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Obesity and Maternal-Placental-Fetal Immunology and Health

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Obesity rates in women of childbearing age is now at 29%, according to recent CDC reports. It is known that obesity is associated with oxidative stress and inflammation, including disruptions in cellular function and cytokine levels. In pregnant women who are obese, associated placental dysfunction can lead to small for gestational age (SGA) infants. More frequently, however, maternal obesity is associated with large for gestational age (LGA) newborns, who also have higher incidence of metabolic disease and asthma due to elevated levels of inflammation. In addition, anthropogenic environmental exposures to "endocrine disrupting" and "forever" chemicals affect obesity, as well as maternal physiology, the placenta, and fetal development. Placental function is intimately associated with the control of inflammation during pregnancy. There is a large amount of literature examining the relationship of placental immunology, both cellular and humoral, with pregnancy and neonatal outcomes. Cells such as placental macrophages and NK cells have been implicated in spontaneous miscarriage, preeclampsia, preterm birth, perinatal neuroinflammation, and other post-natal conditions. Differing levels of placental cytokines and molecular inflammatory mediators also have known associations with preeclampsia and developmental outcomes. In this review, we will specifically examine the literature regarding maternal, placental, and fetal immunology and how it is altered by maternal obesity and environmental chemicals. We will additionally describe the relationship between placental immune function and clinical outcomes, including neonatal conditions, autoimmune disease, allergies, immunodeficiency, metabolic and endocrine conditions, neurodevelopment, and psychiatric disorders.

Keywords: maternal obesity, placenta, inflammation, oxidative stress, trophoblasts, Th cells, macrophages

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INTRODUCTION

Obesity Prevalence and Significance

Obesity is a medical crisis with increasing rates both in the United States (1–5) and worldwide (5–7). Based on CDC and WHO definitions, normal weight ranges from a BMI of 18.5 to 24.9, and overweight is defined as BMI $\geq$ 25. Obesity is defined as BMI $\geq$ 30, and severe obesity is defined in different sources as $\geq$35 or 40. In the United States general population, adult obesity rates have increased from 30.5 to 42.4% from the year 2000 to 2018 (2), with global rates also increasing significantly, from 7% in 1980 to 12.5% in 2015, with similar trends upward despite a large range

of prevalence based on regions, demographics, and socioeconomic differences (5). Obesity-related conditions account for as much as 20% of healthcare spending in the United States totaling $190 billion annually (8), with proportionately high amounts spent world-wide (9).

Obesity rates in women of childbearing age is 31.8%, with half of that group in the severe obesity range (10). Obesity-related conditions in women include diabetes, hypertension, PCOS, as well as many other conditions which create significant risks to fertility and conception (11), and to pregnancy and maternal health before, during, and after delivery. These conditions also have been shown to have significant effects to offspring health, both in the perinatal period (12) and in later childhood and adulthood. The effect of maternal obesity on the adult phenotype of offspring is a common example of Barker's hypothesis of fetal origins of adult disease (13).

Obesity does not affect all races or socioeconomic groups similarly. Obesity rates in women differ widely based on race, with Non-Hispanic Black women at a prevalence of 56.1% vs. Hispanic women at 48.4%, Non-Hispanic White women at 38.8%, and Non-Hispanic Asian women at 13.6%. Higher education level decreases risk for obesity, as does former or current smoking history. In addition, obesity rates increase in women in less urbanized areas (14). These different factors may affect the development and perpetuation of obesity in different ways including access to nutritious food, access to activity, and various cultural and regional practices. Many of these associated demographic factors are also relevant to other sources of maternal stress, such as infections, environmental toxicants, and psychosocial stressors. Additionally, there are transgenerational influences that may be influencing obesity rates that coincide with the changes in diets, increasing exposures to environmental pollutants, and the concomitant effects of climate change.

Because obesity is so prevalent in women of childbearing age and has so many concerning effects on the mother and her offspring, and because this epidemic is differentially affecting women in marginalized populations, it is critical that we understand the mechanisms of these effects in order to be able to target preventative and therapeutic strategies that may improve outcomes for all communities. As obesity can affect maternal-placental-fetal health and the developmental origins of offspring immunity (15, 16), which can influence lifetime health, the converse concept of the offspring's immune system increasing obesity incidence is also suggested (17). It's important to note that with increasing obesity there has been more incidence of immunopathologies such as asthma, allergies, autism and some autoimmune diseases as well as enhanced susceptibility to infections (18) and cancers (19).

Maternal Stressors in Pregnancy

There is increasing evidence that multiple forms of environmental stress during the prenatal period can induce a lifetime of adverse health effects. Regarding the fetus and offspring, the exogenous and endogenous effects on the mother include diet, which can be influential as discussed in papers about the developmental origins of adult diseases. In fact, the influences of malnutrition or a fat rich diet may be transgenerational (20). A rich diet can lead to maternal obesity, which directs paths to metabolic dysfunction and inflammation, and maternal adiposity also increases fat deposition in the placenta and fetus, which affect the developing types of fetal immune cells (21). It is generally believed that these early developmental stresses affect the offspring due to epigenetic and metabolic changes (22).

Maternal and Fetal Cells at Interface and Beyond

The placenta plays a vital role in fetal development. The placenta is unique in that its cell and molecular composition of maternal and fetal tissues influence the maternal delivery of nutrients as well as hormones, cytokines, antibodies, and cells to the fetus, helps to protect mother and fetus during this semi-allogenic relationship (23), and is rejected to enable parturition. In addition to the molecular effects on the fetus, fetal microchimerisms (FMCs) are established during and after pregnancy with beneficial (24) or adverse (25) health consequences for mothers and offspring. These positive and negative effects involve maternal immunity. Conversely, maternal microchimerisms (MMC) may detrimentally affect some offspring. Two rare detrimental outcomes are neonatal lupus (26) and type 1 diabetes (27), which are autoimmune diseases resulting in part from maternal cells in offspring.

Maternal immunity plays a critical role in pregnancy and the development of healthy offspring. Immune cells aid (i) implantation of the trophoblasts into the uterine decidua and the peripheral maternal system, (ii) placental development, (iii) angiogenesis (28–30) to establish needed delivery of nutrients and maternal factors, and (iv) parturition as outlined in **Figure 1**. While maintaining host defense against pathogens, maternal immune cells assist or initiate implantation, placentation, and parturition at the appropriate time, and in the intervening period, maternal immunity can help or hinder fetal development (31). Maternal immunity can help by preventing fetal access of pathogens and transferring protective antibodies to the fetus and hinder by delivery of proinflammatory cytokines, antibodies to fetal antigens, and inappropriate levels of steroids. There are additional aspects of the maternal systemic environment affecting fetal development that are mentioned throughout this review involving neuroendocrine and immune network interactions. For example, maternal obesity can affect the number of maternal macrophages in the placenta and enhance numbers of innate immune cells promoting inflammation, oxidative stress, and mitochondrial and metabolic dysfunction (32–35). Obesity is adipose tissue overload in organs, including the placenta (36), and it influences metabolic complications associated with mitochondrial dysfunction (37). Cardiac dysfunction related to obesity (38) may be especially problematic during pregnancy with the extra vascular remodeling needed for the fetus and increased circulating maternal blood volume. Inadequate or inappropriate delivery of nutrients, cells and cellular products to the fetus could lead to preterm birth and/or underweight births. Placental dysfunction contributes to spontaneous preterm births (SPTBs) and is related to placenta metabolism affected by mitochondria dysfunction and inflammation, which was reported

to display sex disparity with more transcriptomic differences with male SPTB placentas (39). The placentas of male fetuses have been reported to have a profile more inflammatory than the placentas of females, which have more control of immunity and regulation of endocrine involvement and placental growth (40, 41).

Environmental Stresses

Maternal stress may be induced by an infection, environmental pollutants, or physical or psychologic disturbances. Each stressor alone or combined with another may have profound influence on maternal-placental-fetal immunology and the developing fetus, which could affect offspring health for a lifespan (42, 43). Maternal depression and obesity combine to affect fetal development and the offspring's mental and physical health (44). An emotional stress or pollutant exposure during pregnancy is a risk factor for offspring with increased potential development of later cardiovascular disease, cancer, or autoimmune disease (45–48). Perinatal maternal stresses also can impact the offspring's neurodevelopment (49–52).

Maternal obesity is associated with maternal, placental and fetal metabolic dysfunction with enhanced inflammation (21, 53). "Metaflammation" was the term coined by Gregor and Hotamisligil (54) for the chronic, low-grade inflammatory state associated with obesity, which differs from acute inflammatory responses induced by pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs). Metaflammation is triggered by metabolites and nutrients and may lead to systemic insulin resistance due to inflammatory mechanisms associated with obesity (54, 55). Early inflammation affects the developing immunophenotypes of fetal immune cells, which likely relate to obesity effects on epigenetics and the microbiome (56, 57).

Endogenous Stresses

Macrophages in adipose tissue can polarize and affect bioenergetics with obesity (58). With more adiposity, there is more inflammation in tissues due to more fat creating oxidative stress-induced cell damage and release of DAMPs to stimulate pattern recognition receptors (PPRs) such as toll-like receptors (TLRs), which induce proinflammatory cytokines and chemoattractants (chemokines) influencing influx of macrophages, which includes into the placenta. Trophoblasts attract endometrial stomal cells (59) and placentas attract many different immune cells (60). The influence of maternal obesity on fetal inflammation has been reported to be mainly due to regulatory effects on the placenta (61), which may be due to a low circulating level of adiponectin (62). Stress prior to or during pregnancy affects placental development due to posited dysregulated neuroendocrine immune interactions, which cause long-term alterations to the immune and nervous systems of offspring. Psychological stress affects the development of the placenta, which includes placental gene expression and oxidative stress (63); oxidative stress leads to placental pathology and detriments to fetal development (64, 65). Normally, the placenta helps skew the maternal and fetal environment toward a $CD4^+$ helper T cell type-2 (Th2) and anti-inflammatory profile (66); however, as mentioned earlier, obesity and other stresses create a more $CD4^+$ helper T cell type-1 (Th1) and inflammatory gestational environment. Additionally, in normotensive pregnancies, the placenta helps to control the level of stress hormones trafficking to fetus (67); the placenta attempts to control the multiple forms of maternal stress on the fetus (68).

Preeclampsia may begin as early as placentation which is when fetal trophoblasts and maternal uterine cells are aided by uterine immune cells to achieve efficient implantation for proper vascularization (69, 70). Inadequate vascularization will affect placental and fetal growth and is associated with preeclampsia. Stress in the placenta was observed with placental expression of soluble fms-like tyrosine kinase-1 (sFlt-1) and triglycerides in maternal serum (71) and is often accompanied with maternal hypertension and proteinuria, which is induced by sFlt-1 (sVEGFR1); sFlt-1 is an anti-angiogenic protein, because it interferes with vascular endothelial growth factor (VEGF), which triggers angiogenesis. VEGF also has been suggested to recruit macrophages (Mφs) and aid shift toward type-2 Mφs (Mφ2), which enhances immune tolerance and tissue remodeling (72). The endothelial dysfunction in the placenta increases the likelihood of preeclampsia along with an immunophenotype skewing more toward Th1 cells producing proinflammatory cytokines (73). However, clinical signs of preeclampsia usually don't become apparent until the beginning of the 2nd trimester. Early signs of preeclampsia may come from metabolomics (74). Since preeclampsia has higher prevalence with maternal obesity, metabolites predictive of oxidative stress might be informative. One such metabolite is acylcarnitine, a product of fetal fatty acid oxidation disorders (75). An accumulation of acylcarnitine may be indicative of mitochondrial dysfunction or peroxisome to mitochondria processing (76). Mitochondria are posited to be the intermediary between obesity and preeclampsia since higher levels of fatty acids can lead to more reactive oxygen species (ROS) generated by mitochondria in tissues including the placenta (77). Oxidative phosphorylation by mitochondria leads to production of ATP and ROS needed for maternal-placental-fetal cellular functions. Early in pregnancy ROS triggers expression of VEGF and glucose transporters to promote angiogenesis (78); however, too much ROS leads to mitochondrial dysfunction causing placental inflammation and epigenetic changes to fetus that can affect offspring health for life (79, 80). In a rat model of ROS-mediated oxidative stress caused by hyperandrogenism and insulin resistance, fetal loss was associated with dysregulation of the placental mitochondria–ROS–SOD1/Nrf2 axis (81).

Prenatal maternal stress, which includes maternal obesity, affects fetal growth by regulating production of metabolites as mentioned earlier and by influencing delivery of maternal products such as glucocorticoids and nutrients. Glucocorticoids are essential for fetal development and their level is under maternal hypothalamic-pituitary-adrenal (HPA) axis control. Starting in the 2nd gestational trimester, the placenta secretes corticotrophin-releasing hormone to promote cortisol release (82). Obese pregnant women have low cortisol levels throughout pregnancy (83). Obese pregnant women also have a blunted

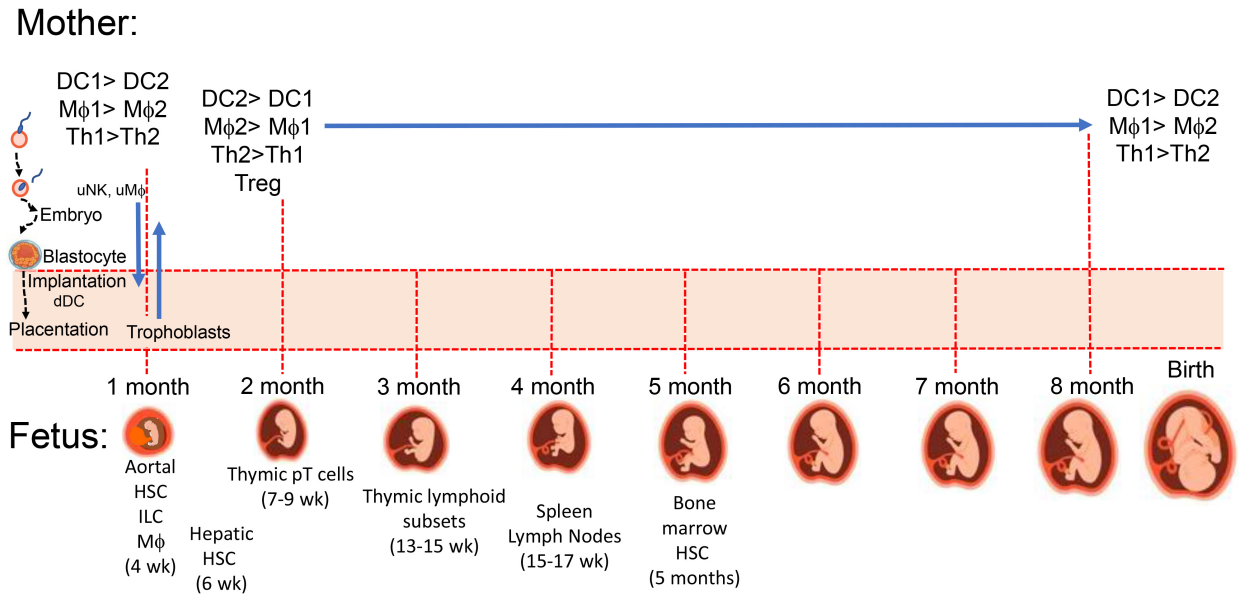

FIGURE 1 | Maternal-placental-fetal immune systems. During implantation and placentation embryonic stem cells and mature maternal immune cells interact to establish maternal immune tolerance to semi-allogenic trophoblasts which invade maternal uterus along with fetal hematopoietic stem cells (HSC) developing from the paraaortic splanchnopleure (aortal) tissue (188). At 4 weeks post-conception, there are myeloid-derived microglia cells in the developing brain, which influence development of neuronal connections. Fetal thymus starts accumulating myeloid cells to support increasing presence of precursor lymphoid T (pT) cells (189) for later development of CD4 and CD8 single positive and γδ TCR^+ thymocytes, and $CD4^+CD25^+$ T regulatory cells (189). Proportions of macrophages and neutrophils (171) as well as B cells shift from liver to marrow between 5 and 16 weeks.

HPA axis, and it has been suggested that maternal obesity increases 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) activity, which metabolizes cortisol to inactive metabolites so that glucocorticoid receptor (GR) is not signaled (84). Conversely, maternal depression may lower placental expression of 11β-HSD-2 allowing too much access of glucocorticoid to the fetus. Both over and under delivery of glucocorticoids to the fetus can be detrimental. Glucocorticoids directly affect the fetus and placental production of neurosteroids and neurohormones, which includes regulation of the HPA axis (85–87). Stress also affects nutrient delivery to the fetus (88), and O-linked-N-acetylglucosamine transferase (OGT), a placental nutrient sensor, is involved with placental epigenetics. OGT affects long-term neurodevelopmental programming, which includes programming of the HPA axis (89, 90). Together, these stress-related modulations enhance long-term detrimental effects on offspring, which includes increased prevalence of metabolic and cardiovascular disorders, and neurodevelopmental sequelae. However, exactly how stress mediates these detrimental outcomes is unclear and stress from obesity may involve different pathways than that from other forms of stress. Placental expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is responsible for preventing high maternal glucocorticoid levels from affecting the placenta and fetus (91). The expression of 11β-HSD2 increases through term in the human placenta (92). Analysis of human mothers with mental health problems have been reported to have lower 11β-HSD2 expression (93), which could propagate mental health issues in offspring, and neurodevelopment is modulated by placental stress effects (94). Interestingly, the steroidogenic pathway for glucocorticoids is shared with progesterone, and an imbalance between progesterone and glucocorticoid has been suggested to cause placental insufficiency, inflammation, and maternal immunity unfriendly toward the fetus (95). Although cortisol is the HPA product often associated with detrimental fetal effects from maternal stress, many other factors have been implicated such as catecholamines, cytokines, serotonin/tryptophan, ROS and maternal microbiota (96).

Maternal-Placental-Fetal Immune Cells During Pregnancy

The mother's innate and adaptive immune cells play a key role in all phases of the pregnancy, and as mentioned earlier, maternal immunity needs to respond appropriately for embryo implantation, placentation allowing semi-allogenic cells into maternal tissue with activation of immunotolerance to the paternal antigens while maintenance of immunity to other foreign antigens, and finally disruption of the cohabitation for parturition. Hormone and cytokine/chemokine levels vary at different stages of the pregnancy; they initially aid immune disruption of the epithelial uterine barrier for decidualization, they help to maintain local unresponsiveness to the fetal antigens until at parturition, and finally they again convert to inflammatory processes to aid placental release (97–99). Maternal decidual innate immune cells assist early invasion of the uterus by fetal trophoblasts, and Mφ-derived angiogenic factors promote development of vascularization establishing

utero-placental circulation. This alone indicates the dynamics of the immune cells because the invasion requires destruction of the epithelial barrier allowing penetration of the semi-allogenic blastocyst through this barrier and entrance into the uterine musculature/tissue (100). To break through the epithelial barrier would require activities of innate natural killer (NK) cells and Mφs promoting inflammation and breakage of epithelial tight junctions with assistance from many other maternal cells such as dendritic cells (DCs), mast cells releasing matrix metalloproteinases (MMPs) and T cells (101), but this would have to be accomplished with no damage to the embryo so entrance relates to the activities of the trophoblasts cooperating with maternal immune cells. However, any weakness in the uterine wall barrier could also allow entry of bacteria, so immune defenses would be needed by mature type-1 Mφs (Mφ1) and DC (DC1) and Th1 cells; therefore, there needs to be plasticity of Mφs, DCs, and lymphoid subsets (102, 103). For implantation and placentation, unlike DC1 and Mφ1, there is an abundance of immature DC cells expressing CD209 (DC-SIGN$^+$) cells (104) and Mφ2 producing immunosuppressive tumor growth factor-beta (TGF-β), IL-10, and indoleamine 2,3-dioxygenase (IDO) (105). DC-SIGN$^+$ cells are required for expansion of CD4$^+$Helios$^-$Foxp3$^+$ adaptive Treg (iTreg) cells and together help to maintain tolerance to placental and fetal antigens until near time for birth, and earlier loss of DC-SIGN$^+$ and iTreg cells will aid preeclampsia (106). Mφ1 and DC1 preferentially activate Th1 cells and Mφ2 and DC2 activate Th2 cells; Th1 response creates more oxidative stress and the Th2 response attempts to mitigate the stress (107, 108). The Mφ1 and Mφ2 balance is affected by oxidative stress on Mφs and/or Th cells (**Figure 2**). The oxidative stress might be lessened with better diet including an increase in vitamins (78, 109–114). Melatonin (78, 115–119) also may mitigate ROS effects and as well as affect sleep. Balance of Mφ1 and Mφ2 is important for a normal pregnancy, but the ratio may vary at different stages (28, 120, 121). When preeclampsia develops Mφ1 predominate (122–124). The Mφ1 and an environment with their products such as IL-1β, TNFα, MMPs, and nitric oxide (NO) are effective in terminating a normal pregnancy but can initiate preterm labor (125). Some trophoblasts may undergo some damage during implantation, but the maternal immune system should remain unresponsive or tolerant to the implanted developing blastocyst and should aid angiogenesis, which would be similar to wound healing as assisted by Mφ2 and decidual natural killer cells (dNK), which are more growth promoting and angiogenic than cytotoxic (100). In the 1st trimester, the predominant dNK are dNK1 (∼55%), which may aid immunotolerance to extravillous trophoblasts (EVTs) and dNK2 (∼15%), which produce more interferon-gamma (IFNγ) and may aid implantation (126). The EVTs, dNK subsets, and decidual macrophages (dMφ) seem to work as a team in remodeling the spiral artery. So there also is need for establishment of tolerance to the paternal antigens and wound healing for development of the vascular placenta. The growth promoting dNK are reported to be CD49a$^+$PBX homeobox 1 (PBX1)$^+$ Eomes$^+$ (127) and produce pleiotrophin, osteoglycin, and osteopontin (128). Absence or mutated PBX1 (PBX1^{G21S}) affects fetal growth and increases prevalence of spontaneous abortion (127). Three uterine Mφ subsets have been immunophenotypically defined CCR2$^-$CD11c^{LO} (CD11c^{low}, ∼80%), CCR2$^-$CD11c^{HI} (CD11c^{high}, ∼5%), and CCR2$^+$CD11c^{HI} (CD11c^{high}, 10–15%) in the 1st trimester (129). The dMφ subset(s) may be a unique linkage unlike that of the bone marrow stem cell derived Mφ1 and Mφ2 subsets (130). Like Mφs, DCs, which are more efficient in presenting antigen for activation of T cells, are in decidua tissue, but at a lower number than Mφs. DCs also show plasticity of phenotype and function (131) including maintenance of immune tolerance (132), which has been suggested to be important for immune control during pregnancy (133). Pregnancy complications may develop when there is a decline in dMφ expressing CD163, CD206, and CD209, which secrete the immunosuppressive factors IL-10, TGF-β, and IDO. This is accompanied by a concomitant increase of dMφ expressing CD80, CD86, and MHCII, which along with Th1 release TNFα, IFNγ and IL-1β (130). Like obesity, insufficient or inappropriate decidual recruitment and involvement of immune populations may result from endocrine disrupting chemical (EDC) such as bisphenol A (134). EDC affect estrogen and progesterone levels as well as MMPs and the activation of MMPs involves mast cell activation, which can be modified by EDC (134).

Like dNK, dMφ, and dDCs, there are uterine, placental, and fetal innate immune cells and unconventional T cells that influence development. In the 1st trimester, there are myeloid cells in many developing tissues such as microglia in the brain (135). During the 2nd trimester there are innate-like T cells in various tissues, which play a protective and homeostatic role (136). The innate-like mucosal-associated invariant T (MAIT) cells increase near term at the placenta; they may be recruited by placental chemotactic factors, and they can be anti-microbial or homeostatic (137). In the 3rd trimester with a decreased proportion of dNK, there is an increased presence of T cells (138); conventional T cells and unconventional T cell proportions, including CD4$^+$ and CD8$^+$ T cells fluctuate throughout pregnancy (139, 140). The innate lymphocytes include NK cells, intra-epithelial lymphocytes (IEL), lymphoid tissue-inducer (LTi), and the innate lymphoid cell subsets (ILC1, 2, and 3), which mimic the Th1, Th2, and Th17 subsets regarding some of their cytokine products, but they develop and respond faster since they bypass the need for antigen-specific stimulation (141). The ILC population is suggested to increase with implantation (142). Like dNK and dMφ subset fluctuations, as pregnancy progresses, there also is plasticity among the ILC subsets (143, 144), which seems to coincide with the local milieu of hormones, cytokine, chemokines, and growth regulatory factors. The unconventional T cells, which include invariant natural killer T (iNKT) cells, MAIT cells, and γδT cells, are enriched in barrier tissues, such as the uterus, and organs that drain these sites, such as the liver (136). In a mouse model, it was reported that intestinal microbes influence early development of thymic lymphocytes (145). Obesity affects intestinal microbiota, which can affect systemic inflammation and insulin resistance (146). Thus, obesity through changes to intestinal microbes may also affect the immune responses to the maternal-placental-fetal relationships.

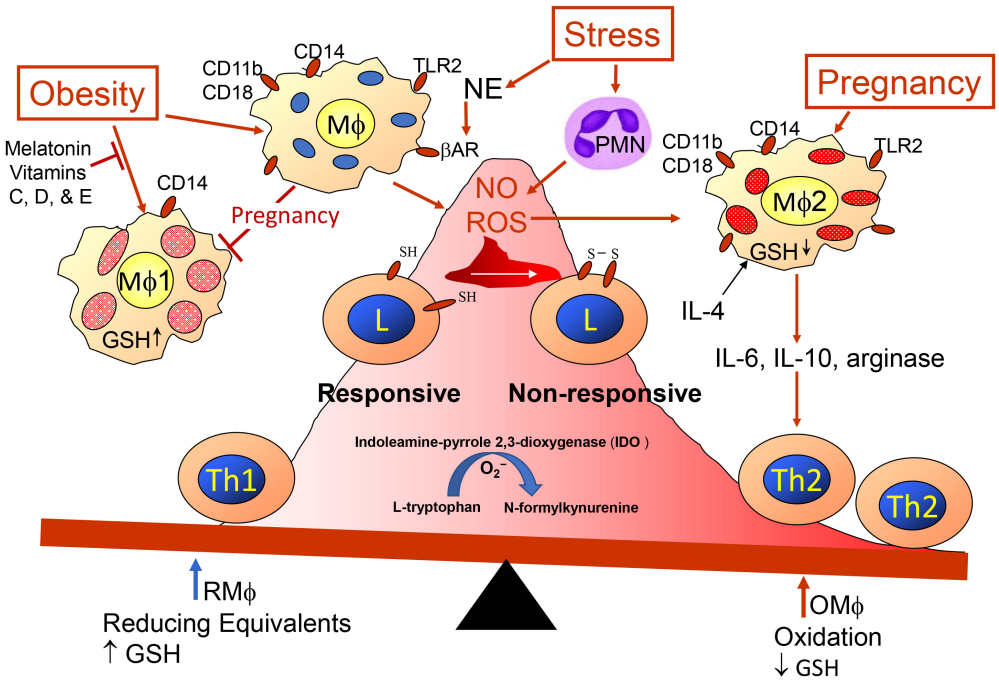

FIGURE 2 | Redox imbalance promoted by obesity, pregnancy and stress. Maternal immunity is skewed more toward Th2 immunity (anti-inflammation) regarding presence of semi-allogenic fetus developing within uterine tissue. Balance is influenced by pregnancy, obesity, and exposome, which may have additive, synergistic, antagonistic or potentiating affects. Redox status is influenced by glutathione (GSH) availability. Psychological stress modifies immunity through sympathetic nerve release of norepinephrine (NE) triggering beta-adrenergic receptors (β-AR) on Mφs (190) and release of polymorphonuclear cells (PMN) from bone marrow (191). Toll-like receptors (TLRs) are triggered by PAMPs and DAMPs.

The mast cell, a myeloid hematopoietic cell, has been associated with some pregnancy problems such as mast cell activation syndrome (MACS) (147). Mast cells have a diversity of functions; they can aid immune activation or immunotolerance, can produce cytokines, chemokines, neurotransmitters and neuropeptides, and can be antigen-presenting cells (APC) expressing MHC class II (58, 148, 149). Interestingly, like some macrophage subsets and other immune cells (150, 151), mast cells exist in adipose tissue and have been reported to cause chronic inflammation with obesity (152, 153). Mast cells also exist in fetuses and can influence early development of allergies with maternal IgE (154). Although mast cells can have detrimental effects on pregnancy and their activities are affected by EDC, they also play important roles such as myometrium contraction aiding birth; as for the other immune subsets affecting pregnancy, too few or too many mast cells can detrimentally affect pregnancy (134).

Since subpopulations of innate and adaptive immune cells continue to be revealed and characterized regarding immunophenotype, derivation, numbers, plasticity, and function, the safest suggestion about immune cell involvement during pregnancy with or without maternal obesity is that fluctuations in decidual, placental, and fetal immune subpopulations exist throughout the gestational period and that the proportions and numbers influence a normal vs. aberrant pregnancy. Additionally, since maternal obesity and stress from exogenous and endogenous factors can alter the balance of the immune subpopulations and affect expression of maternal-placental-fetal proteins, the mother's condition and exposures can complicate and interfere with delivery of healthy offspring.

Obesity, Offspring Immunity and Health

As obesity can influence inflammation and immune cell subpopulations, it also can affect offspring health for their lifetime. The potential increase in preeclampsia, gestational diabetes, hypertension, and delivery complications are all related to the oxidative stress of inflammation which imprints epigenetic changes on the developing fetus. As described earlier, metaflammation affects supply of metabolites and nutrients to the developing fetus, and it affects intrauterine programming due to maternal-placental-fetal responses to the prenatal environment, which includes increased adiposity and resulting inflammation and altered ratios of innate and adaptive immune cell subsets. Placental mRNA expressions of proinflammatory factors IL-1β, IL-8, monocyte chemoattractant protein (MCP)-1 and CXC chemokine receptor 2 (CXCR2) have been reported to be greater with maternal obesity than with non-obese women (155).

Prematurity

Although inflammation is associated with an increase in immune cells creating an inflammatory/oxidative environment, premature oxidative stress will cause preterm birth, either *via* preterm labor or medically induced delivery to address conditions such as preeclampsia, fetal macrosomia, or poor

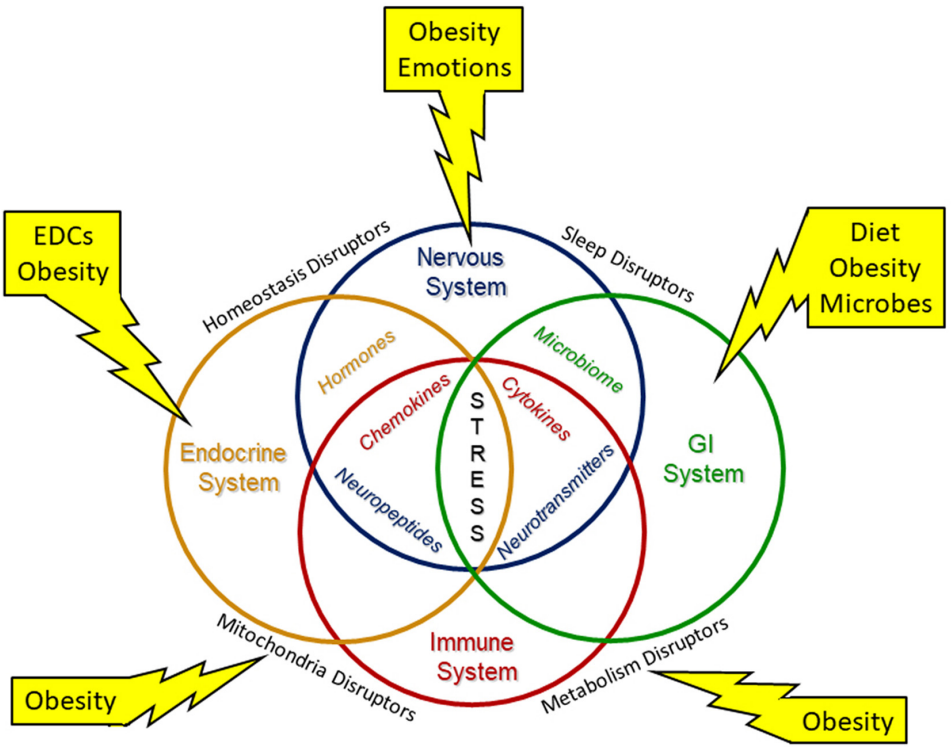

FIGURE 3 | Environmental stressors modify system biology. Environmental stresses modify system biology with alterations of the neuroendocrine immune network and the gut brain axis to disrupt development. Interorgan structural and/or functional connections are needed to maintain necessary homeostasis for development and throughout life. Environmental stressors include diet, endocrine disrupting chemicals (EDCs) and other inorganic and organic chemicals, emotions, microbes, and obesity.

fetal perfusion with intrauterine growth restriction, which are all increased with maternal obesity. Babies born preterm are subsequently known to be at risk for intestinal disorders, increased infection rates, respiratory disease, retinopathy, and a variety of neurodevelopmental and neurobehavioral conditions (156–158).

Sexual differences are observed in preterm infant outcomes, with morbidities in males generally poorer that in females (159). Interestingly, outside of prematurity, males display more inflammation with metabolic syndrome (160), which may be why male offspring tend to have greater prevalence of cardiovascular and neurodevelopmental disorders (161, 162). Sexually dimorphic placental responses to stresses and need for more analyses was reviewed (163). Perhaps male susceptibility to stress and inflammation partially contributes to poorer outcome in preterm males as well. The morbidities in offspring related to maternal obesity are not merely a consequence of the effects of prematurity, however. There are immunologic, metabolic, and neurologic/psychiatric sequelae that are independently associated with maternal obesity.

Offspring Immune Function

Maternal obesity and obesogenic diets have been associated with abnormal immune function in offspring, including decreased response to infection, atopic disease, and asthma (56, 164, 165). The modifications include epigenetic and physiological programming (22, 166) that can lead to conditions such cardiovascular disease, asthma, and allergies as the neonatal immune system undergoes further exposure to environmental modulators (microbes, chemicals, and physical and psychological stressors) (21, 167, 168). In a study reviewing immunologic markers such as IgM in neonatal blood spots collected in newborn screening, this group has previously shown an association with maternal obesity and increased IgM as well as other inflammatory markers which are consistent with later immune dysregulation (169). In a mouse model, maternal high fat diet has been associated with increased incidence of Crohn's disease-like ileitis in genetically susceptible offspring (170). Additionally, marrow adipose tissue (MAT) is endocrinologically active and contributes to bone growth and maintenance as well as hematopoiesis. Increased proportions of MAT in the marrow compartment can negatively affect hematopoiesis (171). Theoretically, the increased fetal adiposity that occurs as a result of maternal obesity may affect multiple hematopoietic cell lines, including leukocytic precursors.

Offspring Metabolism and Obesity

Maternal obesity also increases the offspring's risk for obesity (168). Intrauterine stress has been linked over the past two decades to the development of obesity and metabolic dysfunction

in offspring, both in animal and human studies (172–174). Prenatally and post-natally, obesity and other stressors can affect multiple organ systems with mutual disruption of metabolism and mitochondrial functions (**Figure 3**). The Maternal And Developmental Risks from Environmental and Social Stressors (MADRES) Pregnancy Cohort addressed the disproportionate increase in health issue of predominately low-income Hispanic women in urban Los Angeles (175); this report concluded that obesity and increased exposure to "obesogenic" environmental chemicals as well as higher psychosocial stress levels and less access to proper diet and health care affected both mother and offspring health. In a recent systematic review, Strain et al. (176) described multiple associations of maternal obesity and related exposures such as maternal high fat diet and maternal diabetes to metabolic consequences in offspring, including obesity, non-alcoholic fatty liver disease, and type 2 diabetes. Increasing rates of type 2 diabetes are in part attributed to intrauterine environmental exposures, such as increased inflammation and oxidative stress leading to epigenetic and other endocrine-disrupting factors (22, 151, 167). Metformin, commonly used in the treatment of type-2 diabetes, has been proposed as a treatment to lessen the obesity mediated oxidative stress effects on the placenta (119).

Offspring Neurodevelopment

The fetal growth restriction due to detrimental placental epigenetic programming can influence inflammation including in the developing brain. Post-natally these effects can increase prevalence of cognitive impairment, autism, epilepsy, or cerebral palsy. Improved understanding of placental epigenetics and biomarkers will facilitate early predictions for likely neurodevelopment outcomes (177, 178). Some reported placental modulations such as histone modifications, DNA methylation, and hydroxymethylation, and microRNA expression might associate with metabolite levels altered with metabolic syndrome. Bangma et al. in an extensive review utilizing the ELGAN cohort and other sources, connected maternal obesity and other stressors, such as socioeconomic stress, *via* inflammatory mechanisms and placental reprogramming, to poorer neurocognitive outcomes in preterm infants (157). Maternal obesity has also been associated with increased risk for hypoxic-ischemic encephalopathy, which is significantly dictated by placental function and sufficiency (179, 180). Maternal obesity has also been associated with increased risk in offspring for multiple developmental disorders such as ADHD and autism spectrum disorder, and with psychiatric disorders such as schizophrenia and depression (181). Mechanisms include cytokine interference in neuronal development and migration (182, 183), epigenetic effects (184, 185), and fatty acid immunomodulators (174, 186, 187).

CONCLUSION

In an expanding obesity pandemic, it is crucial to understand the mechanisms leading to poor outcomes for women of childbearing age, their pregnancies and the health of their offspring. We have shown that maternal obesity, an endogenous stressor, and exogenous environmental stressors contribute to abnormal oxidative and inflammatory placental changes, which then affect the fetus *via* a variety of mechanisms. Understanding these mechanisms can offer us insight into prevention, prophylaxis and treatment of this generational set of conditions. It is imperative that the medical community addresses the teratogenicity of maternal obesity and associated stresses to improve global health.

AUTHOR CONTRIBUTIONS

DL and MM-B was contributed to the literature review, writing, and editing of this manuscript. DL created the figures. Both authors contributed to the article and approved the submitted version.

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