Prenatal stress and foetal neurodevelopment: neurobiological mechanisms, developmental consequences, and homeopathic perspectives

Rahul Kumar[*1], T.P. Singh[2], Anju Rani[3], Rajkumar Saini[4]

*[*1]Assistant Professor, Practice of Medicine Department, KGK Homeopathic Medical College, Moradabad, Uttar Pradesh, India*

[2]Medical Officer, KGK Homeopathic Medical College, Moradabad, Uttar Pradesh, India

[3]Homeopathic Medical Officer, Homeopathic Dispensary, Kunderki Bhoor, Amroha, Uttar Pradesh, India

[4]Assistant Professor (Hom. Materia medica), KGK Homeopathic Medical College & Hospital, Moradabad, Uttar Pradesh, India

DOI: 10.5281/zenodo.21624879

Abstract:

Prenatal stress is increasingly recognized as a critical environmental factor capable of influencing foetal brain development and lifelong neurological health. Maternal exposure to psychological, physical, social, or environmental stressors during pregnancy activates complex neuroendocrine, immune, inflammatory, and metabolic pathways that modify the intrauterine environment. These biological alterations affect neuronal proliferation, migration, differentiation, synaptogenesis, myelination, and neural circuit formation during sensitive periods of foetal brain development. Excessive maternal activation of the hypothalamic–pituitary–adrenal (HPA) axis elevates glucocorticoid concentrations, impairs placental regulation, promotes oxidative stress and neuroinflammation, and induces epigenetic modifications that may permanently alter gene expression in the developing foetal brain. Such changes have been associated with an increased risk of neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, depression, cognitive impairment, emotional dysregulation, and schizophrenia. Recent advances in developmental neuroscience have expanded the understanding of prenatal stress beyond endocrine mechanisms, emphasizing the roles of maternal immune activation, placental dysfunction, mitochondrial impairment, gut microbiota alterations, and foetal programming. These interconnected mechanisms influence brain structure and function from early gestation through postnatal life. Consequently, reducing maternal stress has become a major public health priority in prenatal care. Homeopathy has traditionally advocated individualized treatment aimed at improving maternal emotional well-being and promoting holistic health during pregnancy. Although several homeopathic remedies have been used in clinical practice for anxiety, fear, and insomnia, and emotional disturbances, current scientific evidence supporting their effectiveness in preventing adverse foetal neurodevelopmental outcomes remains limited. Therefore, homeopathy should be considered a complementary approach rather than a substitute for evidence-based obstetric and psychological care. This review discusses the current understanding of prenatal stress, its neurobiological mechanisms, developmental consequences, and the potential role of homeopathic perspectives within an integrative maternal healthcare framework.

Keywords:

Prenatal stress, Foetal neurodevelopment, Maternal stress, HPA axis, Placenta, Epigenetics, Neuroinflammation, Homeopathy, Maternal mental health, Developmental programming.

---

1. Introduction:

Pregnancy is a remarkable physiological process characterized by dynamic interactions between the maternal, placental, and foetal systems that ensure optimal growth and development of the unborn child. Throughout

gestation, the developing foetus undergoes rapid structural and functional maturation, particularly within the central nervous system, where billions of neurons are generated, migrate to specific destinations, establish synaptic connections, and form highly organized neural networks. These developmental processes are tightly regulated by genetic programming and environmental influences, and even subtle disturbances during these critical developmental windows may alter brain architecture and predispose offspring to neurological and psychiatric disorders later in life. The sequential stages of normal foetal brain development and their temporal progression are illustrated in Figure 1 (Thomason & Hendrix, 2024). The figure 1 illustrates the major stages of foetal brain development from conception to birth, including neural tube formation, neurogenesis, neuronal migration, differentiation, synaptogenesis, gliogenesis, myelination, and early neural circuit formation. These stages represent critical periods during which maternal stress can significantly influence neurodevelopmental programming.

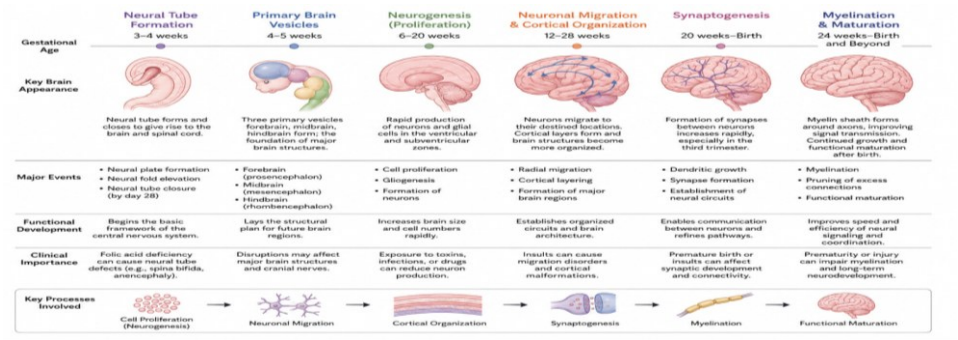

Figure. 1: Overview of Normal Foetal Brain Development During Pregnancy

Prenatal stress has emerged as one of the most extensively studied environmental influences affecting foetal development. It refers to the physiological and psychological responses generated when pregnant women experience adverse life events or chronic stressors that exceed their adaptive capacity. Sources of prenatal stress include anxiety, depression, domestic violence, financial hardship, occupational pressure, environmental pollution, infections, nutritional deficiencies, social isolation, natural disasters, and pregnancy-related complications. While transient activation of maternal stress pathways is considered a normal adaptive response, persistent or excessive stress may disrupt the finely balanced intrauterine environment and adversely influence foetal development (Lautarescu et al., 2020). The concept that prenatal environmental exposures shape lifelong health is explained by the Developmental Origins of Health and Disease (DOHaD) hypothesis. According to this theory, environmental conditions during sensitive developmental periods permanently influence organ structure, physiological function, and disease susceptibility. During pregnancy, maternal stress activates neuroendocrine and immune pathways that modify placental function, alter nutrient transport, and increase foetal exposure to glucocorticoids and inflammatory mediators. These alterations induce developmental adaptations that may enhance immediate foetal survival but increase vulnerability to chronic diseases during childhood and adulthood (Monk et al., 2019). Over the past decade, advances in developmental neuroscience have significantly improved understanding of how prenatal stress affects the developing brain. Modern neuroimaging studies have demonstrated structural alterations in the hippocampus, amygdala, prefrontal cortex, corpus callosum, and cerebellum among children exposed to high maternal stress during gestation. Functional imaging has further revealed abnormalities in emotional regulation, cognitive processing, executive functioning, and stress responsiveness that may persist throughout life (Van den Bergh et al., 2020). Rather than acting through a single biological pathway, prenatal stress exerts its effects through an intricate network of neuroendocrine, immune, inflammatory, vascular, metabolic, and epigenetic mechanisms. Chronic activation of the maternal hypothalamic–pituitary–adrenal (HPA) axis increases circulating cortisol concentrations. Simultaneously, inflammatory cytokines, oxidative stress, placental dysfunction, altered neurotransmitter synthesis, mitochondrial impairment, and epigenetic modifications collectively influence neuronal development and neural connectivity. The interrelationship between maternal stress, placental function, and foetal brain development is summarized in Fig.2, it illustrates the biological pathways linking maternal psychological stress to foetal neurodevelopment. Maternal stress activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, increasing cortisol and catecholamine secretion. Elevated glucocorticoids, inflammatory cytokines, oxidative stress, and altered placental enzyme activity influence neuronal proliferation, migration, synaptogenesis, and brain maturation. Recognition of prenatal stress as a modifiable risk factor has important implications for preventive healthcare. Early identification of maternal psychological distress, implementation of psychosocial interventions, nutritional optimization, and provision of supportive prenatal care may reduce adverse developmental outcomes.

Integrative approaches, including complementary therapies such as homeopathy, have also attracted interest for promoting maternal emotional well-being, however, current evidence supporting their role in improving foetal neurodevelopment remains limited and requires further high-quality clinical investigation (Matas-Blanco & Caparrós-González, 2020).

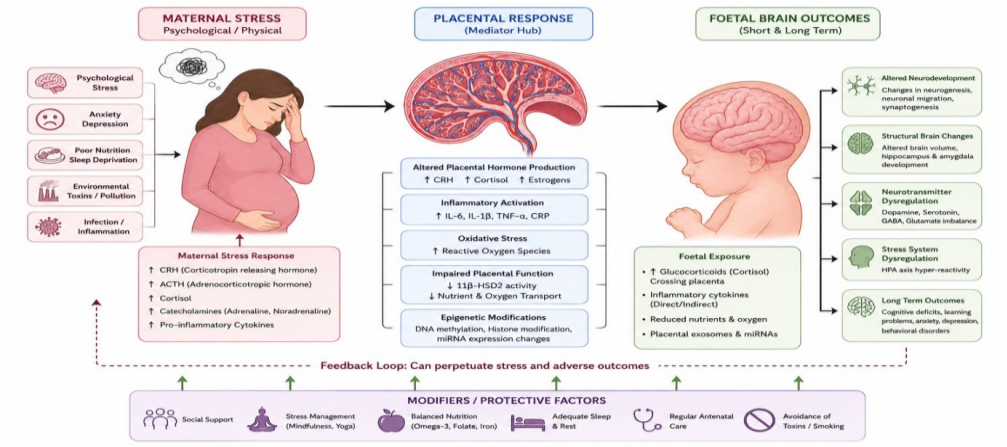

Figure. 2: Maternal Stress–Placenta–Foetal Brain Axis

2. Foetal neurodevelopment during pregnancy:

The human brain is the earliest developing and one of the most complex organs of the body. Its development begins approximately three weeks after conception with the formation of the neural plate, which subsequently folds to form the neural tube. Closure of the neural tube marks the establishment of the primitive central nervous system and serves as the foundation for future brain and spinal cord development. Neural tube formation is highly dependent upon appropriate maternal nutrition, adequate folate availability, genetic regulation, and optimal intrauterine conditions (Stiles & Jernigan, 2016, Molnár et al., 2019). Following neural tube closure, extensive neurogenesis occurs within the ventricular zone, producing billions of neurons through tightly regulated mitotic activity. During peak neurogenesis, an extraordinary number of neurons are generated and subsequently migrate toward predetermined cortical regions with the assistance of radial glial cells, establishing the characteristic six-layered cerebral cortex. Accurate neuronal migration is essential because even minor disruptions may result in abnormal cortical organization, impaired neuronal connectivity, and long-term neurological dysfunction (Silbereis et al., 2016, Bystron et al., 2017). Neuronal differentiation enables immature neurons to acquire specialized structural and functional properties required for neurotransmission. During this period, axons elongate toward target tissues while dendritic arborization increases synaptic surface area. Synaptogenesis establishes trillions of synaptic connections that form the basis of cognition, memory, sensory processing, emotional regulation, language development, and motor coordination. Simultaneously, astrocytes, oligodendrocytes, and microglia develop to support neuronal metabolism, immune surveillance, neurotransmitter recycling, and myelination (Molnár et al., 2020, Tau & Peterson, 2020). The final stages of prenatal brain development involve rapid myelination and refinement of neural circuits. Although myelination continues into early adulthood, substantial maturation occurs during late gestation and infancy. Programmed synaptic pruning eliminates redundant neuronal connections while strengthening frequently utilized pathways, thereby enhancing neural efficiency and cognitive performance. Because these developmental events occur sequentially during distinct gestational periods, disruption at different stages produces unique neurodevelopmental consequences (Semple et al., 2018, Dean et al., 2021). The developing brain exhibits remarkable plasticity but is simultaneously highly vulnerable to adverse environmental influences. Maternal nutrition, endocrine regulation, placental perfusion, oxygen availability, inflammatory status, and psychological health collectively determine the quality of the intrauterine environment. Consequently, maternal stress experienced during pregnancy may influence every stage of neurodevelopment, from early neurogenesis to postnatal synaptic refinement. The principal stages of foetal brain development and their vulnerability to prenatal stress are summarized in Table 1.

Table. 1: Major Stages of Foetal Brain Development and Their Vulnerability to Prenatal Stress

Gestational Period	Major Neurodevelopmental Event	Potential Influence of Prenatal Stress
3–4 weeks	Neural tube formation	Increased risk of neural developmental abnormalities

5–8 weeks	Neurogenesis	Reduced neuronal proliferation
8–20 weeks	Neuronal migration	Cortical disorganization and altered connectivity
20–30 weeks	Synaptogenesis	Impaired synaptic maturation
Third trimester	Gliogenesis and early myelination	Delayed white matter development
Birth to infancy	Synaptic pruning	Long-term cognitive and behavioural alterations

3. Prenatal stress: types, sources and biological significance:

Prenatal stress encompasses a broad spectrum of maternal experiences that activate physiological stress responses during pregnancy. Stress may be acute, resulting from sudden traumatic events, or chronic, arising from persistent socioeconomic, occupational, psychological, or medical challenges. The intensity, duration, timing, and maternal perception of stress determine the magnitude of biological responses and subsequent effects on foetal development (Van den Bergh et al., 2020, Monk et al., 2019). Psychological stress remains the most frequently investigated form of prenatal stress and includes generalized anxiety, depression, panic disorders, fear of childbirth, marital conflict, bereavement, domestic violence, and previous traumatic experiences. Biological stressors include maternal obesity, gestational diabetes mellitus, hypertensive disorders of pregnancy, chronic inflammatory diseases, infections, autoimmune disorders, nutritional deficiencies, sleep deprivation, and chronic pain, while environmental stressors such as air pollution, excessive noise, heat exposure, tobacco smoke, heavy metals, pesticides, and endocrine-disrupting chemicals further contribute to adverse pregnancy outcomes (Lautarescu et al., 2020, Glover et al., 2018). Social determinants of health also exert profound influences on maternal stress, as financial insecurity, unemployment, food insecurity, inadequate social support, migration, discrimination, humanitarian crises, and limited access to healthcare significantly increase psychological distress during pregnancy. The COVID-19 pandemic further highlighted the global burden of prenatal stress by increasing anxiety related to infection risk, social isolation, disrupted healthcare services, and economic uncertainty among pregnant women (Caparros-Gonzalez & Alderdice, 2020, Lebel et al., 2020). Importantly, maternal stress responses vary considerably between individuals. Genetic predisposition, resilience, personality traits, coping strategies, previous life experiences, family support, and cultural influences determine the degree of neuroendocrine activation following stressful experiences. Consequently, women exposed to similar external stressors may exhibit markedly different physiological responses and pregnancy outcomes (Beijers et al., 2019, O'Donnell & Meaney, 2017). Experimental animal models and human observational studies consistently demonstrate that chronic maternal stress alters endocrine regulation, immune function, placental physiology, and foetal neurodevelopment through dysregulation of the hypothalamic–pituitary–adrenal axis, inflammatory pathways, oxidative stress, and epigenetic modifications. These findings support the concept that prenatal stress represents a major modifiable determinant of long-term neurological health (Davis & Sandman, 2020, Zhang et al., 2022). As research in developmental neuroscience has advanced, increasing attention has focused on understanding the biological mechanisms responsible for these associations. The critical developmental windows during which prenatal stress may differentially influence foetal brain maturation are illustrated in Figure 3, Timeline demonstrating the major stages of foetal neurodevelopment and highlighting sensitive periods during which maternal stress may affect neurogenesis, neuronal migration, synaptogenesis, gliogenesis, myelination, and neural circuit formation. The timing, intensity, and duration of stress exposure influence the nature and severity of neurodevelopmental outcomes.

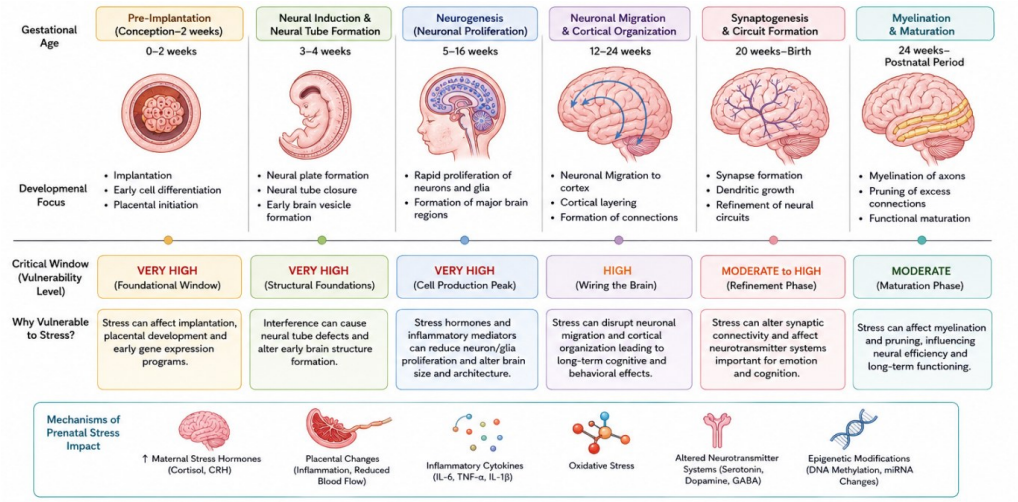

Figure. 3: Critical Windows of Foetal Brain Vulnerability to Prenatal Stress

4. Maternal hypothalamic–pituitary–adrenal (Hpa) axis activation and foetal programming:

The maternal hypothalamic–pituitary–adrenal (HPA) axis represents the principal neuroendocrine system responsible for coordinating physiological responses to stress. Under normal circumstances, exposure to physical or psychological stress activates the hypothalamus, stimulating the release of corticotropin-releasing hormone (CRH), which subsequently induces the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH stimulates the adrenal cortex to produce glucocorticoids, primarily cortisol, enabling the maternal body to adapt to stressful conditions by regulating metabolism, cardiovascular function, immune responses, and energy mobilization. During pregnancy, physiological activation of the HPA axis is essential for normal foetal maturation, lung development, and preparation for parturition, however, chronic or excessive activation can disrupt the intrauterine environment and adversely affect foetal brain development. Emerging evidence indicates that prenatal stress influences offspring neurodevelopment through complex interactions among endocrine, immune, placental, inflammatory, and psychosocial pathways rather than through cortisol alone (Van den Bergh et al., 2020, Davis & Sandman, 2020). Maternal cortisol concentrations normally increase progressively throughout pregnancy due to placental production of CRH, and under healthy physiological conditions this increase contributes to normal foetal growth and maturation. Nevertheless, chronic psychological stress, anxiety, depression, or repeated exposure to adverse life events may further amplify maternal cortisol secretion beyond normal physiological levels, increasing the likelihood of excessive foetal glucocorticoid exposure, particularly when placental protective mechanisms become compromised (Lautarescu et al., 2020, O'Donnell & Meaney, 2017). Excessive glucocorticoid exposure during sensitive developmental periods may impair neuronal proliferation, neuronal migration, dendritic arborization, synapse formation, and neural plasticity, thereby modifying the structural and functional organization of the developing brain. Both experimental and human studies further suggest that the gestational timing, duration, and severity of maternal stress determine which neurodevelopmental processes are most vulnerable, influencing later cognitive, behavioural, and emotional outcomes in the offspring (Monk et al., 2019, Zhang et al., 2022). As the maternal HPA axis serves as the principal biological link between maternal stress and foetal development, its major components and downstream effects are illustrated in Figure 4, it depicting activation of the maternal hypothalamic–pituitary–adrenal (HPA) axis following psychological or physical stress. Maternal stress stimulates hypothalamic corticotropin-releasing hormone (CRH) release, followed by pituitary adrenocorticotropic hormone (ACTH) secretion and adrenal cortisol production. Elevated cortisol influences placental physiology, immune regulation, foetal endocrine function, and neurodevelopment.

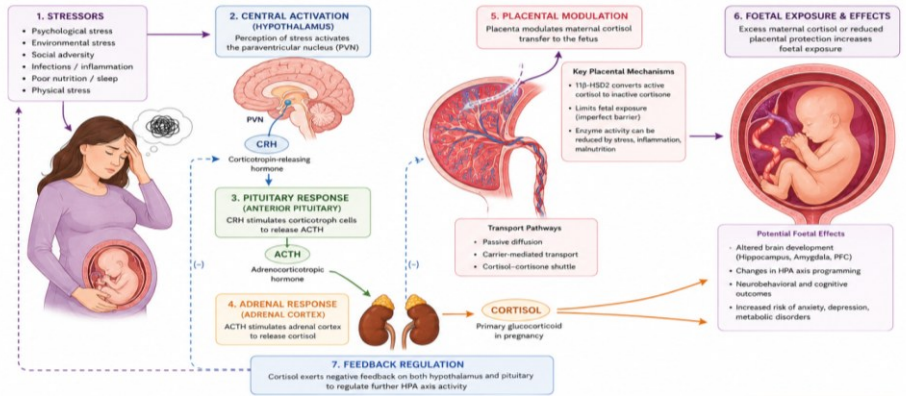

Figure. 4: Maternal HPA Axis Activation during Pregnancy

5. Placental regulation of maternal stress signals:

The placenta is a multifunctional organ that not only transports oxygen and nutrients but also acts as an endocrine, metabolic, and immunological interface between the mother and the foetus. Rather than allowing unrestricted transfer of maternal glucocorticoids, the placenta regulates foetal exposure through the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts biologically active cortisol into inactive cortisone and thereby protects the developing foetal brain from excessive glucocorticoid exposure (Glover et al., 2018, O'Donnell & Meaney, 2017). Persistent maternal stress has been associated with reduced expression or activity of placental 11β-HSD2, resulting in increased transfer of active cortisol into the foetal circulation. In addition to altered glucocorticoid metabolism, prenatal stress may impair uteroplacental blood flow, modify nutrient and oxygen transport, influence placental angiogenesis, increase oxidative stress, and alter the production of inflammatory cytokines and placental hormones, thereby affecting foetal growth, metabolic homeostasis, and brain maturation (Bronson & Bale, 2016, Davis & Sandman, 2020). Emerging evidence further indicates that the placenta functions as an active biosensor of the maternal environment by detecting psychological and physiological stress signals and transmitting them to the developing foetus through endocrine, immune, epigenetic, and molecular signaling pathways. These adaptive placental responses contribute to developmental programming and may influence long-term neurodevelopmental outcomes, including cognitive function, emotional regulation, and susceptibility to neuropsychiatric disorders (Lautarescu et al., 2020, Van den Bergh et al., 2020). The protective role of the placenta in regulating foetal glucocorticoid exposure and the consequences of impaired placental function during chronic maternal stress are illustrated in Fig. 5, showing the protective function of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in converting maternal cortisol into inactive cortisone. Chronic maternal stress may reduce enzyme activity, thereby increasing foetal glucocorticoid exposure and influencing neuronal proliferation, synaptogenesis, neural differentiation, and brain maturation.

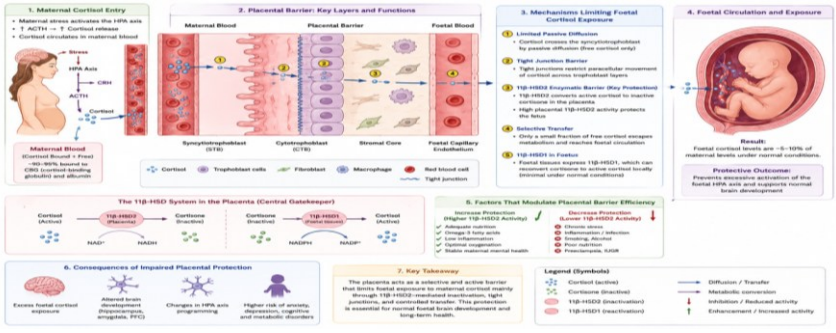

Figure. 5: Placental Barrier and Regulation of Foetal Cortisol Exposure

6. Neurobiological mechanisms linking prenatal stress and foetal neurodevelopment:

Prenatal stress affects the developing brain through multiple interconnected biological pathways rather than a single isolated mechanism. Endocrine, immune, inflammatory, vascular, metabolic, oxidative, and epigenetic processes interact continuously throughout gestation, creating a complex network that influences brain development and explains why similar maternal stress exposures may produce different neurodevelopmental outcomes among individual offspring (Van den Bergh et al., 2020, Davis & Sandman, 2020). One of the earliest consequences of prenatal stress involves altered neurogenesis, as excessive glucocorticoid exposure suppresses the proliferation of neural progenitor cells within the ventricular and subventricular zones, thereby

reducing the number of neurons available for normal cortical development and hippocampal formation. Because the hippocampus contains a high density of glucocorticoid receptors, it is particularly vulnerable to stress-induced alterations that may subsequently affect learning, memory, and stress regulation (Lautarescu et al., 2020, Zhang et al., 2022). Prenatal stress also interferes with neuronal migration, a tightly regulated developmental process during which newly generated neurons migrate to their appropriate cortical destinations. Disturbances in this process may result in subtle abnormalities in cortical layering, altered neural connectivity, and impaired information processing, contributing to long-term cognitive and behavioural dysfunction despite the absence of gross anatomical abnormalities (Silbereis et al., 2016, Molnár et al., 2020). In addition, prenatal stress disrupts synaptogenesis by altering the expression of synaptic proteins, reducing dendritic arborization, and modifying neural network formation, thereby impairing synaptic plasticity, learning capacity, memory consolidation, emotional regulation, and executive functioning during later life (Tau & Peterson, 2020, Monk et al., 2019). Increasing evidence further suggests that prenatal stress adversely affects white matter maturation because oligodendrocyte precursor cells responsible for myelin production are highly sensitive to inflammatory mediators, oxidative stress, and glucocorticoids. Consequently, excessive maternal stress may delay myelination, reduce white matter integrity, and impair neural transmission speed, while neuroimaging studies have demonstrated alterations in white matter microstructure within neural pathways responsible for cognition, emotional regulation, and behavioural control in children exposed to elevated prenatal stress during gestation (Dean et al., 2021, Thomason & Hendrix, 2024). The principal biological pathways linking maternal stress with altered foetal neurodevelopment are summarized in Table 2.

Table. 2: Major Neurobiological Mechanisms Linking Prenatal Stress with Foetal Neurodevelopment

Mechanism	**Biological Change**	**Potential Neurodevelopmental Outcome**
HPA-axis activation	Elevated maternal cortisol	Altered neuronal proliferation
Placental dysfunction	Reduced 11β-HSD2 activity	Increased foetal cortisol exposure
Maternal immune activation	Increased inflammatory cytokines	Neuroinflammation
Oxidative stress	Excess reactive oxygen species	Cellular injury and mitochondrial dysfunction
Epigenetic modification	DNA methylation and histone changes	Altered lifelong gene expression
Neurotransmitter imbalance	Serotonin and dopamine dysregulation	Emotional and behavioural disorders
Impaired synaptogenesis	Reduced synaptic plasticity	Learning and memory deficits

7. Epigenetic modifications and developmental programming:

Epigenetics has emerged as one of the most important mechanisms explaining how prenatal stress produces long-lasting biological effects without altering the DNA sequence itself. Epigenetic regulation includes DNA methylation, histone modification, chromatin remodeling, and microRNA-mediated gene regulation, all of which influence whether specific genes remain transcriptionally active or inactive during critical stages of foetal development (Babenko et al., 2016, Vaiserman & Koliada, 2017). Maternal stress may induce persistent epigenetic alterations in genes involved in glucocorticoid signaling, neuronal differentiation, immune regulation, neuroplasticity, and synaptic function, thereby modifying developmental pathways that regulate brain maturation and stress responsiveness. Altered DNA methylation of genes associated with the hypothalamic–pituitary–adrenal (HPA) axis, particularly those regulating glucocorticoid receptor expression, has been associated with long-term changes in endocrine regulation, emotional behaviour, cognitive function, and susceptibility to neurodevelopmental and psychiatric disorders later in life (O'Donnell & Meaney, 2017, Van den Bergh et al., 2020). Increasing evidence also suggests that prenatal stress influences the expression of multiple microRNAs involved in neuronal proliferation, migration, axonal growth, synaptogenesis, and neuroinflammation, further contributing to altered brain development and developmental programming (Lautarescu et al., 2020, Zhang et al., 2022). Importantly, epigenetic responses are dynamic and appear to be influenced by the timing, intensity, and duration of maternal stress exposure, as well as maternal nutrition,

genetic susceptibility, placental function, and postnatal environmental factors, highlighting the complex interaction between inherited and environmental influences during early neurodevelopment (Monk et al., 2019, Davis & Sandman, 2020).

8. Maternal Immune Activation and Neuroinflammation:

Psychological stress is increasingly recognized as an immunological stressor because chronic maternal stress activates the innate immune system and increases circulating concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). These inflammatory mediators influence placental physiology by altering endocrine signaling, vascular function, and nutrient transport, thereby indirectly affecting the developing foetal brain (Estes & McAllister, 2016, Van den Bergh et al., 2020). Within the foetal central nervous system, excessive inflammatory signaling can activate microglia, the resident immune cells responsible for synaptic pruning, neuronal maturation, immune surveillance, and maintenance of neural homeostasis. Although physiological microglial activity is essential for normal brain development, prolonged or excessive activation may disrupt synaptic refinement, impair neurogenesis, alter neuronal connectivity, and interfere with neural circuit formation, thereby increasing susceptibility to long-term neurodevelopmental abnormalities (Bilbo et al., 2018, Lautarescu et al., 2020). Maternal immune activation has also been associated with increased oxidative stress, mitochondrial dysfunction, and altered neurotransmitter signaling, all of which contribute to abnormal cortical development and impaired neuroplasticity. Consequently, neuroinflammation has become a major focus of developmental neuroscience research because accumulating evidence indicates that inflammatory pathways contribute to the pathogenesis of autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety disorders, schizophrenia, and other neuropsychiatric conditions (Knuesel et al., 2018, Zhang et al., 2022). Current evidence suggests that maternal immune activation represents one of several converging biological pathways through which prenatal stress influences foetal neurodevelopment, interacting closely with endocrine, placental, epigenetic, and environmental mechanisms to shape lifelong neurological health (Monk et al., 2019, Davis & Sandman, 2020).

9. Oxidative Stress and Mitochondrial Dysfunction:

Oxidative stress represents another important mechanism through which prenatal stress may affect foetal neurodevelopment. Under physiological conditions, reactive oxygen species (ROS) participate in normal cellular signaling, neuronal differentiation, and developmental processes, however, excessive production of ROS combined with reduced antioxidant defenses results in oxidative damage to lipids, proteins, and nucleic acids, thereby disrupting normal cellular homeostasis (Benedetti et al., 2020, Burton & Jauniaux, 2018). The developing brain is particularly vulnerable to oxidative injury because of its high oxygen consumption, abundance of polyunsaturated fatty acids, rapid metabolic activity, and relatively immature antioxidant systems. Excessive oxidative stress may impair mitochondrial function, reduce adenosine triphosphate (ATP) production, alter neuronal differentiation and synaptic plasticity, damage cellular membranes, and increase neuronal susceptibility to apoptosis, ultimately compromising normal brain development (Dean et al., 2021, Lautarescu et al., 2020). Mitochondrial dysfunction further amplifies inflammatory responses by increasing ROS generation and activating pro-inflammatory signaling pathways, thereby creating a self-perpetuating cycle of oxidative injury, neuroinflammation, and impaired neurodevelopment (Monk et al., 2019, Zhang et al., 2022). Emerging evidence indicates that oxidative stress interacts closely with glucocorticoid excess, placental dysfunction, immune activation, and epigenetic regulation, collectively influencing neuronal proliferation, migration, synaptogenesis, myelination, and neural circuit maturation during critical periods of gestation. The integrated relationship between endocrine activation, placental dysfunction, immune signaling, oxidative stress, mitochondrial impairment, and epigenetic regulation is illustrated in Figure 6, it showing how maternal stress activates the hypothalamic–pituitary–adrenal (HPA) axis, immune system, oxidative stress pathways, placental dysfunction, mitochondrial impairment, and epigenetic regulation. Together, these interconnected mechanisms influence neuronal proliferation, migration, synaptogenesis, myelination, and neural circuit maturation, thereby affecting lifelong neurological, cognitive, and behavioural outcomes.

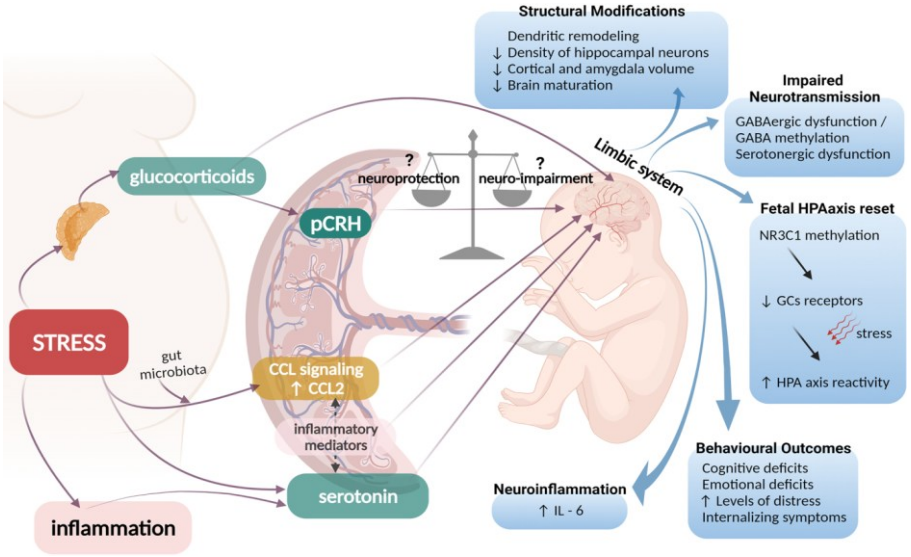

Figure. 6: Integrated Neurobiological Mechanisms Linking Prenatal Stress to Foetal Brain Development

10. Structural and functional changes in the developing foetal brain following prenatal stress:

The foetal brain undergoes rapid structural and functional maturation throughout pregnancy, making it particularly susceptible to alterations in the intrauterine environment. Prenatal stress influences multiple developmental processes simultaneously, resulting in subtle but significant changes in brain morphology, neural connectivity, and functional organization. Rather than producing gross anatomical abnormalities in most cases, maternal stress commonly induces microscopic alterations in neuronal architecture that may influence behaviour, cognition, emotional regulation, and stress responsiveness throughout life. The magnitude of these changes depends on several factors, including the timing, intensity, and duration of maternal stress, genetic susceptibility, placental function, and postnatal environmental influences (Van den Bergh et al., 2020, Lautarescu et al., 2020). Neuroimaging studies have consistently demonstrated that offspring exposed to elevated maternal stress during gestation exhibit differences in the volume and connectivity of several brain regions, including the hippocampus, amygdala, prefrontal cortex, anterior cingulate cortex, corpus callosum, cerebellum, and major white matter tracts. These structures collectively regulate memory, executive function, emotional processing, social behaviour, attention, and adaptive responses to environmental stressors, and their altered development may increase the risk of childhood neurodevelopmental disorders and adult psychiatric illnesses (Qiu et al., 2017, Thomason & Hendrix, 2024). The hippocampus, which plays a central role in learning, memory consolidation, and regulation of the hypothalamic–pituitary–adrenal (HPA) axis, contains one of the highest densities of glucocorticoid receptors in the brain. Excessive prenatal exposure to cortisol may suppress hippocampal neurogenesis, reduce dendritic complexity, impair synaptic plasticity, and contribute to relatively smaller hippocampal volumes observed in some children exposed to chronic maternal stress, indicating that early endocrine disturbances may produce persistent structural adaptations (Davis & Sandman, 2020, O'Donnell & Meaney, 2017). The amygdala, another highly stress-sensitive brain region responsible for emotional processing, fear learning, and social behaviour, undergoes substantial maturation during late gestation. Prenatal stress has been associated with altered amygdala connectivity, increased emotional reactivity, anxiety-like behaviour, and heightened stress sensitivity during childhood, while functional magnetic resonance imaging studies have demonstrated abnormal communication between the amygdala and prefrontal cortex, potentially explaining impaired emotional regulation among stress-exposed offspring (Monk et al., 2019, Posner et al., 2016). The prefrontal cortex, which governs executive functioning, decision-making, impulse control, attention, and cognitive flexibility, continues to mature well beyond birth, however, prenatal environmental influences establish the foundational organization of cortical networks. Excessive maternal stress may reduce cortical thickness, alter neuronal maturation, impair functional connectivity, and disrupt white matter development, thereby increasing vulnerability to cognitive impairment, behavioural disorders, and emotional dysregulation throughout life (Van den Bergh et al., 2020, Zhang et al., 2022). Because several interconnected brain regions are simultaneously affected, prenatal stress influences overall neural network organization rather than isolated structures. The principal structural and functional brain alterations associated with prenatal stress are illustrated in Figure 7, depicting the major regions of the developing brain affected by prenatal stress, including the hippocampus, amygdala, prefrontal cortex, cerebellum, corpus callosum, and white matter tracts. Chronic maternal stress may alter neuronal proliferation,

synaptic plasticity, myelination, functional connectivity, and emotional regulation, thereby increasing susceptibility to neurodevelopmental and neuropsychiatric disorders.

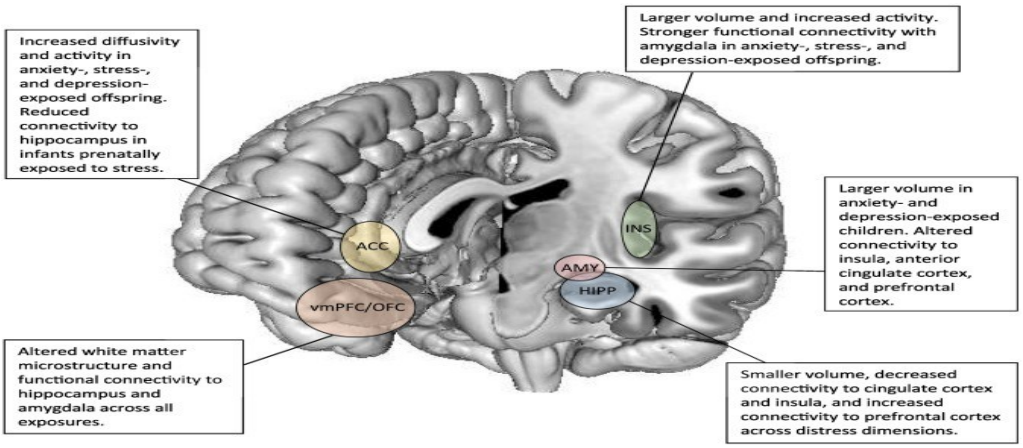

Figure. 7: Structural and Functional Brain Changes Associated with Prenatal Stress

11. Neurotransmitter alterations in prenatal stress:

Proper neurodevelopment depends upon tightly regulated synthesis, release, and signaling of neurotransmitters that coordinate neuronal differentiation, migration, synapse formation, and neural circuit maturation. Prenatal stress influences several neurotransmitter systems, including serotonin, dopamine, gamma-aminobutyric acid (GABA), glutamate, norepinephrine, and acetylcholine, and disturbances within these systems may have long-lasting consequences for cognition, emotional behaviour, and susceptibility to neurodevelopmental and psychiatric disorders (Lautarescu et al., 2020, Van den Bergh et al., 2020). Serotonin functions not only as a neurotransmitter but also as an essential developmental signaling molecule during embryogenesis by regulating neuronal proliferation, migration, axonal guidance, synaptogenesis, and cortical circuit formation. Maternal stress may alter placental serotonin synthesis and foetal serotonergic signaling, thereby affecting cortical development, emotional regulation, and social behaviour, with abnormal serotonergic activity being associated with anxiety disorders, depression, and autism spectrum disorder (Goeden et al., 2016, Monk et al., 2019). Dopamine plays a fundamental role in reward processing, attention, executive functioning, motivation, and motor control, and prenatal glucocorticoid exposure may alter dopaminergic neuron maturation, dopamine receptor expression, and neurotransmission within the mesocorticolimbic pathway. These alterations have been linked to impaired attention, impulsivity, hyperactivity, and an increased susceptibility to attention-deficit/hyperactivity disorder (ADHD) and other behavioural disorders (Davis & Sandman, 2020, O'Donnell & Meaney, 2017). Glutamate and GABA serve as the principal excitatory and inhibitory neurotransmitters of the central nervous system, respectively, and maintaining an appropriate balance between these signaling systems is essential for normal cortical development, synaptic refinement, and neural network stability. Prenatal stress may disrupt this excitatory–inhibitory balance by altering glutamatergic and GABAergic signaling, impairing synaptic plasticity and cortical maturation, and thereby increasing vulnerability to epilepsy, anxiety disorders, autism spectrum disorder, schizophrenia, and cognitive dysfunction later in life (Zhang et al., 2022, Thomason & Hendrix, 2024).

12. Long-term developmental consequences of prenatal stress:

Accumulating evidence indicates that prenatal stress produces effects extending far beyond the neonatal period. Instead of causing immediate neurological impairment alone, prenatal stress modifies developmental trajectories that continue throughout infancy, childhood, adolescence, and adulthood, with these long-term outcomes reflecting complex interactions among prenatal programming, postnatal environment, family support, education, nutrition, and genetic susceptibility (Van den Bergh et al., 2020, Davis & Sandman, 2020). One of the earliest observable consequences involves delayed achievement of developmental milestones, as infants exposed to elevated maternal stress may exhibit altered temperament, excessive crying, sleep disturbances, feeding difficulties, impaired self-regulation, and increased physiological stress reactivity (Lautarescu et al., 2020, Beijers et al., 2019). During early childhood, these children may demonstrate language delays, impaired attention, reduced cognitive flexibility, deficits in executive functioning, and difficulties with emotional regulation and adaptive behaviour, potentially affecting school readiness and social development (Monk et al., 2019, Zhang et al., 2022). School-aged children exposed to chronic prenatal stress have been reported to experience poorer academic performance, reduced working memory, impaired learning ability,

behavioural difficulties, attention deficits, and impaired peer relationships, while longitudinal cohort studies further suggest an increased susceptibility to mood disorders, anxiety disorders, depression, substance use disorders, and chronic stress-related illnesses extending into adolescence and adulthood (O'Donnell & Meaney, 2017, Thomason & Hendrix, 2024). Importantly, prenatal stress should not be interpreted as the sole determinant of neurodevelopmental disorders but rather as one of several interacting biological, genetic, environmental, and psychosocial risk factors that collectively influence developmental outcomes. Positive parenting, early developmental interventions, enriched educational environments, optimal nutrition, responsive caregiving, and strong family and community support can substantially enhance neurodevelopmental resilience and improve long-term cognitive, behavioural, and emotional outcomes despite prenatal adversity (Dunkel Schetter & Tanner, 2017, Van den Bergh et al., 2020).

13. Prenatal stress and autism spectrum disorder:

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent impairments in social communication, restricted interests, and repetitive patterns of behaviour. Although ASD has a substantial genetic basis, accumulating evidence indicates that prenatal environmental exposures also contribute to disease susceptibility through complex interactions with genetic predisposition and developmental programming (Lord et al., 2020, Modabbernia et al., 2017). Maternal stress during pregnancy has been proposed as one of several environmental factors that may increase the risk of ASD by influencing critical neurodevelopmental processes. Chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, maternal immune activation, oxidative stress, placental dysfunction, altered endocrine signaling, and epigenetic modifications may collectively disrupt cortical development, synaptic organization, neuronal connectivity, and neural circuits involved in social cognition and behavioural regulation (Estes & McAllister, 2016, Van den Bergh et al., 2020). Elevated maternal inflammatory cytokines, particularly interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), have been associated with abnormal microglial activation and altered synaptic pruning during sensitive developmental periods, potentially contributing to atypical brain maturation observed in some individuals with ASD (Knuesel et al., 2018, Lautarescu et al., 2020). However, current evidence indicates that prenatal stress alone is insufficient to cause autism and should not be regarded as an independent causal factor. Instead, prenatal stress appears to increase neurodevelopmental vulnerability among genetically susceptible individuals while interacting with numerous additional prenatal, perinatal, and postnatal biological and environmental influences. Consequently, preventive strategies should emphasize comprehensive maternal healthcare, including psychological support, optimal nutrition, management of medical conditions, reduction of environmental risk factors, and early developmental surveillance rather than focusing exclusively on maternal psychological stress (Monk et al., 2019, Lord et al., 2020).

14. Prenatal stress and attention-deficit/hyperactivity disorder:

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by persistent patterns of inattention, impulsivity, and hyperactivity that interfere with academic performance, social relationships, and daily functioning. Numerous epidemiological and longitudinal studies have reported associations between elevated maternal anxiety, psychological distress, or chronic stress during pregnancy and an increased prevalence of ADHD-related symptoms among offspring, suggesting that prenatal stress may contribute to altered neurodevelopment during critical periods of brain maturation (Van den Bergh et al., 2020, Lautarescu et al., 2020). Several biological mechanisms have been proposed to explain this association, including disrupted dopaminergic neurotransmission, impaired maturation of the prefrontal cortex, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reduced white matter integrity, oxidative stress, neuroinflammation, and epigenetic modifications affecting genes involved in attention regulation, executive functioning, and behavioural control (Davis & Sandman, 2020, O'Donnell & Meaney, 2017). Excessive prenatal glucocorticoid exposure may further alter neuronal differentiation, synaptic plasticity, and connectivity within cortical and subcortical brain regions responsible for executive functioning, impulse control, working memory, and behavioural inhibition, thereby increasing susceptibility to attentional and behavioural difficulties later in life (Monk et al., 2019, Thomason & Hendrix, 2024). Nevertheless, ADHD remains a highly multifactorial disorder influenced by genetic predisposition, prenatal and postnatal environmental exposures, socioeconomic conditions, parenting practices, nutrition, educational opportunities, and early childhood experiences. Therefore, prenatal stress should be regarded as one contributing developmental risk factor within a broader multifactorial framework rather than as a direct or independent cause of ADHD (Faraone et al., 2021, Van den Bergh et al., 2020).

15. Anxiety, depression and emotional dysregulation:

Prenatal stress has consistently been associated with an increased vulnerability to anxiety disorders, depression, and emotional dysregulation across the lifespan. Children exposed to elevated maternal psychological stress during gestation frequently exhibit heightened fear responses, behavioural inhibition, emotional instability, increased stress sensitivity, and impaired coping abilities, with many of these behavioural characteristics persisting into adolescence and adulthood (Van den Bergh et al., 2020, Monk et al., 2019). One of the principal neurobiological explanations for these findings is altered structural and functional connectivity among the amygdala, hippocampus, and prefrontal cortex, brain regions that collectively regulate emotional processing, memory, executive function, and adaptive stress responses. In addition, dysregulation of serotonergic neurotransmission, persistent hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, chronic low-grade inflammation, oxidative stress, and stress-induced epigenetic modifications contribute to altered emotional regulation and increased susceptibility to psychiatric disorders (Davis & Sandman, 2020, Lautarescu et al., 2020). Longitudinal birth cohort studies further suggest that maternal stress experienced during pregnancy may influence offspring stress responsiveness decades later, with individuals prenatally exposed to chronic stress often demonstrating exaggerated cortisol responses, impaired physiological resilience, increased anxiety sensitivity, reduced emotional adaptability, and a greater risk of developing depressive and anxiety disorders following subsequent life stressors (O'Donnell & Meaney, 2017, Thomason & Hendrix, 2024). These findings support the concept that prenatal stress contributes to long-term emotional and psychological health through developmental programming of neuroendocrine, neural, and immune regulatory systems, although the ultimate clinical outcome remains strongly influenced by genetic predisposition, early-life experiences, family environment, and psychosocial support (Fava et al., 2019, Van den Bergh et al., 2020).

16. Cognitive, learning and behavioural outcomes:

Cognitive development represents another important domain influenced by prenatal stress, with numerous observational and longitudinal studies reporting associations between elevated maternal anxiety or chronic psychological stress during pregnancy and reduced language development, impaired attention, decreased processing speed, poorer working memory, diminished executive functioning, and lower overall cognitive performance in school-aged children (Van den Bergh et al., 2020, Lautarescu et al., 2020). These neurodevelopmental alterations may manifest behaviourally as impulsivity, reduced frustration tolerance, emotional instability, aggression, social withdrawal, impaired peer relationships, and difficulties adapting to changing social and academic demands. Learning difficulties frequently become more evident during formal schooling, particularly when educational tasks require sustained attention, planning, cognitive flexibility, problem-solving, self-regulation, or emotional control, thereby affecting academic achievement and psychosocial functioning (Monk et al., 2019, Davis & Sandman, 2020). Neurobiologically, these outcomes are believed to result from stress-induced alterations in hippocampal development, prefrontal cortical maturation, white matter connectivity, synaptic plasticity, and neurotransmitter signaling, which collectively influence higher cognitive processes and behavioural regulation (Dean et al., 2021, Thomason & Hendrix, 2024). Despite these associations, the developing brain retains remarkable plasticity throughout infancy and childhood, allowing many stress-related developmental alterations to be mitigated through timely intervention. Early developmental screening, enriched educational environments, responsive parenting, cognitive stimulation, adequate nutrition, psychological support, and multidisciplinary early intervention programs can significantly enhance cognitive, behavioural, and emotional outcomes, promoting resilience and improving long-term neurodevelopment despite prenatal adversity (Dunkel Schetter & Tanner, 2017, Faraone et al., 2021).

17. Assessment of prenatal stress:

Early identification of maternal stress is essential for preventing adverse pregnancy outcomes and minimizing the potential impact on foetal neurodevelopment. Comprehensive assessment should incorporate both subjective psychological evaluation and objective biological indicators whenever appropriate to accurately identify women at increased risk and facilitate timely intervention (Van den Bergh et al., 2020, Monk et al., 2019). Validated psychological assessment tools commonly used in clinical practice include the Perceived Stress Scale (PSS), Edinburgh Postnatal Depression Scale (EPDS), State–Trait Anxiety Inventory (STAI), Generalized Anxiety Disorder-7 (GAD-7), and Pregnancy-Related Anxiety Questionnaire (PRAQ), all of which assist healthcare professionals in identifying maternal stress, anxiety, depression, and pregnancy-specific psychological concerns requiring further evaluation or treatment (Biaggi et al., 2016, Caparros-Gonzalez & Alderdice, 2020). Biological assessment may include the measurement of cortisol concentrations in saliva, serum, urine, or hair, with hair cortisol emerging as a particularly valuable biomarker because it reflects cumulative glucocorticoid exposure over several months rather than short-term physiological

fluctuations. Additional biomarkers currently under investigation include inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), placental hormones, oxidative stress markers, extracellular vesicles, metabolomic profiles, and epigenetic signatures that may provide insight into the biological consequences of prenatal stress (Lautarescu et al., 2020, Davis & Sandman, 2020). A comprehensive evaluation should also consider maternal nutritional status, sleep quality, physical activity, social support, domestic environment, socioeconomic conditions, pregnancy complications, substance use, exposure to environmental stressors, and previous psychiatric history, as these factors interact to influence maternal psychological well-being and foetal development. Integrating psychological, biological, medical, and social assessments provides a holistic understanding of maternal health and enables early multidisciplinary interventions aimed at improving pregnancy outcomes and promoting optimal neurodevelopment in the offspring (Fava et al., 2019, Thomason & Hendrix, 2024).

18. Prevention and management of prenatal stress:

Prenatal stress is a potentially modifiable risk factor, making its prevention an important component of maternal and child healthcare. Effective management requires a multidisciplinary approach involving obstetricians, mental health professionals, physiotherapists, nurses, nutritionists, social workers, and family members. The primary objective is not to eliminate all stress, which is neither realistic nor physiologically desirable, but rather to reduce chronic or excessive stress that may adversely affect maternal well-being and foetal development. Early recognition of psychological distress through routine antenatal screening allows timely intervention before significant neuroendocrine, immunological, and placental alterations occur (Van den Bergh et al., 2020, Monk et al., 2019). Universal screening for maternal anxiety, depression, domestic violence, financial insecurity, and psychosocial stress should be incorporated into routine antenatal care using validated instruments such as the Perceived Stress Scale (PSS), Edinburgh Postnatal Depression Scale (EPDS), and Generalized Anxiety Disorder-7 (GAD-7), which facilitate the early identification of women requiring further psychological assessment and support (Biaggi et al., 2016, Caparros-Gonzalez & Alderdice, 2020). In addition to psychological evaluation, healthcare providers should assess sleep quality, nutritional status, physical activity, social support, occupational stress, substance use, and existing medical conditions because these factors collectively influence maternal resilience and pregnancy outcomes (Dunkel Schetter & Tanner, 2017, Davis & Sandman, 2020). Health education constitutes another cornerstone of prevention, and pregnant women should receive counseling regarding normal physiological changes during pregnancy, healthy nutrition, adequate hydration, stress management techniques, regular physical activity appropriate for pregnancy, sleep hygiene, relaxation exercises, and recognition of warning signs requiring medical attention. Family-centered counseling and partner involvement further enhance emotional support, strengthen coping strategies, reduce maternal anxiety, and promote adherence to antenatal care, thereby contributing to healthier maternal psychological status and more favourable foetal neurodevelopmental outcomes (Lautarescu et al., 2020, Thomason & Hendrix, 2024).

19. Role of nutrition in foetal neurodevelopment:

Maternal nutrition profoundly influences foetal brain development and may partially mitigate the biological effects of prenatal stress by supporting normal neurodevelopment, reducing oxidative stress, and maintaining optimal placental function. The developing nervous system requires a continuous supply of essential nutrients, including folic acid, iron, iodine, choline, zinc, vitamin D, omega-3 polyunsaturated fatty acids, and high-quality protein, all of which are critical for neuronal proliferation, neural tube formation, myelination, neurotransmitter synthesis, synaptic plasticity, and cognitive development. Deficiencies in these nutrients may impair brain maturation and increase susceptibility to adverse neurodevelopmental outcomes, particularly in pregnancies complicated by chronic maternal stress (Cusick & Georgieff, 2016, Caffrey et al., 2019). Among these nutrients, omega-3 polyunsaturated fatty acids, especially docosahexaenoic acid (DHA), are essential structural components of neuronal cell membranes and play important roles in synapse formation, neuroplasticity, visual development, and cognitive function, while folic acid is indispensable for DNA synthesis, one-carbon metabolism, epigenetic regulation, methylation reactions, and normal neural tube development during early gestation (Middleton et al., 2020, Prado & Dewey, 2018). Adequate maternal intake of antioxidant-rich foods, including fruits, vegetables, whole grains, legumes, and nuts, may further reduce oxidative stress, modulate inflammatory responses, and protect placental and foetal tissues from free radical–mediated damage, thereby contributing to a healthier intrauterine environment and supporting optimal foetal brain development (Benedetti et al., 2020, Burton & Jauniaux, 2018). Consequently, nutritional counseling should form an integral component of routine prenatal care, with individualized dietary recommendations based on maternal nutritional status, cultural dietary practices, socioeconomic factors, and existing medical

conditions to optimize maternal health, enhance resilience to prenatal stress, and promote healthy neurodevelopmental outcomes in the offspring (Dunkel Schetter & Tanner, 2017, Thomason & Hendrix, 2024).

20. Physical activity, sleep and stress reduction:

Regular physical activity during uncomplicated pregnancy has been associated with improved cardiovascular fitness, reduced pregnancy-related discomfort, enhanced mood, improved sleep quality, and better overall maternal well-being. Moderate-intensity exercises such as walking, prenatal yoga, stretching, aquatic exercise, and supervised strengthening programs can reduce stress-related symptoms by promoting endorphin release, improving autonomic nervous system balance, enhancing circulation, and decreasing circulating stress hormones, thereby contributing to a healthier intrauterine environment (Mottola et al., 2018, ACOG, 2020). Sleep disturbances are common throughout pregnancy and frequently exacerbate psychological stress, anxiety, fatigue, and emotional instability. Poor sleep quality has been associated with increased cortisol secretion, heightened inflammatory activity, impaired immune function, and adverse pregnancy outcomes, therefore, healthcare providers should educate pregnant women regarding evidence-based sleep hygiene practices, including maintaining consistent sleep schedules, limiting caffeine intake, reducing screen exposure before bedtime, engaging in relaxation techniques, and adopting comfortable sleeping positions, particularly the left lateral position during later pregnancy (Mindell et al., 2017, Okun, 2019). Non-pharmacological stress reduction strategies, including diaphragmatic breathing, progressive muscle relaxation, guided imagery, meditation, mindfulness-based stress reduction, and prenatal yoga, have demonstrated beneficial effects in reducing maternal anxiety, perceived stress, depressive symptoms, and physiological stress responses while improving emotional well-being and quality of life (Dhillon et al., 2017, Hall et al., 2020). Although individual responses to these interventions may vary depending on personal preferences and psychosocial factors, incorporating regular physical activity, healthy sleep practices, and structured relaxation techniques into routine antenatal care provides a safe, effective, and holistic approach to improving maternal mental health and supporting optimal foetal neurodevelopment (Van den Bergh et al., 2020, Thomason & Hendrix, 2024).

21. Psychological interventions:

Psyc2hological support is one of the most effective evidence-based approaches for managing prenatal stress and promoting maternal mental well-being throughout pregnancy. Cognitive behavioural therapy (CBT) remains the most extensively studied psychological intervention for antenatal anxiety and depression, helping pregnant women identify maladaptive thought patterns, develop healthy coping strategies, strengthen emotional resilience, and improve problem-solving skills, thereby reducing psychological distress and enhancing overall quality of life (Biaggi et al., 2016, Loughnan et al., 2019). Mindfulness-based interventions have also gained considerable attention in maternal healthcare because they encourage present-moment awareness, emotional acceptance, self-regulation, and adaptive responses to stressful situations. Several randomized clinical trials and systematic reviews have demonstrated that structured mindfulness programs can significantly reduce anxiety, depressive symptoms, perceived stress, pregnancy-related fear, and physiological stress responses while improving maternal emotional well-being and psychological resilience (Dhillon et al., 2017, Hall et al., 2020). In addition to individual therapies, support groups, family counseling, peer education, and community-based maternal health initiatives play an important role in strengthening psychosocial well-being by reducing social isolation, enhancing partner and family involvement, and improving access to emotional and practical support during pregnancy (Caparros-Gonzalez & Alderdice, 2020, Dunkel Schetter & Tanner, 2017). Furthermore, the rapid expansion of digital health platforms, mobile health applications, and telehealth counseling has improved access to evidence-based psychological services, particularly for pregnant women residing in rural, remote, or underserved areas, enabling timely mental health support and continuity of care while reducing barriers related to distance, transportation, and healthcare availability (Lebel et al., 2020, Van den Bergh et al., 2020).

22. Integrative maternal healthcare:

Modern prenatal care increasingly emphasizes an integrative approach that combines conventional obstetric management with evidence-based lifestyle interventions and selected complementary therapies to promote maternal and foetal well-being. Integrative care aims to improve maternal quality of life while maintaining the highest standards of maternal and foetal safety, recognizing that emotional health, balanced nutrition, adequate sleep, regular physical activity, stress management, and strong social support collectively influence pregnancy outcomes and foetal neurodevelopment (World Health Organization, 2022, Van den Bergh et al., 2020). Collaborative care models involving obstetricians, psychiatrists, psychologists, physiotherapists, nutritionists,

nurses, social workers, and appropriately qualified complementary medicine practitioners facilitate comprehensive assessment and management of maternal stress by addressing its biological, psychological, and social determinants. Such interdisciplinary approaches may improve treatment adherence, maternal satisfaction, continuity of care, and early identification of psychosocial risk factors while enabling individualized care plans tailored to each woman's needs (Biaggi et al., 2016, Dunkel Schetter & Tanner, 2017). Complementary therapies including prenatal yoga, mindfulness meditation, music therapy, massage therapy, acupuncture, and homeopathy have been investigated as supportive interventions for improving maternal relaxation, reducing perceived stress, and enhancing emotional well-being, however, the quality and strength of evidence vary considerably across these modalities. Consequently, their integration into prenatal care should always be guided by current scientific evidence, clinical judgment, patient preferences, and safety considerations, and they should be used as adjuncts to not substitutes for appropriate medical evaluation, psychological assessment, and evidence-based treatment, particularly in women with significant anxiety, depression, or other psychiatric disorders requiring specialized care (Hall et al., 2020, National Institute for Health and Care Excellence [NICE], 2020).

23. Homeopathic perspectives on prenatal stress:

Homeopathy is a complementary system of medicine based on the principle of individualized treatment, in which remedies are selected according to the patient's unique physical symptoms, emotional characteristics, mental state, constitutional features, and personal experiences rather than solely on a specific disease diagnosis. During pregnancy, homeopathic management has traditionally focused on promoting maternal emotional balance, reducing anxiety, improving sleep quality, alleviating stress-related symptoms, and supporting overall well-being while considering the individual symptom profile of each pregnant woman (Mathie et al., 2017, Relton et al., 2020). Although homeopathy is practiced in many countries as part of complementary and integrative healthcare, current scientific evidence supporting its effectiveness in preventing adverse foetal neurodevelopmental outcomes or reducing prenatal stress remains limited and inconclusive. Most published studies evaluating homeopathy during pregnancy are characterized by small sample sizes, heterogeneous methodologies, inconsistent outcome measures, and a high risk of bias, making it difficult to draw definitive conclusions regarding clinical efficacy (National Center for Complementary and Integrative Health, 2022, NICE, 2020). Consequently, major national and international clinical guidelines do not recommend homeopathy as a primary treatment for prenatal stress, anxiety, or depression. However, some women may choose to use homeopathic treatment as a complementary therapy alongside standard prenatal care after consultation with qualified healthcare professionals, provided that it does not delay or replace evidence-based medical or psychological interventions when these are clinically indicated (World Health Organization, 2022, Ernst, 2018). Several homeopathic remedies have traditionally been selected according to individualized symptom patterns rather than specific medical diagnoses, and the commonly described remedies traditionally used for maternal emotional symptoms are summarized in Table. 3, Traditional homeopathic remedies described for emotional symptoms during pregnancy. Selection in homeopathic practice is individualized and should not be interpreted as evidence of proven effectiveness for preventing adverse foetal neurodevelopmental outcomes.

Table 3. Commonly Used Homeopathic Remedies Traditionally Considered for Emotional Symptoms during Pregnancy

Homeopathic Remedy	**Traditional Indications**	**Clinical Remarks**
Aconitum napellus	Sudden fear, panic, shock, restlessness	Traditionally selected after acute fright or anxiety.
Argentum nitricum	Anticipatory anxiety, nervousness, impatience	Used traditionally for anxiety before childbirth or medical procedures.
Gelsemium sempervirens	Trembling, weakness, examination fear, emotional anticipation	Traditionally indicated when anxiety is accompanied by muscular weakness.
Ignatia amara	Grief, emotional disappointment, mood fluctuations	Frequently described for emotional stress following grief or conflict.
Pulsatilla nigricans	Emotional sensitivity, tearfulness, desire for consolation	Traditionally prescribed for mild, affectionate individuals experiencing emotional instability.

Sepia officinalis	Emotional exhaustion, irritability, fatigue	Often considered for women experiencing emotional detachment and exhaustion during pregnancy.
Kali phosphoricum	Mental fatigue, nervous exhaustion	Traditionally used for stress associated with prolonged mental fatigue.
Coffea cruda	Sleeplessness due to excessive thoughts	Selected traditionally when insomnia is associated with mental overactivity.
Chamomilla	Irritability, hypersensitivity, emotional frustration	Traditionally considered when emotional irritability predominates.
Nux vomica	Irritability associated with occupational stress	Used traditionally in individuals experiencing mental overwork and irritability.

Current evidence suggests that if homeopathy is incorporated into prenatal care, it should be viewed as a complementary rather than an alternative therapy. Women experiencing severe anxiety, depression, suicidal ideation, domestic violence, substance misuse, or significant psychiatric illness require prompt evaluation and evidence-based medical management. Homeopathic interventions should never delay appropriate obstetric, psychiatric, or psychological treatment. Recent interest in integrative maternal healthcare has encouraged researchers to investigate complementary therapies using rigorous clinical trial methodology. High-quality randomized controlled trials with standardized outcome measures are required before definitive conclusions regarding the effectiveness of homeopathy in prenatal stress management can be established. As research continues to evolve, an evidence-informed and patient-centered approach remains the most appropriate strategy for supporting maternal mental health while ensuring optimal foetal development. An integrative framework combining biological mechanisms, preventive strategies, and complementary approaches is presented in Fig. 8.

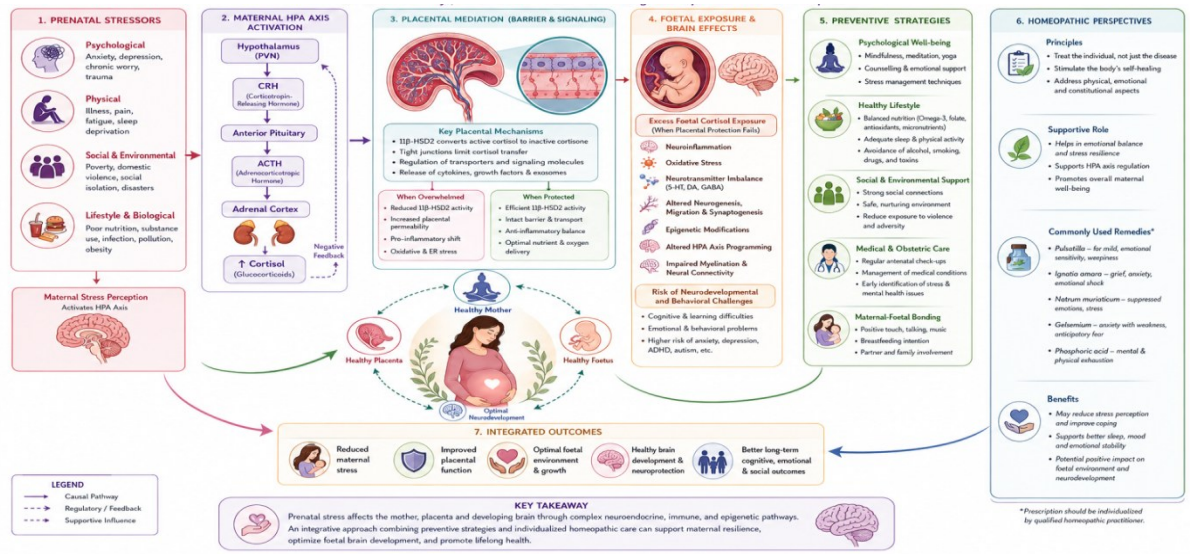

Figure. 8: Integrative Model of Prenatal Stress, Preventive Strategies, and Homeopathic Perspectives

Conceptual diagram illustrating the relationship between maternal stress, HPA-axis activation, placental function, immune responses, oxidative stress, foetal neurodevelopment, preventive interventions (nutrition, exercise, psychological support, mindfulness), and complementary homeopathic care within an integrative maternal healthcare model. The figure emphasizes that homeopathy should be considered complementary to evidence-based prenatal care rather than a replacement for conventional medical management.

24. Future research directions:

Despite substantial advances in understanding the relationship between prenatal stress and foetal neurodevelopment, important knowledge gaps remain regarding the precise molecular and cellular mechanisms underlying stress-induced developmental programming, necessitating further multidisciplinary research integrating neuroscience, obstetrics, genetics, and developmental biology (Van den Bergh et al., 2020). Future investigations should prioritize the identification of reliable multimodal biomarkers by

combining endocrine, inflammatory, epigenetic, metabolomic, and neuroimaging indicators to enable earlier prediction of adverse neurodevelopmental outcomes and individualized risk assessment (Davis & Sandman, 2020). Long-term prospective cohort studies extending from pregnancy into adulthood are required to clarify the lifelong cognitive, behavioural, and psychiatric consequences of prenatal stress while accounting for postnatal environmental influences and genetic susceptibility (Thomason & Hendrix, 2024). Emerging evidence also highlights the importance of maternal nutrition, gut microbiota, mitochondrial function, environmental pollutants, and placental biology as interacting modulators of stress-related neurodevelopment, warranting comprehensive investigation using multi-omics approaches (Lautarescu et al., 2020). Artificial intelligence, machine learning, and digital health technologies may further improve early screening, personalized prenatal care, and remote psychological support, particularly in underserved populations (Topol, 2019). From the perspective of complementary medicine, well-designed randomized controlled trials with standardized outcome measures and long-term follow-up are necessary to determine whether individualized homeopathic treatment offers clinically meaningful benefits beyond placebo as an adjunct to conventional prenatal care (Mathie et al., 2017). Finally, international collaboration and standardized research methodologies will strengthen the evidence base and facilitate the development of effective, culturally appropriate strategies that enhance maternal well-being and optimize lifelong neurodevelopmental outcomes (World Health Organization, 2022).

25. Conclusion:

Prenatal stress is a significant environmental factor that influences foetal neurodevelopment and lifelong neurological health by altering the intrauterine environment during critical stages of brain maturation. Persistent maternal psychological, biological, environmental, or social stress activates interconnected neuroendocrine, immune, inflammatory, metabolic, and epigenetic pathways that affect neuronal proliferation, migration, differentiation, synaptogenesis, myelination, and neural circuit formation. These developmental alterations may increase susceptibility to neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, depression, cognitive impairment, learning difficulties, and emotional dysregulation. However, prenatal stress should not be considered an isolated cause of these conditions, as developmental outcomes are determined by the interaction of genetic predisposition, maternal health, placental function, nutrition, family support, and postnatal environmental influences. Early identification of maternal stress through routine antenatal screening, combined with evidence-based interventions such as psychological counseling, stress management, balanced nutrition, regular physical activity, adequate sleep, and strong social support, can substantially improve maternal well-being and pregnancy outcomes. Homeopathy may offer individualized supportive care for emotional symptoms during pregnancy, but current evidence is insufficient to recommend it as a primary intervention for preventing adverse foetal neurodevelopmental outcomes, and it should be used only as a complementary approach alongside conventional prenatal care. Ultimately, promoting maternal mental health through comprehensive, multidisciplinary, and patient-centred prenatal care remains one of the most effective strategies for optimizing foetal brain development and improving lifelong neurological health for future generations.

26. References:

(1) ACOG. (2020). *Physical activity and exercise during pregnancy and the postpartum period: Committee Opinion No. 804*. Obstetrics & Gynecology, 135(4), e178–e188.
(2) Babenko, O., Kovalchuk, I., & Metz, G. A. S. (2017). Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. *Neuroscience & Biobehavioral Reviews, 48*, 70–91.
(3) Beijers, R., Buitelaar, J. K., & de Weerth, C. (2019). Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes. *Developmental Psychobiology, 61*(5), 636–650.
(4) Benedetti, F., Palladino, R., & Camerota, M. (2020). Maternal nutrition, oxidative stress, and fetal neurodevelopment: Emerging evidence and clinical implications. *Nutrients, 12*(10), 3125.
(5) Biaggi, A., Conroy, S., Pawlby, S., & Pariante, C. M. (2016). Identifying the women at risk of antenatal anxiety and depression: A systematic review. *Journal of Affective Disorders, 191*, 62–77.
(6) Burton, G. J., & Jauniaux, E. (2018). Pathophysiology of oxidative stress in pregnancy complications. *Placenta, 69*, 1–7.
(7) Buss, C., Entringer, S., & Wadhwa, P. D. (2018). Fetal programming of brain development: Intrauterine stress and neurodevelopment. *Current Opinion in Pediatrics, 30*(2), 197–203.

(8) Caffrey, A., Irwin, R. E., McNulty, H., et al. (2019). Maternal folate and neurodevelopmental outcomes in offspring. *Proceedings of the Nutrition Society, 78*(2), 165–176.
(9) Caparros-Gonzalez, R. A., & Alderdice, F. (2020). The role of psychosocial interventions in reducing prenatal stress and improving maternal mental health. *Women and Birth, 33*(6), e531–e540.
(10) Cusick, S. E., & Georgieff, M. K. (2016). The role of nutrition in brain development: The golden opportunity of the first 1000 days. *Journal of Pediatrics, 175*, 16–21.
(11) Davis, E. P., & Sandman, C. A. (2020). Prenatal stress and neurodevelopment. *Annual Review of Clinical Psychology, 16*, 435–463.
(12) Dean, D. C., Laing, J., Scheinost, D., et al. (2021). Prenatal stress and developmental alterations in brain connectivity. *NeuroImage, 241*, 118420.
(13) Dhillon, A., Sparkes, E., & Duarte, R. V. (2017). Mindfulness-based interventions during pregnancy: A systematic review. *Mindfulness, 8*, 1425–1437.
(14) Dipietro, J. A. (2018). Maternal stress in pregnancy and child development. *Developmental Medicine & Child Neurology, 60*(2), 113–118.
(15) Dunkel Schetter, C., & Tanner, L. (2017). Anxiety, depression and stress in pregnancy: Implications for mothers, children, research, and practice. *Current Opinion in Psychiatry, 30*(2), 141–148.
(16) Ernst, E. (2018). Homeopathy: What does the evidence show? *British Journal of Clinical Pharmacology, 84*(7), 1393–1398.
(17) Estes, M. L., & McAllister, A. K. (2016). Maternal immune activation: Implications for neuropsychiatric disorders. *Science, 353*(6301), 772–777.
(18) Faraone, S. V., Banaschewski, T., Coghill, D., et al. (2021). The World Federation of ADHD international consensus statement. *Neuroscience & Biobehavioral Reviews, 128*, 789–818.
(19) Fava, G. A., Cosci, F., & Guidi, J. (2019). The psychological consequences of stress during pregnancy. *Psychotherapy and Psychosomatics, 88*(3), 131–142.
(20) Glover, V. (2017). Prenatal stress and its effects on the fetus and child. *British Medical Bulletin, 123*(1), 75–86.
(21) Goeden, N., Velasquez, J., Arnold, K. A., et al. (2016). Maternal inflammation disrupts fetal neurodevelopment through altered serotonin signaling. *Molecular Psychiatry, 21*, 1571–1579.
(22) Hall, H. G., Beattie, J., Lau, R., et al. (2020). Mindfulness and relaxation interventions during pregnancy: Effects on maternal anxiety and stress. *BMC Pregnancy and Childbirth, 20*, 1–12.
(23) Knuesel, I., Chicha, L., Britschgi, M., et al. (2018). Maternal immune activation and neurodevelopmental disorders. *Nature Reviews Neuroscience, 19*, 251–266.
(24) Lautarescu, A., Craig, M. C., & Glover, V. (2020). Prenatal stress: Effects on fetal and child brain development. *International Review of Neurobiology, 150*, 17–40.
(25) Lebel, C., Walton, M., Letourneau, N., et al. (2020). Prepartum maternal psychological distress and offspring brain development. *Biological Psychiatry, 87*(9), 858–866.
(26) Lord, C., Brugha, T. S., Charman, T., et al. (2020). Autism spectrum disorder. *The Lancet, 392*, 508–520.
(27) Loughnan, S. A., Joubert, A. E., & Haskard-Zolnierek, K. (2019). Cognitive behavioural therapy for antenatal anxiety and depression. *Journal of Affective Disorders, 245*, 404–412.
(28) Mathie, R. T., Ramparsad, N., Legg, L. A., et al. (2017). Randomised controlled trials of homeopathy in humans: A review. *Systematic Reviews, 6*, 1–13.
(29) Middleton, P., Gomersall, J. C., Gould, J. F., et al. (2020). Omega-3 fatty acid addition during pregnancy. *Cochrane Database of Systematic Reviews, 2020*(9).
(30) Mindell, J. A., Cook, R. A., & Nikolovski, J. (2017). Sleep patterns and sleep disturbances across pregnancy. *Sleep Medicine, 38*, 12–18.
(31) Monk, C., Lugo-Candelas, C., & Trumpff, C. (2019). Prenatal developmental origins of future psychopathology. *Annual Review of Clinical Psychology, 15*, 317–344.
(32) Mottola, M. F., Davenport, M. H., Ruchat, S. M., et al. (2018). 2019 Canadian guideline for physical activity throughout pregnancy. *British Journal of Sports Medicine, 52*, 1339–1346.
(33) O'Donnell, K. J., & Meaney, M. J. (2017). Fetal origins of mental health. *American Journal of Psychiatry, 174*(4), 319–328.
(34) Okun, M. L. (2019). Disturbed sleep and pregnancy outcomes. *Sleep Medicine Reviews, 46*, 1–9.
(35) Posner, J., Russell, J. A., Gerber, A., et al. (2016). The relationship between prenatal stress and child emotional development. *Developmental Psychobiology, 58*, 1–13.
(36) Prado, E. L., & Dewey, K. G. (2018). Nutrition and brain development in early life. *Nutrition Reviews, 75*(4), 267–284.

(37) Relton, C., Cooper, K., Viksveen, P., et al. (2020). Prevalence of complementary medicine use during pregnancy. *BMJ Open, 10*, e034102.
(38) Thomason, M. E., & Hendrix, C. L. (2024). Prenatal stress and human brain development. *Development and Psychopathology, 36*, 1–18.
(39) Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*, 44–56.
(40) Van den Bergh, B. R. H., Dahnke, R., & Mennes, M. (2018). Prenatal stress and the developing brain. *Neuroscience, 342*, 1–12.
(41) Van den Bergh, B. R. H., et al. (2020). Prenatal developmental origins of behaviour and mental health. *Neuroscience & Biobehavioral Reviews, 117*, 26–64.
(42) Wadhwa, P. D., Entringer, S., Buss, C., & Lu, M. C. (2016). The contribution of maternal stress to developmental programming. *Current Opinion in Behavioral Sciences, 7*, 71–77.
(43) World Health Organization. (2022). *WHO recommendations on antenatal care for a positive pregnancy experience*. Geneva: WHO.
(44) Zhang, X., et al. (2021). Maternal stress during pregnancy and offspring neurodevelopment. *Frontiers in Psychiatry, 12*, 712045.
(45) Zhang, Y., et al. (2022). Maternal prenatal stress and neurodevelopmental disorders. *Frontiers in Neuroscience, 16*, 842321.