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WOMEN'S HEALTH

Pregnancy as an opportunity to explore brain-immune connections in mental health

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Pregnancy's effects on the brain, behavior, and hormones provide a unique opportunity to study how the immune system integrates these adaptations and influences mental health.

The brain and immune system are broadly interconnected, and psychiatric disorders often demonstrate immunopathology. This is particularly true during the perinatal period (pregnancy through 1 year postpartum), a period of vulnerability and flux both psychologically and immunologically. With perinatal depression affecting 10 to 13% of birthing people (*1*), an urgent need exists for innovative prevention, detection, and treatment strategies. Looking beyond the brain as the only organ implicated in psychiatric disorders, an emerging area of research focuses on brain-immune interactions. With its profound brain and immune changes, pregnancy is a particularly promising period for revealing brain-immune interactions and ultimately for addressing the public health crisis posed by perinatal mental health disorders.

During the transition to motherhood, the maternal immune system strikes a tenuous balance: It must expand tolerance to foreign antigens including those from the half-foreign fetus while also retaining the capacity to combat pathogens. This adaptive shift occurs dynamically alongside neuroendocrine, neurobiological, and behavioral adaptations. If balance is not achieved, maladaptive immune dynamics prevail, driving obstetric and psychiatric disease, which themselves interact. Preeclampsia, preterm birth, and gestational diabetes all increase risk for mental illness; conversely, perinatal maternal anxiety and depression are linked to increased risk for antepartum hemorrhage (a 1.5-fold increase), preterm birth (a 1.61-fold increase), and other proinflammatory pregnancy complications (*2*). This bidirectional psycho-obstetric risk could be driven, at least in part, by neuroimmune mechanisms.

Pregnancy is not a confounder to be controlled for but rather a useful and defined natural experiment. Our central thesis is that pregnancy, arguably one of the most immunologically dynamic periods of the human life span, reveals neuroimmune mechanisms that may be exploited to understand psychopathology more broadly. The immune cell serves as a central hub, integrating canonical immunotolerance with neuroendocrine, neurobiological, and behavioral adaptations across the transition to motherhood, all within the context of broader social determinants (Fig. 1A).

NEUROENDOCRINE-IMMUNE INTERACTIONS

The adaptation of neuroendocrine-immune mechanisms to pregnancy may underlie psycho-obstetric risk. Neuroactive hormones change dramatically across pregnancy. Circulating progesterone, estrogen, and glucocorticoid levels increase with conception, continuously rise throughout gestation, and drop precipitously after childbirth. The neuroendocrine placenta plays a key role in these shifts (*3*). For example, placental corticotrophin-releasing hormone alters hypothalamic-pituitary-adrenal (HPA) function, affecting release of cortisol and norepinephrine. These pregnancy-specific changes in neuroendocrine factors may impact immune cell function via expression of steroid and adrenergic receptors, direct agonism, epigenetic/posttranscriptional changes, and other mechanisms. The placenta also expresses the necessary machinery to take up and metabolize norepinephrine and dopamine, which act as autocrine/paracrine effectors. Other placental factors, such as prolactin or β-nerve growth factor, remodel peripheral-central neuronal networks (*3*). All immune cells express receptors for prolactin and β-nerve growth factor, with implications for the establishment and maintenance of a balanced immune milieu at the maternal-fetal interface. Neuroendocrine-immune adaptations in pregnancy originate in the periphery with effects on centrally regulated axes (Fig. 1B).

In psychiatric diseases common in pregnancy, such as anxiety and depression, neuroendocrine-immune interactions (in flux to adapt to the needs of pregnancy) are disrupted. Such disruptions are associated with changed levels of glucocorticoids, adrenergics, and neuropeptides such as vasopressin. Chronic psychological stress modulates multiple neuroendocrine systems, including two that have been most well characterized: the HPA and sympathetic-adrenal-medullary (SAM) axes with consequences for immune function. For example, glucocorticoids bind immune cell receptors and disrupt NF-κB signaling, while catecholamines trigger transcriptional changes, affecting cytokine production (*4*). These dynamics exemplify how pregnancy may serve as a particularly powerful context for examination of interactions between endocrine and immune factors. Risk for adverse mental health outcomes in pregnancy depends on internal (e.g., sensitivity to neuroendocrine shifts) and external (e.g., sociodemographic) determinants, which may shift neuroendocrine-immune dynamics from beneficial adaptations into harmful disruptions.

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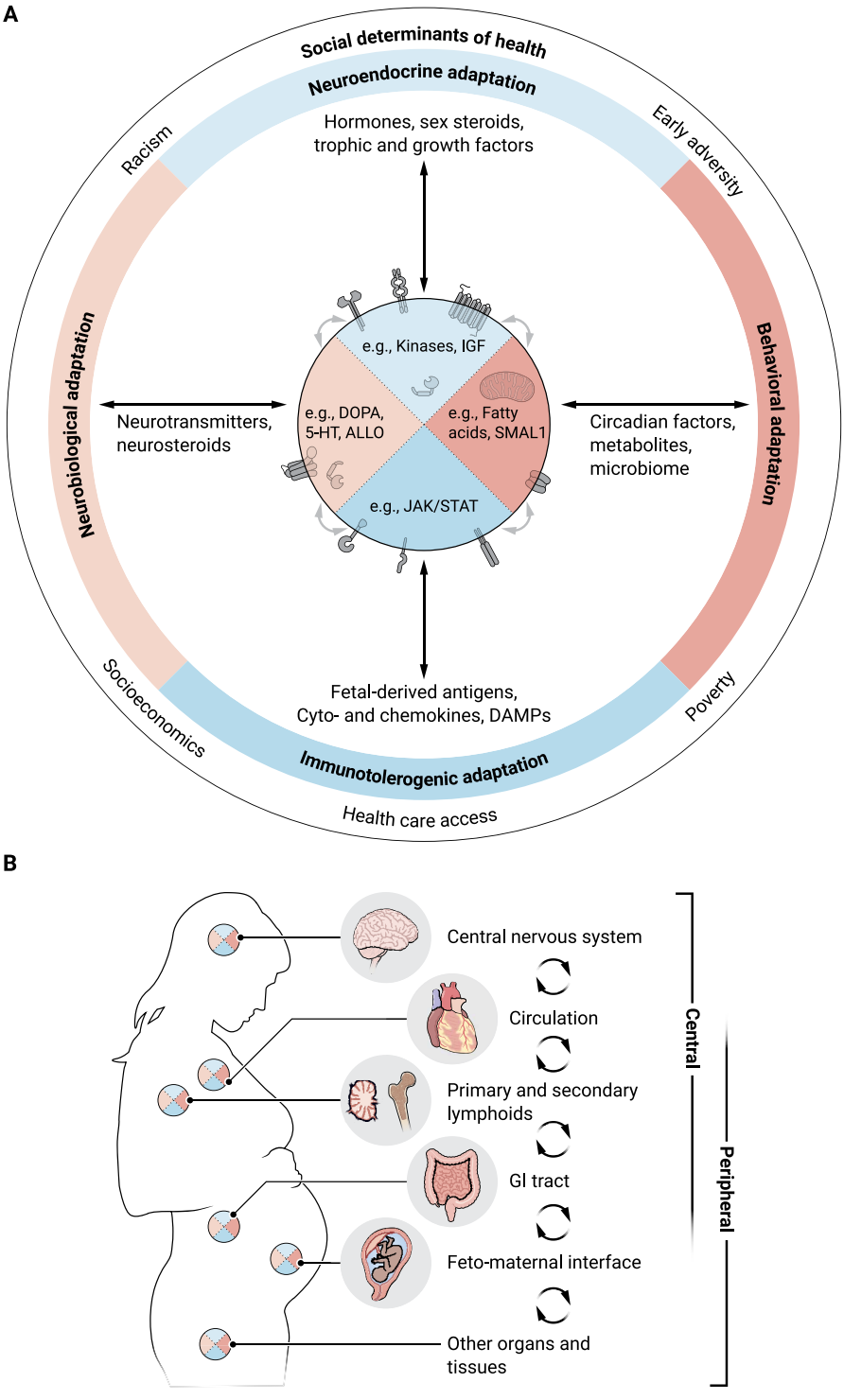

Fig. 1. Neuroimmune interactions in pregnancy. (**A**) Immune cells serve as integrative hubs for neuroendocrine, neurobiological, behavioral, and immunotolerogenic adaptations during the transition to motherhood and (**B**) communicate across a network of central and peripheral niches. Maladaptation in these domains may precipitate psychiatric disease. Illustration credit: Austin Fisher/*Science Advances*.

NEUROBIOLOGICAL-IMMUNE INTERACTIONS

Neurobiological adaptations occur in the central nervous system with consequences both in the nervous system and the periphery. Studies at the level of the whole brain and at single-cell resolution reveal dramatic neurobiological adaptations to pregnancy, which may be sensed by different niches of immune cells, including central (e.g., astrocytes and yolk sac–derived microglia) and peripheral (e.g., hematopoietic stem cell–derived leukocytes) subtypes. Reciprocally, a pregnancy-adapted immune system may contribute to, enhance, or regulate adaptations of the central and peripheral nervous systems to pregnancy. At the level of the whole brain, a recent deep sampling MRI study of the maternal brain before, throughout, and following pregnancy revealed profound structural and connectivity changes in gray and white matter from pre-conception throughout gestation and postpartum (*5*). The few studies available at the level of individual non-neuronal, immuno-competent cell populations in the brain focus on microglia and astrocytes, which play critical roles in immunoregulation and are implicated in psychopathologies such as major depressive disorder. Microglia have altered morphology and function in pregnancy, with some reporting reduced density ante- and postpartum which may reflect immunosuppression. Astrocyte density is also reduced in pregnancy, while these cells express increased proinflammatory markers. It remains to be clarified exactly how glial changes affect brain remodeling in pregnancy. Possibilities include astrocyte-mediated changes in barrier permeability and microglial phagocytic and synaptic remodeling.

In addition to gestational modifications to the brain's hardware (e.g., circuits and cells), neurotransmitters, themselves potent immunomodulators, are altered across healthy pregnancy and postpartum and in perinatal mood disorders (*6*). Neurotransmitters are released in the brain (e.g., from locus coeruleus/norepinephrine or raphe nucleus/serotonin) but also secreted from peripheral nerve endings, neuroendocrine enterochromaffin cells (serotonin) or adrenal chromaffin cells (norepinephrine). They signal to central and peripheral immune cells that express receptors for neurotransmitters including serotonin, dopamine, norepinephrine, or acetylcholine.

Stimulation by these factors modifies migration, proliferation, cytokine production, antibody production, and other key aspects of immune cell function, which can alter brain function both directly and indirectly (*6*).

Potential pathways include sensing via peripheral afferents (e.g., vagus nerve), signaling of inflammatory and immune markers at the blood-brain barrier, circumventricular organs, meninges, or directly in brain tissue, as well as via direct migration of peripheral (e.g., fetal microchimeric) immune cells into brain. Immune cells also have the capacity to synthesize their own neurotransmitters, potentially in response to neuronal signals. The immune system's sensing of neurotransmitters likely occurs in a niche-specific manner. For example, a brain niche may have a different neurotransmitter profile than a gut, uterine, or blood niche. Within each niche, immune cells likely interact with neurotransmitters derived from different sources (for example, the brain or intestines), sensing, synthesizing, and metabolizing them, resulting in complex, niche-specific phenotypic and functional dynamics (Fig. 1B).

Pregnancy modulation of the autonomic state is another neurobiological adaptation likely sensed by immune cell niches across the body. The balance between sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) autonomous nervous system activity is shifted in pregnancy. Sympathetic activation in pregnancy increases placental perfusion and blood volume via vasoactive mechanisms, to allow for adequate oxygen and nutrient supply to the fetus. In addition to increasing necessary feto-placental perfusion, these same changes may also drive immune cell infiltration of reproductive tissues (*3*). Counter-regulation by the parasympathetic system and its endocrine sensors, including the vagus nerve and cholinergic pathways, may also drive maternal immune tolerance to the fetus and adaptations of the uterine musculature and cervix.

The monoamine hypothesis of depression states that depression is caused by insufficient levels of monoamines, including serotonin, in the brain. Recent evidence, however, shows that the action of antidepressants such as selective serotonin reuptake inhibitors (SSRI) may rely on peripheral mechanisms. Flux in neurotransmitters in the brain and periphery in pregnancy, together with shifts in autonomic state, may unmask mental health conditions in those at-risk and sensitize healthy individuals for insults. Sympathetic activity and stress-axis mechanisms may underlie increased inflammatory risks in perinatal depression (*4*). For example, pregnancy-induced hypertension is associated with enhanced activity of the sympathetic nervous system, while preterm birth is associated with elevated levels of mid-trimester catecholamines, exemplifying physiologic links between obstetric and mental health.

IMMUNE-MEDIATED BEHAVIORAL ADAPTATIONS

The intrinsic neuroendocrine and neurobiological mechanisms discussed above interact with pregnancy adaptations in behavior, which themselves have immune-modifying capacities. Behavioral changes in sleep/wakefulness, dietary habits, physical activity, social behavior, and mood often occur during the transition to motherhood (*7*–*9*). Underlying these are circadian, metabolic, and microbiome mechanisms among others, each of which interacts with immunobiology in revealing ways.

Pregnant humans and mice shift to an earlier internal biological clock chronotype in the first half of pregnancy alongside shifts in the release of circadian factors melatonin and glucocorticoids (*4*, *7*). Chronodisruption, a mismatch between an individual's internal biological clock and its ambient environment, is associated with both obstetric complications such as preterm birth, possibly via cytokine-initiated uterine contractions (*7*), and with mental health disorders. Cytokine release and immune cell activity both respond to circadian factors. The hypothalamic-pituitary-thyroid axis is a powerful neuroendocrine system that is diurnally regulated, functionally changed in pregnancy, and affected by chronodisruption. Hypothyroidism is associated with depression and pregnancy complications. As thyroid hormone levels fluctuate, these changes affect the immune system as the hormone binds to thyroid hormone receptors on immune cells, mediating immune cell state adaptations.

Changes in diet, food aversions and cravings, nutrient supplementation, and altered metabolism both directly (e.g., altered sleep-wake cycles directly change glymphatic drainage and immune cell distribution) and indirectly (e.g., food aversion/cravings alter immunoactive nutrient availability and metabolic microenvironments of immune cell niches) modify immune cell function. Together, these mechanisms link behavioral adaptations in pregnancy to altered immune cell phenotypes and function (*8*). Pregnancy appetite changes are related to decreased insulin sensitivity, altered leptin and glucose, and lipid and protein metabolism changes in the brain and periphery, including in immune cells (*9*). These adaptations may be driven in part by the placenta, which produces leptin, prolactin, and placental lactogen to support nutrient availability to the growing fetus (*9*).

Changes in diet, supplementation, and digestive motility also alter the gut and vaginal microbiomes in pregnancy, which in turn impact plasma metabolite and cytokine levels (*9*). For example, nutritional factors in prenatal vitamins such as vitamin D, iron, and folate modify immune cell function and antibody production. Conversely, food aversion and nausea/vomiting, which may be homeostatic mechanisms to guard against noxious or teratogenic exposures, limit immune-supporting nutrients and increase peripheral inflammation. Extreme nausea and vomiting in pregnancy (hyperemesis gravidarum) is likely driven by placental-brain endocrine signaling, linked to marked proinflammation, and associated with an increased risk for mood disturbances in pregnancy (*9*).

Pregnancy provides a powerful window on immune mediation of mental health in part because of the many complex behavioral changes that interact with peripartum intrinsic neuroendocrine and neurobiological mechanisms, which are themselves immune-modifying. These adaptations can impact mental health by altering immune cell function via shared circadian, metabolic, and microbial mechanisms. Understanding these interactions may reveal promising approaches to improve mental health or buffer against peripartum risk.

SOCIAL DETERMINANTS OF HEALTH AND THE EXPOSOME

Psychosocial adaptation to motherhood is complex and involves aspects of acceptance, motivation, partner and community relationships, self-esteem, sense of control, and more (*1*). These many complex psychosocial adaptations to pregnancy involve behavioral shifts. For instance, some seek increased social support, while others modify social interactions to avoid pathogen exposure (e.g., during the COVID-19 pandemic). Social support increases oxytocin release and reduces immune-response modifying cortisol. Conversely, social withdrawal limits exposure to environmental microbes, viruses,

and other immunologic stimuli which may diversify the maternal immune repertoire.

Social determinants of health such as discrimination and economic hardship are external stressors that may be exacerbated by pregnancy (Fig. 1A) (*1*). The perinatal exposome is a construct that captures additional, non-genetic factors impacting health (e.g., diet, climate, education, socioeconomic status) through processes including weathering, whereby chronic stress accelerates biological age. For example, recent work highlights the role of climate change and associated exposures (e.g., to wildfire pollution, fossil fuel emissions, and particulate matter) in driving maternal systemic proinflammation, risk for mental illness, and adverse birth outcomes. These stressful and proinflammatory exposures may alter HPA axis function, autonomic tone, and inflammatory set points in pregnancy, as discussed above, with critical implications for health equity. Underserved and minority communities often sustain the most substantial exposures in the face of insufficient mitigation and health care resources (*1*).

PREGNANCY'S RESEARCH OPPORTUNITY

Immune cell hubs sense and represent adaptations to pregnancy, occurring across peripheral and central systems. Efforts to better understand the molecular and cellular processes underlying neuroimmune adaptations to pregnancy will yield dividends for improved understanding and treatment of the pathoetiology of both obstetric and psychiatric risk. Cancer biology and the emerging field of cancer neuroscience echo many aspects of the dynamic immune adaptations that occur in pregnancy. Drawing parallels between how the developing feto-placental unit, like a tumor, modulates the host's nervous and immune systems to sustain its growth promises to elucidate targetable pathways to either interfere with cancer progression or boost healthy maternal adaptations to sustain fetal development.

A recent meeting held by the Duke-Margolis Center for Health Policy and the US Food and Drug Administration emphasized the "ethical principle of protecting pregnant people, not from research, but through research." (*10*) As rates of psychiatric disease rise, there is a pressing need for innovative strategies for detection, mitigation, and treatment. Thinking beyond the traditional confines of the brain will offer exciting new insights, and the immune system is a particularly promising frontier. The neuroscience and immunobiology communities should consider pregnancy as a period of great opportunity for scientific discovery, rather than a biological complexity to be brushed aside.

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