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Inflammation: A Proposed Intermediary Between Maternal Stress and Offspring Neuropsychiatric Risk

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Abstract

During pregnancy, programming of the fetal central nervous system (CNS) establishes vulnerabilities for emergence of neuropsychiatric phenotypes later in life. Psychosocial influences during pregnancy, such as stressful life events or chronic stress, correlate with offspring neuropsychiatric disorders and with inflammation, respectively. Stress promotes inflammation, but the role of inflammation as a mediator between maternal psychosocial stress and offspring neuropsychiatric outcomes has not been extensively studied in humans. This review summarizes clinical evidence linking specific types of stress to maternal inflammatory load during pregnancy. We propose that inflammation is a mediator in the relationship between psychosocial stress and offspring neuropsychiatric outcomes, potentially influenced by poor maternal glucocorticoid-immune coordination. We present relevant experimental animal research supporting this hypothesis. We conclude that clinical and preclinical research support the premise that stress-induced maternal immune activation (MIA) contributes in part to prenatal programming of risk. Programming of risk is likely due to a combination of vulnerabilities, including multiple or repeated inflammatory events, timing of such events, poor maternal regulation of inflammation, genetic vulnerability, and lifestyle contributors.

Keywords

pregnancy; cytokines; stress; hypothalamic pituitary adrenal; transgenerational; cytokine-glucocorticoid feedback

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INTRODUCTION

Pregnancy represents a key developmental window when prenatal programming of the offspring central nervous system (CNS) occurs (1). Perturbations to the prenatal environment, such as stress or immune activation, are associated with increased risk for offspring neuropsychiatric disorders in the epidemiologic literature (2–20). Numerous reviews have addressed sickness-induced immune activation and offspring neuropsychiatric risk, but few have addressed stress-induced immune activation and offspring neuropsychiatric risk in the context of human pregnancy. In this review, we propose that inflammation is a potential mediator between prenatal stress and offspring neuropsychiatric outcomes (Figure 1). We describe the clinical evidence linking specific forms of stress (stressful life events (SLEs), chronic stress, acute stress, traumatic stress, adverse childhood experiences (ACEs)) to maternal inflammation during pregnancy, and to neuropsychiatric risk in the offspring. Finally, we provide preclinical data to explore potential mechanisms by which inflammation may modulate the relationship between maternal psychosocial stress exposure and offspring neuropsychiatric outcomes.

STRESS AND INFLAMMATION DURING PREGNANCY

Stress and the immune milieu

Decades of research have established that psychosocial stress dysregulates aspects of immune function in healthy, nonpregnant adults (21–28). Elevated circulating inflammatory markers and impaired immune function have been associated with numerous types of stress including SLEs such as death of a spouse (29–31), daily hassles (32, 33), chronic stress such as caregiving or unemployment (34–37), traumatic stress (38, 39), ACEs (40–43), as well as acute laboratory stressors (44–47). At the root of the relationship between stress and inflammation is coordination between the hypothalamic pituitary adrenal (HPA) axis and immune system. Glucocorticoids impact both innate immunity (e.g. inflammation) and adaptive immunity (specific, T/B-cell mediated), modulating activity of numerous immune cell types including monocytes and macrophages, and mediators such as cytokines and chemokines (48). Although historically considered anti-inflammatory, glucocorticoids can suppress or potentiate immune function, in a biphasic manner (49). This reciprocal relationship maintains an appropriate allostatic load, however, simultaneous elevation of proinflammatory cytokines and cortisol indicate dysregulated glucocorticoid-immune feedback, often resulting from stress (50). A meta-analysis of over 300 studies found that different types of stress impact different aspects of immune function: acute laboratory stressors upregulated innate immunity and downregulated adaptive immunity; brief naturalistic stressors such as academic examinations shifted function away from cellular immunity (T-helper type 1; Th1) and toward humoral immunity (Th2); and chronic stressors, which are pervasive and unrelenting, suppressed both innate and adaptive immunity (28). A well-regulated, flexible glucocorticoid-immune system responds appropriately to stimulation, e.g., a brief spike in proinflammatory cytokines in response to acute stress is physiologically appropriate, but an exaggerated or prolonged immune response is maladaptive, and chronic stress may result in glucocorticoid resistance (34).

During pregnancy, the immune and glucocorticoid milieu shift. The first and third trimesters are often considered broadly proinflammatory with increased activation of peripheral leukocytes (51), while the second trimester is conceptualized as anti-inflammatory (52). The immune system is tightly regulated during pregnancy, as it is involved in cervical ripening, rupture of membranes, and myometrial contractivity (53). It is possible that perturbations to the normal trajectory of immune function across pregnancy (54–57), impaired coordination of glucocorticoid-immune function, or compromise to immune system flexibility, could contribute to increased offspring risk (28). As inflammatory response to acute stress is dampened during pregnancy (45), an exaggerated inflammatory response to stressors, or inability to dampen this response in the face of routine stressors, could contribute to inflammatory burden over the course of pregnancy. Appropriate coordination between the glucocorticoid and immune systems are important for materno-fetal health (58, 59). While studies have assessed the potential moderating role of glucocorticoids in the association between prenatal stress and offspring outcomes (60–63), there has been little focus on inflammation as a component of this relationship. It may not be glucocorticoids alone, but poor regulation of cytokine-glucocorticoid negative feedback (64), that influences the relationship between maternal stress during pregnancy and offspring outcomes.

Stressful life events

Stressful life events (SLEs), such as death of a loved one or divorce, range from mild to severe (65). Healthy adults who recently experienced an SLE exhibit immune dysregulation (29, 66). In particular, meta-analysis found a decline in natural killer (NK) cell cytotoxicity among those who had experienced recent death of a spouse (28). There is less research on SLEs and immune function specifically in pregnancy. Offspring of women who experienced an interpersonal SLE during the prior trimester of pregnancy had higher levels of interleukin (IL)-1β in umbilical cord blood at delivery compared with women who did not experience an SLE, and those who had a health-related SLE in the first trimester had higher cord blood levels of IL-5, IL-6, and IL-8 than women who had not experienced SLEs (67). However, elevated cord blood cytokine levels among those with a health-related SLE may have been confounded with the health issue itself.

While offspring neurocognitive outcomes were not assessed in the aforementioned studies, epidemiologic studies suggest that SLEs during pregnancy increase risk of poor offspring neuropsychiatric outcomes. Death of a close relative during pregnancy was associated with greater risk for offspring schizophrenia in some studies (68, 69). Women in the Avon Longitudinal Study of Parents and Children (ALSPAC) who experienced more SLEs during pregnancy were more likely to have a child with psychotic experiences at age 12 than women with fewer SLEs, although this was not significant after adjusting for maternal anxiety and depression (70). SLEs similarly increase risk of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and depression among offspring in multiple studies (18–20, 71, 72), with some suggesting a male risk bias (14, 73–75). While some studies found that SLEs during pregnancy were associated with increased risk for offspring schizophrenia or psychotic experiences (68–70), ASD (18), or ADHD symptoms (14, 18–20, 73), not all did (76–78). The mixed findings may result from differences in severity of stress, maternal psychological reaction to the stress, maternal inflammatory

response to the stressor, or mitigating factors such as social support. For instance, impact of SLEs on offspring neuropsychiatric outcomes in ALSPAC was driven by maternal anxiety and depression (70). Similarly, perceived stress (79) and exposure to interpersonal violence (80) predicted higher levels of proinflammatory cytokines during pregnancy particularly in the context of low social support (81). Thus, it is important to consider maternal SLE exposure in the context of moderating influences that could potentiate or dampen impact of the SLE on immune function.

Chronic stress

Stressors that persist for an extended duration -- caregiving for an individual with severe chronic illness, extended work stress or unemployment, racial discrimination, poverty -- are considered chronic. A meta-analysis revealed that chronic stress impacted nearly all aspects of functional immunity studied, including T cell proliferative response and antibody response to vaccine (28). This was generally associated with duration of the stressor; longer duration was associated with decrements in functional immunity, versus shorter term stressors associated with declines in cell counts consistent with redistribution (28). Of the few studies on chronic stress and immune function during pregnancy, minority status and low income, both chronic stressors, were associated with higher IL-1:IL-10 ratio, as well as poor coordination of glucocorticoid-immune response, at weeks 32 - 36 of pregnancy (58). African-American women reporting greater racial discrimination had elevated levels of circulating IL-6 and IL-4 in the second trimester (82), and greater Epstein-Barr viral capsid antigen (EBV VCA) IgG antibody titers across pregnancy and postpartum (83), suggesting immune dysregulation. Greater exposure to chronic stressors was associated with elevated peripheral inflammatory markers in the first and third trimesters (81, 84), which partially mediated the impact of stress on gestational age at delivery (85). Low income during pregnancy was associated with chronic inflammation in placental tissue at delivery (86) and a transcriptional profile suggesting higher immune activation (87). In a study of 560 newborns, maternal exposure to chronic stressors during pregnancy, including financial hardship, community violence, and poor housing conditions, was associated with increased stimulated chemoattractant cytokine IL-8 and pro-inflammatory cytokine tumor necrosis factor (TNF)-α production in cells isolated from cord blood (88). The authors propose that this is evidence for prenatal psychosocial stress contributing to programming of the infant immune response.

Forms of chronic stress such as racial discrimination or poverty may be distinct from other types of chronic stress (89). Further, poverty is often associated with confounding factors such as exposure to environmental pollutants or poor diet (87). As these factors also directly affect the health of the pregnancy and fetal development, it is a challenge to isolate the specific effects of prenatal stress on offspring neurodevelopment. Regardless, studies focusing on the chronic stress of discrimination or socioeconomic disadvantage consistently report adverse impacts on offspring neuropsychiatric risk (90). Maternal socioeconomic disadvantage during pregnancy was associated with 4.6-fold greater odds of offspring neurologic abnormalities at four months of age, an effect that was modulated by peripheral levels of IL-8 (91). Further, maternal daily stress compounded the effect of second trimester infection on offspring depression scores; offspring who were exposed to prenatal infection

alone had significantly lower levels of depression than offspring who were exposed to both infection and stress in utero (92). This supports the notion that stress potentiates the inflammatory effects of infection or illness during pregnancy.

Acute laboratory stress

Acute laboratory stressors, meant to evoke physiologic responses similar to what one would experience in the face of routine daily stressors, reliably increase cortisol and proinflammatory cytokines (93). The magnitude and duration of the inflammatory response is regulated by glucocorticoids (94), and thus laboratory stressors provide useful information about individual regulation of inflammation and immune-glucocorticoid feedback. While acute stressors such as the Trier Social Stress Test (TSST) have been extensively studied in nonpregnant adults, inflammatory response to acute laboratory stress is not well characterized in pregnant women. One study found that inflammatory response to TSST is blunted in pregnant women relative to nonpregnant women overall, but pregnant African-American women's IL-6 response was still greater than that of nonpregnant Caucasian women (45). Poor ability to regulate glucocorticoid-immune response to routine stressors may contribute to persistent inflammation over time, thus potentially increasing inflammatory load across pregnancy.

Traumatic stress

Individuals with PTSD have elevated cerebrospinal fluid (CSF) IL-6 (95), elevated peripheral inflammatory markers (96, 97), and impaired immune cell glucocorticoid sensitivity (98). In pregnant women, history of trauma exposure was associated with elevated circulating TNF-α (99) and elevated IgE levels in cord blood at delivery (100).

Prenatal traumatic stress, such as exposure to war, is associated with deficits in child neurodevelopment and mental health in the epidemiologic literature (101–103). Natural disasters, such as floods or hurricanes, are variably stressful depending upon individual factors such as access to resources or ability to escape. Children of women pregnant during the 2011 Queensland flood (QF2011) or 1988 Quebec ice storm had more difficult or irritable temperaments (104, 105). QF2011 offspring had lower social-emotional intelligence scores the later in pregnancy they were exposed and the more severely their mothers rated their exposure (105). Higher-rated subjective exposure to the Quebec ice storm among mothers was associated with increased maternal report of internalizing and externalizing problems and severity of autistic-like traits in children (106, 107). Among children prenatally exposed to heightened maternal anxiety during the Chernobyl disaster, there was a 2.32-fold risk of lifetime depression symptoms, an increased risk of meeting criteria for MDD, and a two-fold risk of ADHD symptoms (108), noteworthy in those exposed from the second trimester onwards. In war or natural disaster, it is difficult to disentangle whether the effects on the developing child are due to physical deprivation, emotional strain or ongoing difficulties after birth. Further, none of these studies assessed maternal markers of inflammation resulting from trauma exposure during pregnancy, failing to establish relationships between maternal stress, inflammation, and offspring outcomes.

Maternal adverse childhood experiences

Adverse childhood experiences (ACEs), such as abuse or chronic stress, are associated with elevated markers of inflammation in non-pregnant adults (42, 109), including at baseline (41), in response to acute stress (40), in response to daily stressors (42), and in the context of chronic stress (36). Few studies have assessed the impact of ACEs on inflammation during human pregnancy. Pregnant teenagers who reported a history of abuse had elevated IL-6 levels in the second trimester, particularly among those with current major depression (110). Childhood physical abuse, emotional abuse and emotional neglect were associated with elevated serum CRP across pregnancy (111). Women with gestational diabetes who had a history of childhood maltreatment had elevated IL-15 in pregnancy (112).

Epidemiologic studies suggest possible links between maternal ACEs and offspring neuropsychiatric outcomes. Offspring of high ACE mothers had higher rates of behavioral problems in childhood (113), and as newborns, had altered brain structure (114). Strikingly, among pregnant women, it was not depression nor anxiety that was associated with elevated inflammatory markers, but history of trauma (99). Maternal childhood economic hardship, a proxy for adversity, was associated with adverse pregnancy outcomes, and this relationship was partially mediated by elevated maternal IL-6 (115). Finally, our group found that postpartum women with a history of childhood adversity exhibited a dampened glucocorticoid response to a mild stressor compared to women without such history, a finding that was mirrored by their 6-month old infants in response to stress (116). Dysregulated glucocorticoid function allows exaggerated inflammatory response (58), leading us to hypothesize that poor glucocorticoid regulation of inflammation during pregnancy may impact prenatal programming.

Summary of Clinical Literature and Proposed Mechanism

Epidemiologic and clinical data indicate that offspring neuropsychiatric outcomes are associated independently with maternal stress experience and with MIA. The few studies that have assessed all three factors in conjunction -- maternal stress, MIA, and offspring outcomes -- suggest a mediating effect of inflammation on pregnancy outcomes or offspring neurodevelopment (85, 91, 115). IL-8 modulated the association between maternal chronic socioeconomic stress during pregnancy and increased risk of offspring neurologic abnormalities (91). Although not a neuropsychiatric outcome, maternal IL-6 partially mediated the relationship between maternal childhood adversity and poor pregnancy outcomes (115). Similarly, maternal stress predicted peripheral IL-6 and TNF- α, which in turn predicted gestational age at delivery (85). These findings are also consistent with recent studies demonstrating that maternal IL-6 across pregnancy is associated with greater amygdala volume and connectivity in infants and poor impulse control at age two (117), functional brain connectivity in infants and poorer working memory function at age two (118), and reduced frontolimbic white matter integrity in newborns and poorer cognitive function at twelve months (119).

A potential mechanism for the proposed relationship between maternal stress, inflammation, and offspring neuropsychiatric outcomes is poor HPA regulation of inflammatory response. Numerous studies have assessed the potential moderating role of glucocorticoids in the

association between prenatal stress and offspring outcomes (60), finding associations between placental CRH, glucocorticoid exposure, and maternal cortisol levels with offspring internalizing symptoms, cortical thinning, and increased amygdala volume, respectively (61–63). However, there has been little focus on inflammation as a component of this relationship. It may not be glucocorticoids per se, but poor regulation of cytokine-glucocorticoid negative feedback (64), that influences the relationship between maternal stress during pregnancy and offspring outcomes. To test the hypothesis that stress induces impairments in glucocorticoid-immune function that then affects prenatal programming of offspring neuropsychiatric risk in humans, at minimum one would need to collect data on clearly characterized forms of maternal stress exposure, maternal markers of glucocorticoid function and inflammation at multiple points in pregnancy, and offspring neuropsychiatric outcomes. This requires careful, well-integrated study of both maternal and offspring factors. Maternal glucocorticoid-immune coordination could be studied via glucocorticoid and cytokine response to acute stress, examining correlations among cytokines and cortisol (59), or *ex vivo* measures of immune cell responsiveness to glucocorticoids. Dysregulated control of placental inflammation is also a potential factor, and could be examined via placental tissue at delivery. Offspring outcomes would benefit from both biological and clinical measures. Maternal IL-6 across pregnancy has been associated with altered offspring brain structure and function as well as neurocognitive deficits (117–119), suggesting that MIA during pregnancy confers risk by inducing potentially subtle neurocognitive patterning that may or may not be unmasked later in life depending on environmental factors. While no studies of this nature have been conducted in humans, such work has been done in animals, providing information on potential mechanisms.

THE ANIMAL LITERATURE: POTENTIAL MECHANISMS

Prenatal inflammation influences offspring brain and behavior

Directly inducing inflammation during the perinatal period, using pathogens or chemicals that mimic pathogenic infection, or direct injection of IL-6, produces altered brain structure and behavior in offspring (120–126). Administration of the viral mimic polyinosinic:polycytidylic acid (poly(I:C)) results in the production of pro-inflammatory cytokines IL-1β, TNF-α, IL-17a, and IL-6 in the plasma and placenta, which are correlated with fetal brain damage (127, 128). When pregnant mice were administered poly(I:C) at 13-15 days post-conception (dpc), poly(I:C)-exposed offspring had altered cerebellum structures and increased numbers of Purkinje cells, and both male and female animals had reduced performance on motor function tests and perturbed social behavior (120). Co-administration of anti-IL-6 antibody with poly(I:C) prevented the neurobehavioral deficits (125). In mouse MIA models, CD4+T helper 17 (T_H17) cells, that produce IL-17a, are required for ASD-like phenotypes (121). Antibody-mediated blocking of IL-17a protected against the development of MIA-induced behavior changes and also rescued fetal cortical development. This indicates that pathological activation of T_H17 cells and the IL-17a pathway during gestation alters fetal brain development and results in ASD-like behavioral phenotypes, but future work to determine downstream pathways of maternal IL-17a producing T cells is necessary to understand the mechanisms of ASD development resulting from *in utero* inflammation.

Prenatal stress induces inflammation and alters behavior in a sex-specific way

In rodents, prenatal stress causes extended inflammation in the fetal brain, with elevated *ex vivo* microglial production of pro-inflammatory cytokines IL-1β, IL-18, TNF-α, and IL-6 and chemokines CCL1 and CXCL12 (129), which are mediators of local immune responses during neuro-inflammation. Prenatal stress induced increased expression of immune response genes in the placenta, including IL-6 and IL-1β, resulting in male-specific locomotor hyperactivity and increased HPA axis response (130, 131); pretreatment with nonsteroidal anti-inflammatory drugs (NSAIDS) prevented stress-induced immune gene expression changes and ameliorated the behavior defects (130). Maternal coordination of glucocorticoid-immune function was not assessed. Prenatal stress increased serum glucocorticoid levels in male offspring but not females, and exposure to air pollutants exacerbated male-specific inflammation in the brain, with elevated IL-1β levels and increased expression of innate immune genes *Tlr4* and caspase-1 (132). Interestingly, the female brains had increased levels of the anti-inflammatory cytokine IL-10 after exposure to air pollutants, suggesting that the female brain may mount a more effective anti-inflammatory response. Similarly, a restraint stress model of pregnant dams increased IL-1β expression in placentas and female fetal brain (male animals were not examined), and female adult amygdalae from stress-exposed mothers and controls had similar levels of IL-1β expression, suggesting that female immune system may tolerate or remediate prenatal-induced inflammation better than males (133). When female rats were exposed to early life stress (ELS), a proxy for ACE, their offspring exhibited increased repetitive behavior and less time in social interactions, suggestive of an ASD-like phenotype (134). While the female offspring of ELS-exposed mothers had double the baseline interferon (IFN)γ levels of control offspring, the researchers did not include male rats in their study, which could have exhibited more pronounced deficits with social interactions. Indeed, some studies suggest sexually dimorphic effects of MIA, with males more susceptible to brain development perturbations resulting from inflammation (135). LPS treatment of pregnant rats reduced juvenile social play behavior exclusively in males (136). TNF-α injections in neonatal mice increased anxiety and despair-like behaviors later in life exclusively in male animals (137). MIA can also induce sex-specific changes with astrocyte markers and morphology, where male cells are more affected (138). However, sufficiently powered research investigating sex differences resulting from immune challenges is necessary to elucidate sex-specific responses to early-life inflammation.

Together, these studies support the model that prenatal stress may negatively impact offspring behavioral outcomes via inflammation. While the majority of animal research suggests males are more vulnerable to prenatal insults, more work is needed to elucidate the sex differences with immune responses and behavioral outcomes, including glucocorticoid-immune coordination and the identification of immune cell types responsible for increased pro-inflammatory cytokine production.

CONCLUSIONS

Clinical research demonstrates clear connections between maternal stress and elevated inflammation, and between maternal inflammation and offspring CNS development,

although human studies have not assessed these factors simultaneously. In rodents, stress increases inflammation peripherally and at the placenta, and induces behavioral dysregulation in offspring, establishing causal links (130, 131). Preclinical research suggests that MIA, particularly the cytokines IL-6 and IL-17a, are key in the link between maternal stress and offspring outcomes (121). In humans, maternal stress was associated with elevated peripheral IL-6, IL-8 and TNF-α during pregnancy (67, 82, 85, 88, 91, 99, 110). Intriguingly, these three proinflammatory cytokines were also found to mediate relationships between maternal stress and offspring outcomes in clinical studies (85, 115, 117–119). Peripheral cytokines may cross the placenta and fetal blood-brain barrier to access the fetal CNS, thus influencing prenatal patterning (139). Prolonged elevation of peripheral cytokines as a consequence of stress are likely due to poor maternal glucocorticoid-immune coordination (58, 116). Placental inflammation was also associated with fetal brain damage and altered behavioral phenotypes in offspring among rodents (130, 131), and in humans, placental tissue at delivery showed evidence of inflammation (86) and a transcriptional profile consistent with elevated immune activation (87) among women experiencing chronic stress. In rodents, NSAID treatment prior to maternal stress prevented placental stress-induced immune gene expression changes and ameliorated the behavior defects (130). Similarly in women who were ill during pregnancy, antipyretic medications attenuated offspring neuropsychiatric risk (140). In sum, the clinical and preclinical research support the premise that stress-induced MIA contributes in part to prenatal programming of risk, potentially due to poor coordination or plasticity of the glucocorticoid-immune axes.

However, the role of inflammation in prenatal programming is multifaceted, with diverse contributors ranging from diet to infection that should be considered in conjunction with psychosocial stress. It is likely that a combination of vulnerabilities, including multiple or repeated inflammatory events, timing and duration of such events, poor maternal regulation of inflammation, genetic vulnerability, and lifestyle contributors are synergistic factors in increased risk for neuropsychiatric disorder in offspring. Factors such as type, number and chronicity of stressors and their associated context and consequences, timing of events in relationship to the mother’s development or gestational age of the fetus, and the mother’s ongoing physiological response to additional stressors during pregnancy should be considered for future studies (92). For instance, low-grade inflammation induced by psychosocial stress is typically more chronic than the transient inflammation induced by acute infection or injury (22). Hence, psychosocial or other chronic stressors that affect women across multiple trimesters may have a greater impact than an isolated infection (92, 108, 141), and this can be modeled in animals to determine how persistent inflammation during pregnancy impacts adult behavior. Animal research suggests that inflammation during different stages of pregnancy exhibits variable vulnerability to the developing CNS (142), which is supported by observations in humans where elevated cortisol in early pregnancy had deleterious effects on offspring neurocognitive outcomes, yet elevated cortisol later in pregnancy was beneficial (143). Finally, while a full exploration of genetic contributors is beyond the scope of this review, it is possible that only offspring who are genetically vulnerable and experience MIA are at risk, in a gene x environment interaction. MIA may induce CNS vulnerabilities, perhaps manifesting as subtle neurocognitive changes in the offspring (104–107, 118, 141) that do not develop into frank psychiatric disorder.

However, interactions with the environment through childhood and adolescent development may elicit or perpetuate stressors in a gene-environment correlation (144), eventually resulting in emergence of neuropsychiatric disorder.

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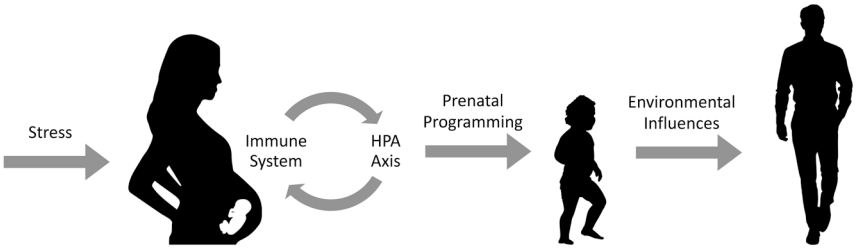

MATERNAL STRESS EXPOSURE	IMPACT ON IMMUNE PARAMETERS DURING PREGNANCY	CHILD NEUROPSYCHIATRIC OUTCOMES	ADULT NEUROPSYCHIATRIC OUTCOMES
Stressful Life Events	Elevated IL-1β , IL-5, IL-6, IL-8 in cord blood [67] Elevated TNF-α [80]	Increased psychotic experiences risk [70] Increased ASD, ADHD risk [14, 18–20, 73, 74]	Increased schizophrenia risk [68–70] Greater psychiatric hospitalization risk [75] Increased depression risk [71, 72] No increased risk [76–78]
Chronic Stress	Impaired HPA-immune coordination [58] Elevated IL-1: IL-10 ratio [58] Elevated IL-4, IL-6 [82] Elevated EBV VCA IgG [83] Elevated IL-6, IL-10, CRP [81, 84] Greater stimulated IL-6, IL-1β production [81] Placental inflammation [86, 87] Greater stimulated IL-8, TNF-α from cord blood cells [88] Lower IL-8 [91]	Behavioral problems, mental health morbidity [90] Neurologic abnormalities [91] Depression [92]	
Traumatic Stress	Elevated TNF-α [99] Elevated IgE in cord blood [100]	Difficult or irritable temperament [104, 105] Lower social-emotional intelligence [105] Internalizing, externalizing behaviors [106] ASD-like traits [107]	Increased schizophrenia risk [103] Risk of major depression [108] ADHD symptoms [108]
Adverse Childhood Experiences	Elevated IL-6 [110] Elevated CRP [111] Elevated IL-15 [112] Blunted cortisol response [116]	Behavioral problems [113] Altered brain structure [114] Blunted cortisol response [116]	

Figure 1. Impact of Stressors on Maternal Inflammation During Pregnancy

We propose that inflammation is an intermediary in the relationship between maternal psychosocial stress and offspring neuropsychiatric outcomes, potentially influenced by poor maternal glucocorticoid-immune coordination. In this model, stress-induced maternal immune activation (MIA) may induce CNS vulnerabilities in the offspring, potentially manifesting as subtle neurocognitive changes. Interactions with the environment through childhood and adolescent development may eventually result in emergence of neuropsychiatric disorder.