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Fetal brain and placental programming in maternal obesity: A review of human and animal model studies

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Abstract

Both human epidemiologic and animal model studies demonstrate that prenatal and lactational exposure to maternal obesity and high-fat diet are associated with adverse neurodevelopmental outcomes in offspring. Neurodevelopmental outcomes described in offspring of obese women include cognitive impairment, autism spectrum disorder (ASD), attention deficit hyperactivity disorder, anxiety and depression, disordered eating, and propensity for reward-driven behavior, among others. This review synthesizes human and animal data linking maternal obesity and high-fat diet consumption to abnormal fetal brain development, and neurodevelopmental and psychiatric morbidity in offspring. It highlights key mechanisms by which maternal obesity and maternal diet impact fetal and offspring development, and sex differences in offspring programming. In addition, we review placental effects of maternal obesity, and the role the placenta might play as an indicator vs mediator of fetal programming.

1 | INTRODUCTION

Maternal obesity has become a worldwide epidemic.[1,2] In the United States, 55% of women start pregnancy overweight (body mass index [BMI] ≥25 kg/m^2 and < 30 kg/m^2) or obese (BMI ≥30 kg/m^2), with an 8% increase in prepregnancy obesity from 2011 to 2015.[3] Concerningly, the prevalence of Grade 3 obesity (BMI ≥40 kg/m^2) in adult women has risen from 6% to 10% in the United States over the last two decades, increasing by 14% from 2011 to 2015 alone.[4] In Europe, the prevalence of maternal obesity is lower, estimated at 7% to 25%.[1] Low- and middle-income countries are also experiencing dramatic increases in maternal obesity rates, particularly in urban settings.[2]

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this review.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

What are the implications for the physical and mental health of the next generation, when nearly half of children born today are exposed to maternal overweight or obesity during fetal life? Although the developmental origins of health and disease paradigm was based on the observation that maternal malnutrition predisposed offspring to adverse outcomes later in life, the current obesity epidemic has shifted attention toward the potential deleterious programming effects of maternal *over*nutrition and obesity.[5]

As the prevalence of maternal obesity has risen, so too has the prevalence of neurodevelopmental disorders in children.[6,7] Large mother-offspring cohort studies have demonstrated consistent associations between maternal obesity and childhood physical and mental health disorders, and data from animal and molecular models have led to important insights into causal pathways that cannot be elucidated through epidemiologic approaches alone.[8,9] The purpose of this review is threefold:

1. To summarize the human and animal data linking maternal obesity with offspring neurodevelopmental and psychiatric morbidity.
2. To provide an overview of putative mechanisms by which prenatal exposure to maternal obesity may impact neurologic programming in the fetus.
3. To elucidate the potential role of the placenta in fetal brain programming.

2 | MATERNAL OBESITY AND NEURODEVELOPMENTAL AND PSYCHIATRIC MORBIDITY IN OFFSPRING

2.1 | Human studies

Epidemiologic studies demonstrate an association between maternal obesity and neurodevelopmental morbidity in offspring, including intellectual disability and impaired cognition, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety and depression, and disordered eating. A summary of epidemiologic studies examining associations between maternal obesity and offspring neurodevelopmental outcomes is presented in Table S1.

2.1.1 | Intellectual disability and impaired cognition—Maternal prepregnancy obesity has been associated with a 2 to 5-point decrement in offspring IQ,[10–12] as well as increased rates of intellectual disability (defined as IQ <70).[13,14] Two studies using samples from the Danish National Birth Cohort describe a linear inverse dose–response relationship, with every unit increase in BMI corresponding to a 0.2 to 0.3 decrease in IQ points.[15,16] Excess gestational weight gain (GWG) and maternal diabetes appear to augment the associations.[11,14]

Studies have found evidence that children born to obese mothers may be at higher risk of deficits in language and visual processing.[17,18] Two studies investigating cognitive performance in school-aged children found that children born to obese women and women with excess GWG had lower scores in reading, mathematics, and executive functioning.[19,20] A recent study found an association between maternal obesity and impaired verbal skills at age 5.[21] Exposure to maternal obesity was independently associated with increased odds of

lower verbal IQ, processing speed and visuomotor function at age 10 in children born preterm.[22]

2.1.2 | Autism spectrum disorder—The majority of observational studies examining a link between maternal obesity and a childhood diagnosis of ASD have found a significant positive association.[14,23–28] A recently published meta-analysis estimates the strength of association between maternal overweight and obesity and ASD at an adjusted odds ratio of 1.2 (overweight) and 1.4 (obesity).[29] This risk may be further augmented by preterm birth,[28] high GWG,[25] and gestational or pregestational diabetes.[14,27] Two studies have shown a J-shaped association between maternal BMI and ASD, with both maternal underweight and maternal obesity associated with increased ASD risk in offspring.[23,30] Recent studies have also demonstrated a significant positive association between maternal obesity and the expression of autism-like traits and impaired psychosocial development, outcomes that are gaining traction in the ASD research community.[26,31,32] However, three other recent studies, one of which included matched sibling analyses, failed to find a relationship between ASD and maternal BMI after controlling for confounding factors,[21,33,34] and other investigators have found increased ASD risk to be associated with postnatal factors such as accelerated postnatal growth and paternal obesity.[35,36]

2.1.3 | Attention deficit hyperactivity disorder—Multiple large, population-based Scandinavian studies have found an association between maternal obesity and ADHD in children, reporting an approximately twofold increased risk in children born to obese mothers.[23,37–39] Several additional studies in US populations have further supported the link between prepregnancy BMI and ADHD.[26,40–42] Maternal prepregnancy BMI appears to affect offspring ADHD risk in a dose-dependent fashion, with one study reporting a 4% increase in ADHD risk for every 1 unit of BMI increase.[43] Potential confounding factors, including maternal race and offspring cognitive deficits, have been implicated in the observed association between maternal obesity and ADHD.[40,44] Two sibling comparison studies have demonstrated that unmeasured familial confounding may explain the observed association between maternal BMI and risk of ADHD in offspring.[37,43]

2.1.4 | Anxiety and depression—Epidemiologic studies pose an inherent challenge in assessing the impact of intrauterine exposures on offspring risk for anxiety and depression, as these diagnoses are often made in adolescence or adulthood after additional exposures can exert influence. However, emotional or behavioral problems manifesting as early as age 2 can predict an increased risk for psychosocial impairment later in life.[45,46] Two studies have demonstrated that maternal obesity is associated with an increased risk of negative emotions and emotional dysregulation in offspring, as well as increased risk of internalizing problems (withdrawal, depression).[38,47] A recent study also found an association between maternal obesity and gestational diabetes with offspring internalizing and externalizing behaviors, although the associations did not maintain significance after adjusting for gestational diet, socioeconomic status, and postpartum depression.[48]

2.1.5 | Eating disorders and food addiction—A limited number of studies have examined the relationship between maternal obesity and the development of pathological

eating disorders, including anorexia and bulimia, that are associated with a high risk of mortality.[49,50] An Australian study of over 1500 adolescents reported that each one-unit increase in maternal BMI increased the odds of eating disorders in offspring by 11%.[49] A 5-year prospective study found that over the first 5 years of life, children exposed to maternal obesity demonstrated increased secretive eating behaviors.[50] The authors of this study concede that it is impossible to isolate the influence of prenatal exposure from eating patterns modeled by parents in early childhood.

Studies exploring the connection between maternal obesity and offspring overeating behaviors are particularly important in light of the increasing prevalence of childhood obesity. Worldwide, 18% of children and adolescents age 5 to 18 were overweight or obese in 2016, a dramatic rise from 4% in 1975.[2] Although the etiology of childhood obesity is certainly multifactorial, several studies have demonstrated a connection between maternal obesity and an increased risk of disordered eating in infancy or early childhood that may portend food addiction later in life.[51,52] In one observational study, infants of obese mothers were shown to have increased drive to consuming high-carbohydrate foods compared to infants with normal-weight mothers.[52] Another study demonstrated that 1-year-old infants of mothers who consumed more sweet foods in pregnancy exhibited an increased drive to overeat sweets.[51]

2.1.6 | Limitations of epidemiologic studies—While many epidemiologic studies report positive associations between maternal obesity and adverse neurodevelopmental outcomes, negative results have also been published in the literature,[53,54] highlighting differences in study populations, study design and methodology, and the potential for publication bias. Methodological limitations of the reported studies that have been highlighted[55] include large attrition,[35,56] sampling biases for control groups,[27,57] parental reporting of exposures and current diagnoses of children,[35,56–58] inability to completely adjust for confounders,[25,57] and lack of statistical power.[57] Additionally, many epidemiologic studies have relied on data from 20th century US or European cohorts, which may not be representative of today's modern obese population. For example, two Finnish birth cohorts sampled two decades apart failed to find consistent associations between maternal obesity/overweight and impaired offspring cognition.[13]

Although epidemiologic studies can identify associations between exposures and outcomes worthy of further investigation, they cannot establish direct causal relationships. Positive associations between maternal obesity and offspring neurodevelopmental outcomes may in fact reflect confounding by genetic, socioeconomic, or postnatal environmental factors such as lactation and/or the early childhood nutritional environment. Investigators have turned to study designs that use sibling or paternal obesity data as a way of attempting to isolate potential familial and genetic factors that may play a role in driving observed associations. Regardless of the methodology used, isolating the contribution of maternal obesity from early or late childhood exposures remains a significant challenge in understanding how offspring exposure to maternal obesity in utero contributes to the associations with adverse offspring neurodevelopmental outcomes.

2.2 | Animal model studies

Given these inherent challenges in investigating the relative contributions of the obese intrauterine vs the postnatal environment to neurodevelopmental morbidity in offspring, researchers have turned to animal models to investigate the impact of maternal obesity and/or high-fat diet (HFD) during gestation and lactation on offspring development.[59–61] These studies have clarified mechanisms underlying adverse neurodevelopmental and psychiatric outcomes in offspring.

2.3 | Neurodevelopmental deficits

2.3.1 | Learning and memory—The cognitive deficits noted in offspring of women with obesity are most frequently modeled in animals using tests of hippocampal learning and memory. Offspring born to obese mothers displayed hippocampal learning deficits on both the Morris water maze and Barnes maze tests, which test spatial learning and memory.[62–64] Impaired learning was also seen in male offspring of diet-induced obese dams during an operant conditioning task.[65] Male offspring may be particularly vulnerable to the effects of maternal obesity with regard to learning and cognition.

2.3.2 | Social interaction—Animal studies have demonstrated reduced offspring sociability, although data are conflicting regarding which sex is more affected in the setting of maternal obesity.[66–68] In the three-chamber social interaction test, female offspring of obese dams displayed decreased sociability, with deficits restored by a maternal dietary intervention during lactation.[66] Another group reported that male offspring of HFD-exposed dams spent less time exploring a novel object than offspring born to lean mothers.[67] A third study found no differences in social approach or preference in a three-chamber social interaction test in offspring of HFD-fed dams compared to controls.[68]

2.3.3 | Hyperactivity—Locomotion has been evaluated in rodent offspring as a proxy for hyperactivity/ADHD-type behaviors in humans. Rodent studies have shown increased locomotor activity in the offspring of obese dams, although data are conflicting regarding which sex is more affected by this exposure.[66,69,70] Male offspring exposed to a maternal HFD demonstrated increased hyperactivity in the open field test, which was not corrected by maternal dietary intervention during lactation.[66] Maternal Western diet during pregnancy was associated with increased locomotor activity in juvenile female offspring, while adult female, but not male, offspring demonstrated decreased locomotor activity.[69]

2.3.4 | Anxiety-like and depressive behavior—Anxiety has been evaluated in offspring of obese dams using the elevated plus maze, the open field test, and the light-dark transition test. Depression-like behavior has been evaluated with the Porsolt forced swim test. Multiple studies have shown that offspring of HFD dams spend less time in the open arms of the elevated plus maze compared to controls, consistent with increased anxiety.[71–77] Anxiety-like behavior in offspring of obese dams has also been noted in the morris water maze task, open field test, and light–dark transition tests.[66,71,74.] Depression-like behaviors have been observed in offspring exposed to maternal obesity and HFD on the forced swim test.[76,78] Data are again conflicting regarding sex-specific effects of maternal obesity on anxiety and depression. While some studies have demonstrated increased male offspring

vulnerability to anxiety in the setting of maternal obesity or HFD,[71] others have suggested female offspring have increased risk for anxiety-like behavior.[66,79]

2.3.5 | Reward-based eating and addiction behavior—Studies have shown that maternal overnutrition can also impact feeding behavior of offspring. Offspring exposed to maternal HFD during gestation and lactation were more prone to overeat food high in sugar and fat.[80,81] Rat offspring exposed to a HFD during pregnancy and lactation demonstrated increased drive to obtain high-fat food on operant conditioning and reduced dopamine in the nucleus accumbens, consistent with addiction-type behavior.[82] A maternal high-fat, high-sugar diet during pregnancy and lactation predisposes offspring to overeating and obesity, with hedonic feeding behaviors mediated by enduring changes in the central reward system.[83,84] Similar results were observed in a macaque model: offspring of obese, HFD-fed mothers consumed more high-fat, high-sugar food compared to offspring of lean control mothers.[85] Maternal HFD exposure predisposes offspring to hedonic-like behaviors not only in response to palatable foods, but also to drugs of abuse, including alcohol, cocaine, and amphetamine.[81] Offspring with pre- and post-natal exposure to HFD have a reduced behavioral response to repeated doses of amphetamine and other substances that engage the mesolimbic dopamine system.[86–88]

2.3.6 | Summary of animal model studies—Animal studies have demonstrated that offspring exposed to obese dams are at increased risk of adverse outcomes, including cognitive deficits, decreased sociability, hyperactivity, increased anxiety-like and depressive behaviors, and increased reward-based eating and other addictive behaviors. Data are conflicting regarding which offspring sex is more vulnerable to these adverse outcomes. These findings recapitulate many of the associations observed in human epidemiologic studies and provide further insight into sex-specific neurodevelopmental vulnerabilities. Research that uses animal models to probe the biological mechanisms underpinning the observed associations may yield important insights that cannot be gained from human studies.

3 | PUTATIVE MECHANISMS UNDERLYING OFFSPRING NEURODEVELOPMENTAL MORBIDITY IN MATERNAL OBESITY

3.1 | Fetal brain inflammation and microglial priming

Maternal obesity is known to be a state of chronic low-level immune activation, and offspring of obese dams are exposed to inflammatory mediators during early brain development.[67,89,90] Animal studies have demonstrated that proinflammatory cytokine expression is significantly increased in the brains of fetuses and offspring of HFD-fed dams.[66,71,85] Multiple animal models of maternal obesity have demon strated that increased brain inflammation contributes to impaired neurodevelopment in offspring.[66,71,91–96] A chronic inflammatory environment during critical developmental windows has been shown to lead to inappropriate microglial priming in utero,[71,92,94,96] and has been posited to be a mechanism underlying offspring hippocampal learning deficits.[71] A recent study has shown that maternal obesity-exposed embryonic microglia did not exhibit more pro-inflammatory cytokine production at baseline, but had an exaggerated TNF-α response to an immune

challenge (lipopolysaccharide) compared to embryonic microglia from lean control dams. This finding was more pronounced in male offspring.[96] These data suggest that maternal obesity may "prime" fetal brain microglia toward a proinflammatory phenotype that can be unmasked with a second hit immune challenge, with male fetuses more vulnerable.

3.2 | Synaptic impairments

Decreases in hippocampal dendritic spine density, reduced branching and dendrite length, as well as altered expression of synaptic marker proteins such as synapsin, have all been reported in animal offspring born to obese mothers.[64,97–99] Deleterious effects of maternal obesity on offspring learning and memory may occur, in part, through alterations in Brain-derived Neurotrophic Factor (BDNF)-mediated synaptic plasticity.[100] Rodent studies have demonstrated that maternal obesity and HFD consumption significantly decrease BDNF levels in the cerebral cortex and hippocampus.[62,64,100–102] Decreased BDNF levels are associated with reduced synaptic plasticity, and deficits in spatial learning and memory in offspring in the setting of maternal obesity.[62,64] Studies also suggest that maternal HFD leads to the instability of dendritic spines in offspring, with increased oxidative stress secondary to peroxidized lipid accumulation as a putative mediator of synaptic impairment.[103,104]

Microglia play a critical role in the promotion of synaptic formation and synaptic maturation in embryonic and early postnatal life.[105,106] Thus, any perturbation affecting microglial physiological function during a critical developmental period could result in defective maturation of synaptic circuits, impaired synaptic pruning, and an increase in redundant or unnecessary synapses.[107,108] A better understanding of the roles of microglia and BDNF in regulating synaptic development, pruning and repair may provide insight into the mechanisms underlying neurobehavioral abnormalities in offspring of obese dams.

3.3 | Impaired serotonergic and dopaminergic signaling

Maternal obesity is also associated with aberrant development of serotonergic and dopaminergic signaling in the developing fetal brain. Serotonin (5-HT) plays a significant role in neural development, influencing synaptogenesis, neurogenesis, and neuronal migration.[79,109,110] Reduced serotonin synthesis is associated with the increased incidence of ADHD, ASD, anxiety, and depression (or animal correlates of these pathologies) in human and animal studies.[55,72,79,110] Perturbations in serotonergic signaling noted in offspring of obese females was associated with increased hyperactivity and anxiety-like behavior.[55,72] Decreased 5-HT synthesis was observed in female nonhuman primate offspring exposed to maternal obesity, resulting in anxiety-like behavior.[79] High levels of proinflammatory cytokines have been shown to be associated with reduced serotonin axon density and reduced embryonic neuronal survival in brain regions critical for behavioral regulation in rodents.[111,112]

Maternal obesity also impairs the dopaminergic system, which plays a key role in governing reward-based eating and other addictive behaviors.[81,105,113] Animal studies have demonstrated that impaired mesolimbic dopaminergic signaling in offspring of HFD-exposed mothers is associated with aberrant reward response to food in the offspring.

[82,85,86,114] Similarly, maternal "junk food" diet during pregnancy and lactation promotes an exacerbated taste for junk food and a greater propensity for obesity in rat offspring.[82,83] It has been suggested that chronic overstimulation in the setting of maternal obesity and HFD consumption can cause "burnout" of the mesolimbic dopaminergic pathway, contributing to over-consumption of palatable foods to obtain an equivalent sense of reward.[113] Dysregulation of the dopamine reuptake transporter in offspring exposed to maternal HFD has been associated with increased offspring preference for high-sugar, high-fat foods.[80] Similar to serotonin dysregulation, limited evidence suggests that the proinflammatory developmental environment in maternal obesity may contribute to abnormal dopaminergic signaling in offspring.[115] Figure 1 depicts the maternal biology and putative mechanisms underlying offspring morbidity in the setting of maternal obesity.

4 | THE ROLE OF THE PLACENTA IN FETAL NEURODEVELOPMENTAL PROGRAMMING

The placenta plays a critical role in programming the fetal brain in response to maternal challenges such as malnutrition, stress, and infection.[116] Studies using animal models of placental insufficiency or intrauterine infection have shown altered astrocyte development, microglial activation, white-matter damage, and impaired blood brain barrier integrity in offspring.[117,118] Exposure to maternal inflammation has also been shown to upregulate placental production of 5-HT, which is associated with blunting of axonal growth.[119] In the following section, we review evidence that the placenta is a key, active mediator in programming the fetal brain in response to maternal obesity. Although the mechanisms are incompletely understood, there is growing evidence that obesity-induced changes in the placenta are linked to obesity-associated effects on fetal brain development, and therefore to adverse long-term offspring neurodevelopmental outcomes.

4.1 | Altered maternal cytokine and adipokine profile in obesity

The human placenta produces an array of proinflammatory cytokines that contribute to the observed elevation of circulating maternal cytokine levels compared to the non-pregnant state.[120] Obesity in pregnancy has been associated with low-grade metabolic inflammation through an increase in adipokines such as leptin, insulin, and free IGF-1 and a decrease in the insulin-sensitizing factor adiponectin.[121,122] Obese pregnant women have been shown to have elevations in multiple circulating proinflammatory cytokines such as C-reactive protein, IL-6, IL-1β, and TNF-α, compared to nonobese controls.[123–125] These elevations do not appear to directly correlate with fetal levels, making it unlikely that the maternal cytokine response to obesity passes to the fetal circulation directly.[126] Rather, alterations in the maternal cytokine profile impact fetal development in part through their effects on placental function.

4.2 | Placental inflammation and immune activation

Evidence suggests that obesity-associated alterations in peripheral cytokine profiles impact placental pathways involved in inflammation and immune activation, insulin resistance, oxidative stress, and nutrient transfer to the fetus. Obesity is a state of chronic low-level immune activation,[89] and pregnancy itself is inflammatory, augmenting underlying obesity-

associated inflammation.[127–129] As the interface between the maternal and fetal environments, the placenta has been implicated in developmental programming,[130,131] including effects on the developing fetal brain.[116,132–135] Placental macrophage accumulation, activation of proinflammatory immune pathways and histopathological evidence of inflammation have all been noted in obese human pregnancy.[124,127,136]

In histopathological studies of full-term placentas from uncomplicated pregnancies of obese and lean women, obesity was associated with an increase in placental inflammatory and maternal vascular territory lesions.[136,137] RNA-seq analysis of obese placentas at term found differential expression of proinflammatory interleukins and chemokine receptors as well as decreased expression of the adiponectin receptor—involved in anti-inflammatory signaling and insulin-sensitization—compared to lean controls.[138] In a study of matched maternal, placental, and cord blood specimens obtained from obese and lean women, maternal obesity was positively associated with placental activation of p38 mitogen-activated protein kinase (MAPK) and signal-transducer-activated transcription factor 3 (STAT3) pathways, both of which regulate proinflammatory gene expression and are implicated in the innate immune response.[123,139] The observed increase in proinflammatory p38-MAPK/STAT3 signaling may be attributable in part to stimulation of Toll-like receptor 4 (TLR4) by high levels of circulating fatty acids found in maternal obesity.[140] TLR-4 signaling has been implicated in obesity-associated neuroinflammation,[141–143] and trophoblastic TLR4 has been shown to be involved in the propagation of inflammation at the maternal-fetal interface.[144,145]

Data on placental immune activation in obese pregnancy have been conflicting, and immune cell number and function may differ between the maternal and fetal placental compartments. An examination of macrophage subsets of obese human placentas demonstrated lower levels of M1 or proinflammatory macrophages in the decidua parietalis, with no change in M2 or anti-inflammatory macrophage levels.[146] Another study noted increased neutrophils in the maternal interstitial space and increased expression of chemotactic cytokines in the placenta but did not identify changes in the number of fetal placental immune cells.[147] This study assessed only the number of fetal placental immune cells, however, rather than differences in reactivity. Challier and colleagues noted a two to threefold increase in resident CD68+ and CD14+ placental cells (fetal placental macrophages), with increased expression of proinflammatory cytokines IL-1, TNF and IL-6.[124] Animal studies have also supported the concept that resident placental macrophages are both increased in number and programmed toward a pro-inflammatory phenotype by maternal obesity.[96,148,149]

Chronic placental inflammation and stimulation of the placental innate immune response may be an important link between maternal obesity and fetal neurodevelopmental outcomes. Resident placental macrophages (Hofbauer cells) and resident brain macrophages (microglia) have a common origin in the fetal yolk sac.[150–157] Our laboratory has previously demonstrated that both placental and fetal brain macrophages are primed in parallel by maternal obesity toward a proinflammatory phenotype.[96] Yolk-sac-derived macrophages colonize the developing brain in the first trimester in humans and on embryonic day 9.5 in rodents.[150,152,153,156,158] Microglia continue to proliferate throughout the first postnatal weeks in humans and rodents, comprising a self-renewing pool that lasts throughout the lifespan.[150,153,158–163] Thus, fetal exposure to inflammation can have enduring

consequences for microglial function across the lifespan. Indeed, aberrant microglial priming has been implicated in multiple later-onset neurodevelopmental morbidities, including ASD, schizophrenia, obsessive compulsive disorder, and neurodegenerative conditions.[164–167]

4.3 | Placental lipotoxicity and oxidative stress

Animal studies demonstrate that maternal HFD consumption is associated with increased placental fatty acid uptake, transport, and fetal lipid accumulation.[168] In humans, placental lipid content is approximately 17% to 50% higher in placentas of obese women compared to lean women.[138,169] Deposition of lipid in the placenta may stimulate an inflammatory response and overwhelm mitochondrial capacity for lipid oxidation, leading to increased oxidative stress. One study demonstrated that the increased lipid deposition in obese placentas was associated with a 25% decrease in total antioxidant capacity and lipotoxicity evidenced by decreased 5' AMP-activated protein kinase (AMPK) and increased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[138] In the same study, obesity was associated with higher lipid esterification and depressed mitochondrial function, which was compensated for by an increase in peroxisome fatty acid oxidation.

How obesity-induced placental lipotoxicity and oxidative stress contribute to adverse fetal brain programming is an area of active investigation. Lipotoxic intermediates can act indirectly as nuclear transcription factors in developing fetal tissues and thus impact gene expression.[170] Analysis of the fetal cord blood transcriptome in pregnancies complicated by maternal obesity shows an altered gene expression profile that implicates both oxidative stress and neurodevelopmental pathways.[171] Additionally, peroxidized lipid accumulation in fetal brain tissue can act directly by impairing synapse development.[104] Placental lipid oxidation may also induce trophoblastic and endothelial dysfunction, leading to the development of conditions such as preeclampsia that can be associated with offspring neurodevelopmental morbidity.[170]

4.4 | Sex-specific placental programming

The observation that males are at least 2 to 3 times more likely to be diagnosed with ASD and ADHD than females may be a reflection of intrauterine programming, mediated in part by the placenta.[172] Animal studies have demonstrated that the placenta responds in sex-specific ways to maternal stressors, which differentially impact the developing male and female fetal brains.[132] Decreased expression of X-linked genes in male placentas, placental production of sex hormones, and sex-specific susceptibility to placental inflammation and immune activation, have all been implicated as potential mechanisms whereby the placenta drives sex-specific differences in offspring neurodevelopmental outcomes.[133,135]

As previously described, animal studies have demonstrated that male and female offspring show different neurodevelopmental susceptibilities in the setting of maternal obesity.[66,67,69–71,79,96] Human placenta studies suggest that maternal obesity affects oxidative stress and antioxidant activity in a sexually dimorphic manner, with male placentas demonstrating a more significant reduction in antioxidant capacity than females, and a significant upregulation in the activity of the antioxidant selenoprotein enzymes, glutathione peroxidase

and thioredoxin reductase.[173] Whether a sex-specific placental response to oxidative stress plays a role in the observed sex differences in neurodevelopmental outcomes is an open question. Future research into the role of the placenta in sex-specific programming of neurodevelopmental disorders in the setting of maternal obesity is needed.

4.5 | Summary of obese placental programming and putative links to fetal neurodevelopment

Both human and animal studies demonstrate proinflammatory placental changes in the setting of maternal obesity. Some studies of obese human placenta have also demonstrated activation of the maternal and fetal innate immune response, mediated in part through TLR4 signaling, although data are conflicting in this regard. Whether placental immune activation kindles or simply mirrors fetal brain immune activation in maternal obesity remains an important question that can be addressed using animal model systems. Sex differences in placental gene expression, inflammation and immune activation, and oxidative stress that correlate with offspring vulnerability to neurodevelopmental morbidity suggest the potential for a brain-placenta connection.

5 | SUMMARY

Given the rising prevalence of maternal obesity in the United States and throughout the world, a majority of children born in the United States in 2020 will have been exposed to maternal overweight or obesity during fetal life. Human epidemiologic studies have linked maternal obesity to adverse offspring neurodevelopmental and psychiatric outcomes including cognitive impairment, ASD, ADHD, anxiety and depression, and disordered eating. Animal studies have shed light on underlying mechanisms, including but not limited to fetal brain inflammation and in utero priming of brain microglia, alterations in synaptic pruning and synaptic plasticity, and impaired central serotonergic and dopaminergic signaling. Both human and animal studies suggest a critical role for the placenta in mediating the deleterious impact of maternal obesity on fetal brain development via inflammation, fetal immune activation, lipotoxicity, increased oxidative stress, and reduced antioxidant capacity. Future research should focus on further elucidating the fetal-brain placental connection using Cre-lox systems or other conditional/tissue-specific knockouts in animal models, and on targeted perinatal therapy that can be administered to the pregnant or lactating woman during key developmental windows, to ameliorate harmful obesity-associated placental and fetal brain programming. Therapeutic strategies should be guided by an understanding of underlying mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's already known about this topic?

- Maternal obesity is associated with an increased risk for neurodevelopmental and psychiatric disorders in offspring, including cognitive impairment, ASDs, attention deficit hyperactivity disorder, anxiety and depression, eating disorders, and food addiction.

What does this study add?

- This comprehensive review integrates data from both human epidemiologic and animal model studies linking maternal obesity and high-fat diet consumption with increased risk of neurodevelopmental and psychiatric morbidity in offspring.
- We address sex differences in maternal obesity-associated programming.
- We link immune and inflammatory placental changes to downstream programming of the fetal brain.

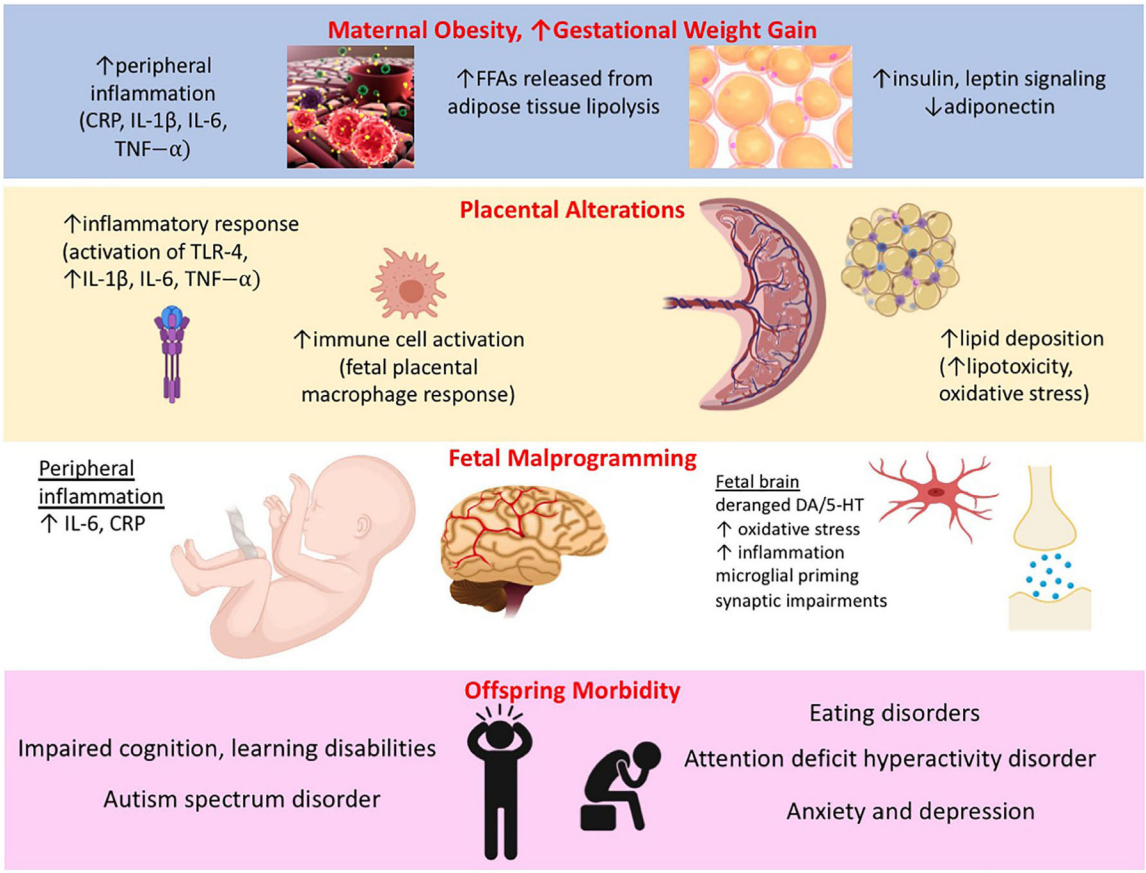

FIGURE 1.

Altered maternal and placental physiology in maternal obesity contribute to fetal organ malprogramming and adverse neurodevelopmental outcomes in offspring. CRP, C-reactive protein; DA, dopamine; FFA, free fatty acid; FGR, fetal growth restriction; IL-1β, interleukin 1-beta; IL-6, interleukin 6; TG, triglyceride; TNF−α, tumor necrosis factor alpha; 5-HT, serotonin