during embryonic days 14.5–18.5 in mice fed a HFD before and during pregnancy. Adiponectin treatment did not affect maternal fat mass, but normalized maternal fasting leptin and insulin and fetal hyperglycemia with maternal obesity. Further, adiponectin normalized nutrient transport and insulin signaling in the placentas from mothers fed a HFD.

Placental inflammation and dysfunction

The placenta has a vital role during pregnancy, supplying the developing fetus with nutrients and oxygen from the mother to accommodate fetal development. Maternal obesity is associated with a lipotoxic placental environment, including increased lipid accumulation, reduced expression of angiogenic markers and increased expression of markers related to inflammation and oxidative stress.[83]

Challier *et al.*[68] compared the placentas of obese and lean women at term. Obese women had increased circulating IL-6, CRP and leptin concentrations and increased IR. This was accompanied by increased accumulation of macrophages in the placenta and increased expression of IL-6, TNFα, IL-1β and MCP1 compared with lean women. The authors speculated that fetal exposure to an inflammatory environment might contribute to the programmed alterations observed in offspring following a maternal obesogenic environment. Interestingly, increases in maternal peripheral blood mononuclear (PBMC) inflammatory gene expression in obese women were not mirrored in the expression in umbilical PBMCs. In contrast, Dosch *et al.*[84] reported increased CRP and TNFα in umbilical cord plasma from class II obese women (BMI 35–39.99), as well as increased mononuclear secretion of TNFα, IL-1β and IL-6 when stimulated. Thus maternal obesity and the resulting placental inflammation may act as programming factors with or without directly inducing fetal inflammation.

Using a sheep model, Zhu *et al.*[69] examined whether maternal obesity-induced inflammatory changes in the placenta were evident in mid-gestation. Obese dams had increased expression of toll-like receptor (TLR)2, TLR4, CD11b, CD68, TNFα, IL-6, IL-8 and IL-16 in the cotyledonary tissue of their placentas, which was accompanied by increased NF-κB and JNK signaling. Fetuses from obese ewes had elevated free fatty acids, cholesterol and triglycerides in their circulation. These findings suggest that increased fatty acid uptake by the placenta may cause a TLR4-mediated activation of inflammatory pathways in the placenta.

Abnormal placentation and trophoblast differentiation and invasion can result in a number of complications, including those associated with maternal obesity such as pre-eclampsia

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and intrauterine growth restriction (IUGR).[85] In maternal obesity, trophoblast invasion is altered and there is reduced remodeling of the spiral arteries.[86] These proposed changes occur as a result of the increased cytokines in maternal obesity. Elevated IL-6 concentrations also increase fatty acid accumulation in trophoblasts, which could contribute to increased fetal nutrient transfer.[87] Placentas from obese women are also more likely to have placental insufficiency, increased pathology including vascular lesions, villous lesions and fetal membrane meconium compared with placentas of women of normal weight.[88] In the rat, a maternal HFD results in fetal and placental junctional zone growth restriction, maternal and fetal hyperleptinemia but gene expression of markers of placental vascular development were not altered.[89] It has also been shown experimentally that the inflammatory state of the placental labyrinth zone increases near term coincident with the known increase in local glucocorticoid concentrations. These data suggest that the classic anti-inflammatory actions of glucocorticoids do not occur in the placental labyrinth zone.[90]

Altered placental nutrient transport

Farley *et al.*[91] found that obese pregnant women with hyperleptinemia and placental leptin resistance had decreased placental sodium-dependant neutral amino acid transporter activity. These changes did not affect birth weights, however it is unclear if these results were confounded by small sample size (only an $n = 7$ women per group) or offspring sex. A larger cohort of over 400 women compared placental histopathology between normal and obese women. Independent of diabetes (T2DM and gestational), obese women had larger placentas, decreased placental efficiency, increased hypoxic stress, increased placental inflammation (measured by chronic villitis, increased vasculopathy of the decidua and a higher proportion of fetal overgrowth).[92] The large sample size allowed the data to be stratified by offspring sex, revealing that in obese women placentas had greater inflammation when offspring were female rather than male. Ditchfield *et al.*[93] also demonstrated that obese women had decreased placental taurine transporter protein, which they speculated may reduce taurine concentration in the syncytiotrophoblast, thus hampering the development and function of the placenta, while also reducing taurine transport to the fetus. Obese women had increased lipoprotein lipase activity and placental expression of fatty acid translocase and reduced expression of fatty acid-binding protein (FABP) 1 and FABP3.[94] Therefore in human obese pregnancy, a range of nutrient transporters have been shown to be altered. It is possible that these alterations affect nutrient supply to the fetus, contributing, at least in part, to the programmed effects in offspring.

Potential intervention strategies to prevent developmental programming

Developmental programming was once believed to result in permanent physiological effects that contributed to obesity and metabolic disease risk.[95] Accumulating evidence demonstrates the capability to ameliorate or reverse programming by targeted interventions during specific periods of developmental plasticity. In particular, intervention before pregnancy, during pregnancy or in the early life of offspring before disease has manifested appear to be the most effective times for intervention.[96] The following section will discuss lifestyle, pharmaceutical and nutritional intervention strategies which have impacted maternal and/or offspring inflammatory status.

Maternal exercise

In addition to the benefits of weight loss, it has been proposed that the anti-inflammatory effects of exercise may partially contribute to the beneficial health effects of exercise.[97,98] While there are a number of studies examining maternal exercise as an intervention in obese pregnancy, these studies have not thoroughly assessed inflammatory regulation in the mother and/or offspring in response to maternal exercise, highlighting a need for further research in this area.

In a Wistar rat model of maternal obesity, exercise improved maternal metabolism (circulating glucose, insulin, triglycerides and oxidative stress markers), and partially reduced triglycerides, fat mass and circulating leptin in P36 male (but not female) offspring.[99] Although this study demonstrated a clear benefit of maternal exercise independent of weight loss, it did not examine if inflammatory markers were altered. A recent study examined the impact of voluntary maternal exercise during pregnancy in HFD-induced obese mice.[100] At postnatal day 21, male offspring from obese and obese exercised dams had similar weights and fat mass. However, male offspring from obese dams had impaired glucose tolerance and significantly increased circulating, hypothalamic and adipose tissue IL-6 expression, while these changes were blunted in offspring from obese exercised dams. Tinius *et al.*[101] compared obese women who were either active or inactive during late pregnancy. Maternal circulating CRP and circulating lipids were significantly higher in inactive obese women compared with active obese women. While there were no significant differences in offspring birth weight, fat mass, skin fold thickness or cord blood CRP, longer term follow-up is still required.

Pharmaceutical interventions

Exendin-4

Exendin-4 (EX4, an analog of glucagon-like peptide-1) is a hypoglycemic drug. Chen *et al.*[102] treated male offspring from mothers who were fed either a control or HFD before and throughout pregnancy and lactation with EX4 (intraperitoneal injection of 15 μg/kg/day) at weaning for a period of 6 weeks. They found that EX4 administration to males was effective at reducing the programmed effects of a maternal HFD (increased adiposity, glucose intolerance and hyperlipidemia), and was beneficial when these offspring were fed a HFD postnatally. These improvements were accompanied by reduced adipose

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tissue expression of TNFα and hepatic expression of IL-6 and MCP1.

Pioglitazone

Pioglitazone is a thiazolidinedione which activates PPARγ, and has antidiabetic and anti-inflammatory effects.[103] In mice fed either a control or HFD for 3 months before and throughout gestation and lactation, pioglitazone administration to offspring daily between weeks 10 and 12 was effective at reducing body weight, visceral adipose tissue, triglycerides, insulin and increasing insulin sensitivity in male offspring.[104] The authors speculated that drugs which activate PPARγ may be beneficial in preventing developmental programming induced metabolic syndrome in offspring.

Metformin

Desai *et al.* investigated the effect of the antidiabetic drug metformin in a rat model of maternal obesity on maternal, placental and fetal outcomes. Metformin treatment did not significantly affect increased maternal weight, and altered lipid, insulin, leptin or cytokine concentrations associated with maternal obesity.[105] Fetal weight, litter size and placenta weight were not significantly affected by metformin treatment. Maternal metformin decreased inflammatory markers in both the placenta and the fetus. Direct treatment of metformin to the placental JAR cell line indicated that metformin inhibits inflammatory signaling by reducing TNFα dependent IL-6 production via the NF-κB pathway. Furthermore, in a similarly designed study by the same research group, maternal metformin treatment prevented a programmed increase in fetal hepatic inflammation.[106] In a separate study prenatal exposure to metformin in HFD-fed mice was protective against weight gain when adult offspring were challenged with a period of HFD feeding.[107]

The EMPOWaR trial is a unique multicentre, double-blind randomized clinical trial investigating a preventative treatment for the adverse offspring outcomes associated with maternal obesity (in the absence of diabetes).[108] The primary study outcome, birth weight as a surrogate marker for later life health of offspring, was not significantly altered by maternal metformin.[109] However, researchers will follow-up the children for potential long-term effects of maternal metformin.

Nutritional interventions

Omega-3 polyunsaturated fatty acids (PUFAs)

Omega-3 PUFAs exhibit beneficial anti-inflammatory effects by regulating NF-κB-mediated inflammatory gene expression[110] and lipid metabolism and adipogenesis through PPARs.[111] A number of studies have investigated their therapeutic potential in pregnancies complicated by maternal obesity.

Omega-3 PUFA supplementation reduces maternal adipose tissue and placental inflammation in obese pregnant women.[112] Treatment of human placental explants with physiologically relevant mixtures of omega-6 and omega-3 PUFAs, found no benefit of omega-3 PUFAs in reducing placental inflammation.[113] Several human studies report no significant effects of maternal omega-3 PUFA intake on offspring body composition or cardiometabolic outcomes.[114–116] Indeed a meta-analysis has concluded that there is insufficient evidence that omega-3 PUFA supplementation during pregnancy or lactation reduces childhood adiposity.[117] These findings may be due to the critical role of the omega-3 to omega-6 PUFA ratio in cardiometabolic disease.[118] This ratio can vary among participants depending on the PUFA content of their diet (also population dependent) and with genetic variants in PUFA metabolism.[119] However, there is still a need for more clinical trials with larger sample sizes and longer term follow-up.

In contrast, in animal models maternal omega-3 PUFAs have been shown to modulate adiposity and adipose tissue metabolism in offspring.[120–122] For example, male offspring from Fat-1 transgenic mice (capable of converting endogenous omega-6 PUFAs to omega-3 PUFAs) were protected from development of metabolic inflammation, and their offspring were protected from programmed adiposity, adipose tissue macrophage accumulation, IR and systemic inflammation.[120] In contrast, maternal omega-3 supplementation to a control diet has been shown to increase adiposity in male and female rat offspring.[123] In a rat model of glucocorticoid-induced programming, postnatal administration of omega-3 PUFAs mitigated programmed hypertension and hyperlipidemia in male offspring[124] and adipose tissue inflammation in male and female offspring.[125] Post-weaning incorporation of fish oil into the diet prevented programmed dyslipidemia and liver steatosis in males in a high sucrose diet programming model.[126] In a model of uteroplacental insufficiency-induced IUGR, maternal administration of docosahexaenoic acid during pregnancy and lactation prevented programmed adiposity and alterations in PPARγ expression and increased circulating adiponectin concentrations in males but not females.[127]

Omega-3 PUFA administration has been shown to be beneficial in a range of programming models, and effective during various exposure periods. Nevertheless, interpreting the current data is complicated given the differences in study design including range of doses used, timing of exposures and potential for sexually dimorphic outcomes in offspring. Consequently, there is still disagreement about the effectiveness of omega-3 PUFAs during pregnancy/lactation on reducing adiposity in offspring. Further research is warranted.[128,129]

Conjugated linoleic acid (CLA)

CLA refers to a mixture of positional and geometrical isomers derived from the omega-6 PUFA linoleic acid (C18:2 *cis*-9, *cis*-12).[130] CLA is naturally produced in ruminants through biohydrogenation[131] or endogenous synthesis in tissue.[132] Meat and dairy products from cattle are one of the richest dietary sources of CLA.[133] A total of 28 isomers of CLA have

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been found, but the *cis*-9,*trans*-11 (*c*9,*t*11) and *trans*-10,*cis*-12 (*t*10,*c*12) isomers are the most common naturally occurring and bioactive isomers attributed to beneficial health effects.[134]

There is strong evidence in animal models that administration of a mixture of the *c*9,*t*11 and *t*10,*c*12 isomers has anti-obesity[135], antidiabetic[136] and anti-atherosclerotic[137] effects. While many studies administer a mixture, the two isomers actually have distinct functions.[138] The *c*9,*t*11 isomer is associated with anti-inflammatory effects in conditions including inflammatory bowel disease and T2DM.[139–141] *c*9,*t*11-CLA has the capability to regulate gene expression as a potent ligand of the PPAR group of nuclear receptors which regulate the expression of genes involved in adipogenesis, inflammation and lipid metabolism.[141,142] *c*9,*t*11-CLA also modulates NF-κB activation,[143] contributing to decreased pro-inflammatory cytokine production.[144,145] The anti-obesity effects of CLA are linked to the *t*10,*c*12 isomer.[146]

We have previously demonstrated that maternal CLA supplementation to a HFD during pregnancy and lactation significantly reduced maternal metabolic inflammation (circulating TNFα and IL-1β concentrations) during pregnancy, independent of changes in body weight.[147] Furthermore, male and female offspring from HFD-fed dams displayed significantly reduced fetal size at gestation day 20, accelerated postnatal catch-up growth and impaired insulin sensitivity at postnatal day 24. These parameters were completely normalized in offspring from CLA-supplemented mothers on a HFD.

Discussion

The evidence that maternal obesity programs obesity and related metabolic complications in offspring is overwhelming. Obesity is an incredibly complex syndrome, with a number of key negative features. In the case of obese pregnancy, a complex interplay of these factors contribute to adverse developmental programming (Fig. 1). One of the key features of obesity is low-grade metabolic inflammation, which is maintained in pregnancy and induces inflammation in the placenta. While these relationships have been established there is a considerable gap in our knowledge of the precise role of inflammation and whether it directly contributes to developmental programming or simply arises a consequence of metabolic dysregulation.

Given the consequences for offspring, there is growing interest in interventions which can mitigate developmental programming. These interventions typically aim to improve maternal metabolism and reduce body weight, however some have directly administered interventions to offspring in early life. There are limited numbers of studies which focus on the use of anti-inflammatory agents as an intervention strategy in the developmental programming paradigm. While some animal models show promise, many of the interventions that have been translated to human studies do not show the same clear benefits. Furthermore, many of these studies have reported sex-specific differences in offspring, underscoring a complexity in translating intervention strategies from animal models to humans. Further research is required to better understand the

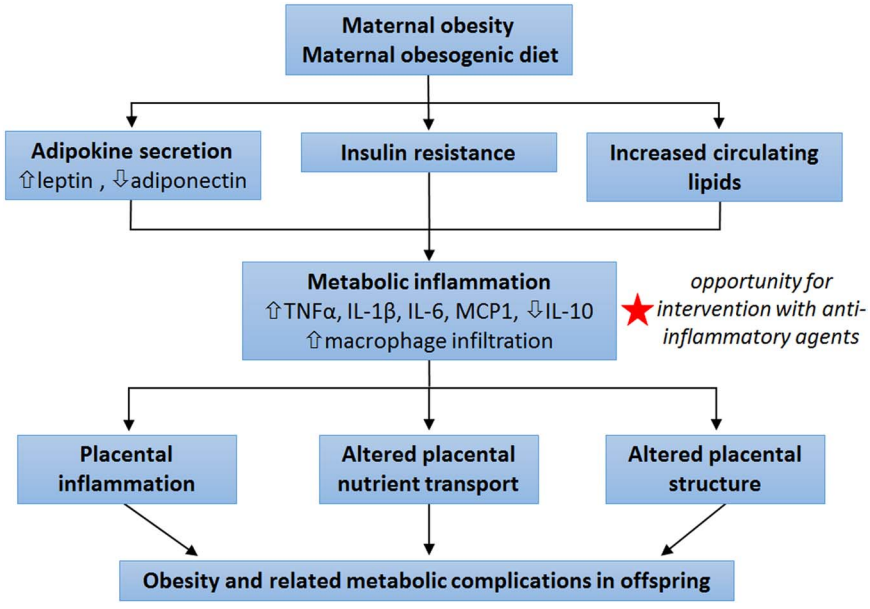

Fig. 1. Summary of the impact of maternal obesity on inflammation. Maternal obesity (or maternal consumption of an obesogenic diet) can result in altered adipokine secretion, insulin resistance and/or increased circulating lipids in the mother. These alterations are associated with metabolic inflammation. Reducing maternal metabolic inflammation with anti-inflammatory agents may represent a key target for preventing developmental programming. Maternal metabolic inflammation is also linked to placental inflammation, altered placental nutrient transport and altered placental structure. These changes may mediate developmental programming of obesity and related metabolic conditions in offspring.

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precise role of inflammation in developmental programming thereby allowing development of targeted interventions.

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Conflicts of Interest

The authors declare that that there is no conflict of interests regarding the publication of this paper.

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