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The impact of maternal obesity during pregnancy on offspring immunity

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Abstract

In the United States, approximately 64% of women of childbearing age are either overweight or obese. Maternal obesity during pregnancy is associated with a greater risk for adverse maternal-fetal outcomes. Adverse health outcomes for the offspring can persist into adulthood, increasing the incidence of several chronic conditions including cardiovascular disease, diabetes, and asthma. Since these diseases have a significant inflammatory component, these observations are indicative of perturbation of the normal development and maturation of the immune system of the offspring in utero. This hypothesis is strongly supported by data from several rodent studies. Although the mechanisms of these perturbations are not fully understood, it is thought that increased placental inflammation due to obesity may directly affect neonatal development through alterations in nutrient transport. In this review we examine the impact of maternal obesity on the neonatal immune system, and potential mechanisms for the changes observed.

Keywords

pregnancy; obesity; immune system; neonatal; inflammation; placenta; epigenetics

Introduction

Obesity is defined as the accumulation of excess body fat and is traditionally reported by the body mass index (BMI), which is a calculation of weight (kg) divided by height (meters) squared. Healthy individuals have BMI values >19 and <25 kg/m² whereas persons with a BMI >25 kg/m² are considered overweight and those with a BMI >30 kg/m² meet the criteria for obesity. Obesity is a metabolic disease that results in a chronic low-grade inflammation (1–4), characterized by high levels of inflammatory mediators such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF α). More importantly, excess weight/adiposity is associated with several co-morbidities including:

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diabetes, cardiovascular disease, pulmonary complications, and cancer (5) resulting in decreased life expectancy (6). According to the Centers for Disease Control and Prevention (CDC), as of 2012, 69% of the adults aged 20 years and older in the United States have a BMI>25, and 35.1% are obese (7). The American Heart Association estimates that in 2013, 154.7 million people were overweight, and of these, 78.4 million were obese (8). Unfortunately, the rates of obesity are expected to continue to rise (9).

Clinical Impact of maternal obesity on maternal health

It is generally believed that a high BMI entering pregnancy, and excess weight gain during pregnancy can exacerbate the natural inflammatory state associated with pregnancy resulting in detrimental health outcomes for the mother (2, 10). A retrospective study by Leung et al. that assessed adverse outcomes associated with maternal obesity in a cohort of 29,303 Chinese women between 1995–2005, found that high maternal BMI assessed during the first antenatal visit correlated with increased rates of preeclampsia, gestational diabetes (GDM), caesarean section, and preterm delivery (11). Similarly, a study of 6,959 singleton pregnancies from 2001 to 2005 by Gaillard et al., in the Netherlands found that maternal obesity prior to pregnancy and excessive weight gain during pregnancy were both associated with increased incidence of preeclampsia, GDM, hypertension, and caesarean section despite adjusting for familial and lifestyle factors (12). A third retrospective study of 30,298 subjects from 2004–2011 by Scott-Pillai et al. also reported similar outcomes in the UK, and showed that these risks are further exacerbated as BMI (measured during first pre-natal visit) increases above 35 (13).

Maternal environment and origin of disease

The “origins of fetal and infant disease hypothesis,” was first proposed in 1990 by Dr. Barker to serve as an explanation for the increase in coronary heart disease in western countries (14, 15). In 2001, Drs. Hale and Barker expanded the “origins of fetal and infant disease hypothesis” into the “thrifty phenotype” hypothesis, which was based on the observations that children born to undernourished women during famine were better able to survive than children born to normally nourished women. This adaptation, while beneficial in times of famine, became a disadvantage when conditions became plentiful and children became predisposed to obesity and impaired glucose tolerance (16, 17). This theory was further expanded by Dr. Barker in 2002 into the “Fetal Origins of Adult Disease” (FOAD) based on the observation that children who were small at birth/infancy, as a result of intrauterine growth restriction in undernourished mothers, subsequently underwent accelerated weight gain in childhood and experienced higher incidence of coronary heart disease, type 2 diabetes, and hypertension as adults compared to normal birth weight children (18, 19). The FOAD proposes that changes in the gestational milieu directly impact fetal growth and development (18, 20), and consequently disease incidence later in life (21). Two cornerstones of the FOAD hypothesis are developmental plasticity and compensatory growth (19). Developmental plasticity refers to changes in neural connections during development as a result of in utero environment. Compensatory growth, or “catch-up growth”, is accelerated growth following a period of slowed development. Therefore,

adaptations acquired in utero during limited nutritional intake were later detrimental in the adult offspring or when food became plentiful.

Although the initial Barker hypothesis focused primarily on nutritional deficiencies and low birth weight, there is evidence that over-nutrition also alters in utero programming (22). The “fetal over-nutrition hypothesis” was developed based on epidemiological evidence that greater maternal adiposity, (self-reported/measured pre-pregnancy/ first antenatal visit weight), increased lifetime risk of type 2 diabetes (23) and obesity (24) in the offspring. In the latter study, both maternal and paternal BMIs were taken before pregnancy, and the child’s BMI was assessed at birth, 5 years, and 14 years. Only maternal BMI had an effect on offspring BMI, which wasn’t evident until 14 years of age.

Taken together, there is strong evidence that in utero instruction by maternal nutritional environment can influence growth rate and disease risk during adulthood (18, 22, 24, 25). A fetus can adapt its physiology and metabolism to the supply of nutrients crossing the placenta (25). Excess supply of nutrients can lead to permanent changes in metabolism, behavior and appetite regulation in offspring resulting in adverse health outcomes later in life (26). In summary, this phenomenon is known as “early-life programming” which recognizes that events in utero have long term influences on risks of disease later in life (26).

Clinical Impact of maternal obesity in offspring

Increased incidence of stillbirths, abnormal growth, cardiac defects, and neural tube defects has been reported in the offspring of obese women after adjustment for various factors including age, familial and lifestyle factors, and ethnicity ((11–13, 27, 28) and Table 1). Furthermore, children born to women who enter pregnancy in an obesogenic state are at higher risk for several adverse long-term health outcomes including increased incidence of obesity (29), cognitive development deficits and ADHD (30), type-2 diabetes (31, 32), cardiovascular disease (33, 34), cancer (35), and greater all-cause mortality (33) in comparison to children born to lean mothers. A Finnish study of coronary heart disease found that men born to mothers with a high BMI (assessed at time of labor admission) experienced a higher incidence of coronary related deaths (34). A prospective cohort study in the Netherlands, utilizing data from the Generation R study in which growth and development, behavior, asthma childhood disease and genetics were documented from fetal life until young adulthood, found that high maternal pre-pregnancy BMI was associated with adverse cardiometabolic profiles in the offspring (36). Adverse cardiovascular outcomes were detected despite the exclusion of women with both pre-pregnancy, and pregnancy complications including diabetes/GDM (33, 34, 36). In addition to cardiovascular disease, the periconceptional environment affects gene expression for at least 10 years and may result in lifelong increased risk of cancer in the offspring (35). Finally, increased incidence of childhood asthma and wheezing is emerging as a common adverse health outcome for the offspring of mothers with a pre-pregnancy BMI >30 or excessive weight gain during pregnancy following adjustment for sex of child, maternal age, smoking, maternal history of asthma/allergy, maternal BMI, and maternal weight gain during pregnancy (37–39). The immune system plays a critical role in the pathogenesis of cardiovascular disease (40), asthma (41–43), and diabetes (1). Since maternal obesity is associated with increased

incidence of these diseases, it is highly likely that maternal obesity disrupts normal development and maturation of the offspring's immune system in utero.

Overview of the immune system

The immune system is our first line of defense against microbial infection and cancer. It is composed of leukocytes that secrete various immune molecules such as cytokines, chemokines, immunoglobulins, and complement proteins in order to eliminate pathogens as well as mediate cell-to-cell communication. The immune system can be divided into two main branches: innate and adaptive immunity (44). The innate immune branch is composed of neutrophils, eosinophils, basophils, natural killer (NK) cells, monocytes/macrophages, and dendritic cells (DCs); as well mucosal barriers and antimicrobial peptides (45). These cells can distinguish self from invading pathogens by expressing pattern recognition receptors (PRR) that recognize pathogen associated molecular patterns (PAMPs). Signaling through these PRRs results in signaling cascades that culminate in the production of cytokines, chemokines and complement proteins that can interfere with pathogen replication and recruit additional immune cells to the site of infection. The innate response responds immediately to pathogens but, in contrast to T and B cells, it lacks pathogen specificity.

Activation of the innate immune branch is critical to the initiation of the adaptive immune response; which is required to fully clear pathogens and establish long-term immunological memory. The adaptive immune branch is comprised of T cells and B cells. Innate immune cells such as macrophages or dendritic cells can activate T cells by presenting pathogen-derived peptides in the context of major histocompatibility molecules (44). T cells can be divided into CD4⁺ T helper (Th) cells and CD8⁺ cytotoxic T cells. CD4 T cells can be further divided into Th1, Th2, Th17, regulatory (Treg), and follicular helper (Tfh) cells. Th1 cells produce cytokines such as IL-2 and IFN γ and play a critical role in anti-viral and anti-bacterial pathogens; Th2 cells primarily produce cytokines such as IL-4 and IL-10 and mediate responses to parasites; Th17 cells are responsible for immunity against extracellular bacteria and fungi; Tfh cells regulate development of B cell immunity; finally, Treg cells are negative regulators and play a role in the termination of the immune response and protect against auto-immunity (46). The primary function of B cells is to secrete antibodies that coat pathogens thereby targeting them for destruction through opsonization, activation of the complement system, and neutralizing their ability to infect new target cells (44). Activation of both innate and adaptive immune responses results in acute inflammation, which is critical for pathogen clearance. However, chronic inflammation can cause and exacerbate several diseases such as cardiovascular disease (40, 47–49), diabetes (50–54), and asthma (55, 56).

The development of the immune system begins in conjunction with the vascular and cardiac systems early during embryogenesis (57). In both mice and humans, blood cells in the yolk sac develop into hematopoietic stem cells (HSC) (57). In humans, the thymus can be detected at 8 weeks of gestation and is colonized by hematopoietic stem cells (57). Early T cell development begins between 14 and 17 week of gestation (58) and mature T cells emigrate to form the peripheral T cell pool 16–20 weeks of gestation (57, 58). By the 20th week, organogenesis of the thymus is complete (57). Secondary lymphoid tissues such as the

lymph nodes are detectable by 12 weeks of gestation (59). T cells appear in the lymph nodes at approximately week 14 of gestation, shortly after the beginning of T cell development (57, 60).

In addition to the thymus, the liver is also seeded early on by HSCs from the yolk sac around week 3–4 of gestation (57, 61). By 9 weeks of gestation the liver functions as both an early source of red blood cells and pre-B lymphocytes prior to formation of bone marrow (60). In parallel with pre-B cell development, the spleen is detectable by 8 weeks (59). B cells are present in the primary follicles of lymph nodes by 17 weeks of gestation (57, 60). It has been seen that humans HSCs travel from the liver to the bone marrow around 20 weeks of gestation (62) which takes over as the producer of red blood cells, B cells and phagocytic cells.

Some of the first phagocytic cells seen in the fetus are embryonic macrophages around week 3–4 of gestation (61, 63, 64). These early monocytes are produced by the liver as their appearance precedes the development of bone marrow (61). Blood circulating monocytes and dendritic cells, as seen in adults, develop in the bone marrow starting in the second trimester (61). The population of monocytes and dendritic cells increase throughout gestation (57, 64, 65), but dendritic cell levels don't reach those of adults until almost 5 years of age (57). In contrast to monocytes/macrophages and dendritic cells, granulocytes, specifically neutrophils, are not present until 31 weeks (66). Neutrophils are derived from granulocyte/monocyte progenitors in the bone marrow (61). By birth, neutrophils become the dominant cell population (65). In utero, the fetal immune system is predominantly Th2 biased, presumed to prevent Th1 type alloimmune responses to maternal tissues (67).

The adaptive immune system of the newborn lacks antigenic experience as evidenced by the exclusive presence of naïve T and B cells (44, 68), and therefore it must rely on its innate immune system (69). Additional protection against infection during the first 6 months of life is provided by maternal antibodies acquired in utero and through breast-feeding that help protect against gastrointestinal and respiratory infection (70). Moreover, newborns display Th-17 (IL-6, IL-23) responses, low production of type-I interferons, and weak Th1 support (TNF, IL-1) following TLR stimulation (71). In the early weeks following birth, there is a large increase in the number of peripheral lymphocytes (57). However, T cell responses remain biased towards Th2 phenotype, with low IL-2 and IFN γ production (72). This bias is believed to be due to functional differences in dendritic cells that may prevent differentiation of naïve CD4 T cells towards Th1 (68). Through infancy and early childhood, the newborn's immune system undergoes a shift from a predominantly Th-2 to Th-1 responses, which promote cellular immunity and macrophage activation (67, 69). By two years of age, production of Th1 supporting cytokine IL-12p70 by dendritic cells is detected, which further promote development of Th1 responses (71). With age and antigen experience, T cell responses increase, and Cytotoxic and Helper T cells develop central and effector memory populations (44, 57). Similarly, B cells are largely naïve at birth and generate limited responses (57), most likely due to both extrinsic factors such as reduced dendritic cell co-stimulation and intrinsic factors such as decreased B cell receptor signaling in naïve neonatal B cells (68). Immature B cells undergo maturation in the spleen where switch from high expression of IgM to high expression of IgD (73).

Impact of maternal obesity on immune system development

Recent studies have begun to characterize the effect of maternal obesity on the development of the neonatal immune system. Children born to obese mothers have a 16 fold higher risk of having detectable CRP levels at 12 years of age after adjustment for BMI z-score, Tanner stages (scale of physical development), and gender (29) compared to children born to lean mothers, suggesting that higher CRP levels in the offspring are a result of high maternal BMI during pregnancy. Studies using murine models have shown detrimental changes in the immune system of pups born to dams fed a high fat diet during gestation regardless of postnatal diet (74, 75). In one study, pups born to dams fed a high fat diet (HFD) during gestation and maintained on a HFD after weaning generated lower ovalbumin (OVA)-specific IgG, but higher OVA-specific IgE, after immunization compared to pups born to control diet fed dams and pups (74). The increase in IgE production could potentially explain the increased incidence of allergy in children born to obese mothers. In addition, *ex vivo* stimulation of splenocytes from pups born to dams fed a HFD during gestation with lipopolysaccharide (LPS), produced higher levels of TNF α regardless of their post-weaning diet (74).

Another rodent study found that pups born to dams fed a western diet (WD) both prior to and during gestation exhibited worse outcomes in response to bacterial infection and experimentally induced autoimmunity, higher colonic inflammatory responses, and muted systemic responses to antigen despite being weaned on a control diet and not being obese or diabetic themselves (75). Specifically, the offspring exhibited greater mortality rates in an *E.coli* sepsis model, and exhibited greater bacterial burden and larger abscesses after infection with Methicillin-resistant *Staphylococcus aureus* (MRSA) (75). These pups were also statistically more likely to develop signs of experimental autoimmune encephalitis (EAE) following injection of myelin oligodendrocyte glycoprotein than mice born to dams fed a control chow diet (75). Frequency of Tregs was reduced in both colonic lamina propria lymphocytes (LPL) and splenocytes collected from pups born to dams fed a WD. In addition, *ex vivo* stimulation of colonic LPLs isolated from pups born to dams fed a WD with LPS resulted in greater levels of IL-6, IL-1 β , and IL-17, whereas LPS stimulated splenocytes from the same group generated decreased levels of TNF α and IL-6 compared to control groups (75).

A nonhuman primate study compared the transcriptome of fetal peripheral blood mononuclear cells (PBMC) from offspring of obese and lean baboons (maternal BMI was assessed prior to pregnancy). Analysis conducted using Kyoto Encyclopedia of Genes and Genomes (KEGG) revealed 29 significantly affected pathways including antigen presentation, complement and coagulation cascades, leukocyte transendothelial migration, B cell receptor signaling pathways, tight junctions, and MAPK and VEGF signaling pathways (76). Taken together, these studies support the concept that high fat intake during pregnancy or a high maternal BMI can interfere with normal development of the offspring's immune system in utero.

Mechanisms of neonatal immune system dysregulation

The mechanisms underlying maternal obesity-induced changes in immune system of the offspring are just beginning to emerge. The placenta is responsible for transport of nutrients to the fetus and is likely to influence fetal growth and development and therefore play a key role in the development of the neonatal immune system (16) (Table 2). Accumulation of lipids has been seen in the placentas of obese women, notably in the villi stroma (77). In a nonhuman primate study, excess lipid build up in the microvilli created a structural impairment that resulted in decreased amino acid transport by *System A* (76). Increased lipid accumulation can also result in higher expression of inflammatory genes in the placenta (78). Indeed, increased concentrations of pro-inflammatory mediators TNF α , IL-1, and IL-6 in the placentas of obese compared to lean pregnant women (2, 79, 80) as well as increased production of Th2 cytokines (81) have been reported. Increased inflammation within the placenta may alter fetal cytokine levels thereby affecting immune system development and resulting in differential response to vaccination and allergens later in life (82).

Inflammation within the placenta may also be a result of increased accumulation of macrophages (79). Increased macrophage infiltration in the placenta as a result of maternal obesity was also described in a baboon model (76). It has been hypothesized that activated peripheral monocytes or adipose tissue-derived macrophages are recruited to accumulate in the placenta of obese pregnant women due to increased levels of monocyte-chemoattractant protein-1 (MCP-1), IL-6, and TNF α secreted by adipose tissue (83) and the greater circulating levels of CRP and IL-6 seen in obese pregnant women (79, 84–86). Increasing maternal BMI and fat mass also correlates with increased placental surface and thickness, and chronic endothelial cell activation (87). These changes can lead to reduced blood flow and structural damage in the placenta. Indeed, in a nonhuman primate study using a cohort of 24 Japanese Macaques, a high fat diet during pregnancy resulted in a 38–56% reduction in uterine volume blood flow regardless of the dam's weight (80). This obesity-induced placental ischemia was associated with the upregulation of 13 proinflammatory cytokines including GM-CSF, IL-2, IL-4, IL17, MCP-1, and TNF α (80).

Some studies have implicated p38-MAPK and STAT3 as key pathways involved in placental inflammation, while others have suggested NF-kB and JNK pathways (88, 89). A study by Aye et al. showed that maternal BMI is associated with activation of placental p38-MAPK and STAT3 signaling but not NF-kB, JNK, or caspase 1 pathways (88). Work by Basu et al found that in pregravid obesity, the stromal vascular cells of adipose tissue express higher levels of TNF- α and IL-6 (90). Increased secretion of TNF α and IL-6 provide a potential explanation for the activation of the p38-MAPK and STAT3 pathways. TNF α activates p38-MAPK, whereas TNF α and IL-6 activate STAT3 (91, 92). Finally, Zhu et al. found that, maternal obesity resulted in up-regulation of NF-kB and JNK pathways in mid-gestation sheep placenta (89). The authors proposed that free fatty acids (due to excess adiposity) activate the Toll-Like Receptor (TLR) 4 pathway, which in turn activates the NF-kB and JNK pathways leading to placental inflammation.

Another potential mechanism by which maternal obesity can modulate development of the offspring's immune system is through changes in gut microbiome. Recent studies have

shown that the diversity of microbes in the gut is instrumental for the normal function and development of the immune system (93). In one of the rodent studies discussed in the previous section (75), microbiome analysis of colon section from pups born to dams fed a western diet showed an increased Firmicute/Bacteroidete ratio that corresponded to increased colonic inflammation (75). In a recent human study, maternal BMI was found to be a strong predictor of increased Shannon Diversity Index (SDI, or the measure of overall diversity within a microbial community) in gut microbiota of toddlers between 18 and 27 months (94). The authors proposed that the increase in both the alpha and beta diversities was due to reduced immune surveillance resulting in greater bacterial growth. Additional studies are required to understand the role of bacterial diversity in shaping the developing immune system.

Epigenetic and in utero programming

Changes in the transport of nutrients and levels of inflammatory mediators in the placenta are also likely to influence the development of the neonatal immune system through epigenetic modifications, which in turn lead to alterations in gene expression (76). Epigenetic modifications include posttranslational modification of proteins and histones (such as ubiquitination, methylation, acetylation, and phosphorylation) and DNA methylation that lead to either suppression or activation of gene expression (95). For instance, the histone marker H3K4me is associated with active transcription whereas the marker H3K9me3 is associated with transcriptional repression (96). DNA methylation is the addition of a methyl group to the 5-position of a cytosine (97) which either inhibits transcription directly, or recruits methyl-CpG-binding domain proteins which repress transcription by chromatin compaction through chromatin remodeling complexes (97). DNA methylation is a highly regulated process that is inherited by daughter cells. Several studies have reported epigenetic changes in response to diet (21), environmental pollutants (98, 99), or chronic conditions such as asthma (100) and cancer (101).

Maternal BMI before and during pregnancy affects DNA methylation in the offspring's peripheral blood cells. A recent study demonstrated that maternal pre-pregnancy BMI inversely correlated with overall methylation levels in cord blood samples, with the greatest methylation changes occurring within genes associated with cancer (WNT16) and diabetes (BTN3AI) (102). In a zebrafish model, WNT16 was found to regulate the hematopoietic stem cell specification during embryonic development; therefore, increased methylation could potentially interfere with Notch ligand signaling required for HSC specification (103). BTN3A1 is a regulator of molecules that activate CD4⁺ T cells (104); therefore, increased methylation could theoretically result in lower CD4⁺ T cell responses. Another recent study that examined DNA methylation patterns in cord blood leukocytes obtained from children born to obese mothers and then again at three years of age showed lower global methylation relative to children born to lean mothers at 3 years (105). Lower global methylation in leukocytes could result in dysregulated immune responses or cellular differentiation. An additional study by Godfrey et al. compared cord blood methylation profiles at 68 CpGs sites from 5 genes to adiposity measurements in the same children at 9 years of age (106). This study showed that methylation at retinoid X receptor- α (RXRA) and endothelial nitric oxide synthase (eNOS) correlated with increased adiposity in children at 9 years (106).

RXRA is a receptor that enhances Th2 development following stimulation by RXRAs agonist Vitamin A (107). Endothelial nitric oxide synthase (eNOS), is important in the upregulation of inos and other inflammatory factors such as NF- κ B (108). Finally, pups born to dams fed a western diet during gestation exhibited greater H3K9Me3 histone methylation at TLR4 and LPS binding protein loci in splenocytes compared to pups born to dams fed a control diet (75). These data provide a rationale for the lower cytokine response generated by splenocytes isolated from pups born to obese dams compared to those born to dams fed a control diet following LPS stimulation (75). Moreover, these methylation profiles were identical to those observed in the obese dams indicative of germ line inheritance (75).

Alterations in DNA methylation of circulating PBMCs of children due to maternal obesity (102, 105, 106) can have significant impact on gene expression and consequently function of immune cells. For instance, reduced DNA methylation at genes associated with T cell activation can lead to aberrant cytokine production and inflammation. Indeed, it has been seen that in activated CD4 and CD8 T cells, loci of cytokines have less methylation compared to naïve cells (109). Additional studies are needed to better understand the relationship between maternal body composition during pregnancy and epigenetic changes, differences in gene expression and functional alterations of immune cells in the offspring.

Conclusion

Prevalence of obesity has increased dramatically over the last 20 years, especially in women of reproductive age. Entering pregnancy in an obese state and/or gaining excessive weight during pregnancy are associated with several complications for the mother including increased rates of preeclampsia, GDM, caesarean section, and preterm delivery. Adverse health outcomes for the neonate include abnormal growth and birth defects. Long-term adverse health outcomes for the offspring include increased incidence of chronic inflammatory diseases such as cardiovascular disease, diabetes and asthma (Table 1). The mechanisms by which maternal obesity induces changes in immune system of the offspring are poorly understood, but it is thought that increased accumulation of lipids in the placenta result in increased infiltration of macrophages, a reduction placental blood flow which lead to hypoxia and exacerbate placental inflammation, and altered nutrient transport thereby resulting in poor fetal health outcomes (Figure 1 and Table 2).

Changes in nutrient transport and levels of inflammatory mediators can contribute to epigenetic modifications and changes in gene expression. This hypothesis is supported by reported changes in global methylation and transcriptome analysis of PBMC or umbilical cord blood mononuclear cells. Future studies will need to focus on epigenetic changes within individual immune cell populations, as important changes in small populations may not be apparent when analyzing total leukocytes. Specifically, it might be interesting to examine epigenetic changes in monocytes or CD4 T helper cells as we have shown recently a dampened response by monocytes and myeloid dendritic cells stimulated by TL4 or TLR1&2 agonists and a reduction in IL-4 production by CD4 T cells (110).

In addition to CpG islands, future epigenetic studies should include variably methylated regions (VMR). VMRs are regions of DNA that have a great propensity for changes in

methylation, can sometimes overlap with CpG islands, are involved in embryonic patterning, and vary across individuals including family members (111). VMRs can be used in identifying disease vulnerability traits (112). In addition, further studies examining changes in the transport of lipids, nutrients, and immune molecules across the placenta would better elucidate their role in modulating epigenetic modifications and regulation of gene expression. Additional studies into the role of miRNAs in mediating the effects of maternal obesity on placental and fetal health are also needed given their integral role in regulating gene expression. Future work should also address the effect of maternal obesity in subsequent generations to assess whether these long-term epigenetic changes are compounded over successive generations.

Finally, an important consideration for future studies is the choice of model organism. There are several advantages to working with rodent models: short time of fetal development and pup maturation, and the availability of recombinant strains that facilitate mechanistic studies. However, rodent models also present several challenges when studying neonatal immunity because the peripheral adaptive immune system develops only after birth in mice whereas primates are born with a fully populated peripheral immune system (113). Large animal models such as nonhuman primates provide robust models for studying immunity at the maternal-fetal interface and in the offspring. Their large size facilitates longitudinal studies, imaging of the placenta, and importantly, exhibit greater similarity to humans in their susceptibility to metabolic disease (114).

In summary, maternal obesity is becoming one of the biggest threats to the offspring's health. However, the effects of maternal obesity on the development of the offspring's immune system are poorly understood. A better understanding of the mechanisms by which maternal obesity interferes with normal development as well as maturation of the offspring's immune system will lead to treatment strategies and prevention of diseases such as asthma, diabetes, and atherosclerosis which are more prevalent in the offspring of obese mothers.

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Highlights

- Children of obese mothers have higher incidence of diabetes and asthma
- Atherosclerosis and all cause mortality are increased in children of obese mothers
- Maternal obesity exacerbates systemic inflammation in offspring
- Offspring of obese mothers have reduced responses to infection
- Maternal obesity changes epigenetic profiles within offspring's leukocytes

Figure 1.
Overview of how obesity or over nutrition during pregnancy leads to adverse health outcomes for the offspring

Table 1

Impact of pre-gravid obesity on infant outcomes

Species	Finding	Time of maternal BMI Assessment	Age of offspring assessed	Covariates adjustment*	References	Association with offspring BMI
Human	Increased incidence of abnormal growth	Pre-gravid	Birth	1–4, 19	11	Unknown
Human	Increased incidence of stillbirth, abnormal growth	Pre-gravid, and throughout	Birth	1, 2, 5, 9	13	Unknown
Human	Increased incidence of neural tube defects	Pre-gravid	Unknown	1, 4, 6–7, 14, 16, 17	28	Unknown
Human	16x higher likelihood of detectable CRP	Pre-gravid	12 years	9, 10	29	Unknown
Human	Increased coronary artery disease and all-cause mortality	Pre-gravid	34–61 years	1, 2, 8, 10–12, 19	33	Yes
Human	Increased coronary heart disease	Pre-gravid	37–70	1, 2, 8, 10, 11, 12, 19	34	Yes
Human	Increased adverse cardiometabolic risk	Pre-gravid	24 month	4, 8, 14, 15, 17, 19, 20	36	Yes
Human	Increased risk of childhood asthma, and wheezing	Pre-gravid	14 months to 16 years	1–2, 10–11, 14, 16, 18,	37	Unknown
Human	Increased risk of childhood, wheezing	Pre-gravid	6 months, 2, 4, and 6 years	5, 12, 14, 16, 19, 21	39	Unknown
Human	Increased risk of childhood asthma, ectopic eczema, and hay fever	2nd trimester (16 weeks)	6 and 18 months, and 7 years	1, 4, 8, 10–11, 17–19, 21	38	Unknown
Human	May increase risk of ADHD/cognitive deficits	Pre-gravid	From birth to childhood	2, 8, 10, 12, 14, 16	30	Unknown
Murine	Lower IgG and higher IgE responses	HFD at start of study	17–19 weeks		74	Yes
Murine	Lower systemic responses and higher colonic inflammation	HFD at start of study	5–6 weeks		75	Yes
Baboon	PBMC gene expression changes	HFD at start of study	Pre-term: 165 days gestation		76	Yes

* Covariates: 1) maternal age, 2) parity, 3) social deprivation, 4) smoking, 5) maternal diabetes, 6) drug use, 7) maternal chronic conditions (diabetes, high blood pressure, history of seizures), 8) birth weight, 9) Tanner stages, 10) offspring gender, 11) socio/economic status, 12) current age of offspring, 13) placental weight, 14) maternal education, 15) paternal BMI, 16) Maternal ethnicity, 17) alcohol consumption, 18) mode of delivery, 19) gestational age, 20) childhood height, 21) history of maternal allergy (asthma, atopic eczema, hay fever)

Table 2

Impact of maternal obesity on placental health

Species	Finding	Maternal HFD diet/BMI measurement	References
Human	Increased Macrophages, increased expression TNF α IL-1, IL-6	Pre-gravid	78
Baboon	Increased Macs, increased expression TNF α , IL-1, IL-6 Lipi accumulation in placenta	Pre-gravid	75
Human	Lipid build up in villi stroma	Pre-gravid	76, 77
Rhesus Macaque	Reduced uterine blood flow, increased TNF α , IL-1 β , MCP-1, CCL2	Pre-gravid	79
Human	Increased placental surface thickness; chronic and impaired endothelial activation function; increased production of IL-6	Pre-gravid	80, 86
Human	Activation of placental p38-MAPK and STAT3 signaling	Pre-gravid	87
Sheep	Upregulation of NF-kB and JNK pathways	Mid-Gestation	88