Perinatal Psychiatry: Ready for Prime Time?

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Abstract Perinatal psychiatry deals primarily with women's mental health before labor and up to the first year post-childbirth and the growth and development of their offspring. Early insults to the developing brain of the fetus are consistently linked to later neuropsychiatric disorders. Maternal stress and depression, for instance, can trigger inflammation in the fetal brain, and studies consistently show the link between these events and the development of psychiatric disorders in the offspring. Postnatal mental disorders increase maternal morbidity and interfere with maternal bonding, thus impacting the health and development of the offspring. The aim of this chapter was to provide a brief overview of the field of perinatal psychiatry.

Keywords Maternal mental health · Child psychiatry · Developmental neurology · Neuroinflammation

1 Introduction

The World Health Organization's study on the global burden of disease lists psychiatric disorders among the leading causes of disability worldwide [1–3]. Despite their personal and societal impacts, psychiatric disorders are plagued by stigma, preventing their proper recognition and management. The related stigma can be traced back to the history of theories about causation of mental illness as discussed later in this chapter.

Perinatal psychiatry is the area of psychiatry dedicated to the care of pregnant and parturient women. In 2011, the Centers for Disease Control and Prevention

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estimated the prevalence of perinatal depression as 9% among pregnant women and 10% among postpartum women who all meet the criteria for major depression disorder. Such numbers pose a significant cost to individuals, children, families, and the whole society as untreated perinatal psychiatric disorders can increase maternal morbidity and interfere with maternal bonding [3]. Due to the consequences of maternal symptoms in the emotional and physical health of the offspring, perinatal psychiatry has gotten significant attention lately. Indeed the need for early recognition and treatment to avoid or minimize negative outcomes for the mother, baby, and family cannot be overemphasized. Perinatal psychiatry requires knowledge from psychological constructs (e.g., attachment theory), neuroscience (specifically the neurodevelopment of the neonate and the infant), and an integrated effort with obstetrics and pediatrics [4].

Children and adolescents affected by psychiatric disorders have also been a growing focus of medical interest as these conditions prevent the individual to achieve his/her full potential in life [5–7]. Between 13% and 20% of children and adolescents worldwide are estimated to suffer from disabling mental illness [8]. The US Census Bureau estimated, in 2014, a population of approximately 1.8 billions youth (4–19 years old) around the world, among which approximately 241 million are affected by psychiatric disorders. One interesting fact is that the majority of the epidemiological research on the determinants of mental health has been conducted in high-income country populations, while the greatest burden and health disparities are observed in low- and middle-income countries. Multiple studies showed that children and adolescents coming from families with low socioeconomic status are more likely to develop mental health problems than their peers with higher socioeconomic status [9–11].

2 A Brief Historical Perspective on the Etiopathogenesis of Mental Illnesses

Documented human knowledge of mental illnesses dates back to ancient civilizations that attributed their causation to demons or wrath of angels, while exorcism techniques were employed to drive demons out of the afflicted person's body as treatments [12]. In the fifth century B.C., the Greek historian Herodotus wrote about a king who was driven mad by evil spirits [13]. The Greek physician Hippocrates, considered the Father of Medicine, proposed the humoral theory that viewed causation of mental illnesses due to an imbalance of the four body fluids called "humors." [5] Hippocrates reported four types of humors: yellow bile, black pile, phlegm, and blood; and he postulated that depression was caused by too much "black bile," hence the name "melancholia." [14]. Melancholia is derived from the Ancient Greek "melas" meaning black and "kholé" meaning bile. The therapeutic interventions targeted, therefore, the restoration of the body balance or equilibrium.

Current medical knowledge about mental illnesses evolved in the nineteenth century when psychiatric syndromes were beginning to be characterized, and brain anatomy was being detailed. Studies of the "general paralysis," later identified as neurosyphilis, showed the link between central nervous system infection and behavioral syndromes [15]. Over a few decades, the neuropathology of dementia and other neurodegenerative diseases was characterized by postmortem brain studies, while no consistent brain pathological changes were identified in "functional mental illnesses." To address the causation of these latter conditions, psychological theories were proposed [16] and psychoanalysis became highly influential, giving significant emphasis on early life events, such as the attachment of the mother to the baby [17, 18].

In parallel to diverse psychological theories, several physicians and researchers believed that disturbances in brain development could predispose for psychiatric disorders, but this concept remained largely underappreciated until the neurobiological research got back to the mainstream. The development of psychopharmacology after the 1950s and its strong impact in the treatment of mental illness were the underlying force for this paradigm shift. The dopaminergic hypothesis of schizophrenia [19] and the catecholamine hypothesis of affective disorders [20] were proposed. Advances in genetics confirmed the heredity of several psychiatric disorders but also suggested the role played by non-genetic, i.e., environmental, factors.

The current understanding of the etiopathogenesis of mental illnesses views that they are multifactorial, likely resulting from the interplay of genetics and environment factors, including prenatal events and life stress. Twin and adoption studies have demonstrated that heredity is a significant factor in the etiopathogenesis of schizophrenia [21, 22] and bipolar disorder [23]. As studies trying to identify specific genes predisposing to major psychiatric disorders were largely unsuccessful, the summation of multiple genes has been implicated in the etiopathogenesis of such complex conditions [23]. Currently, schizophrenia has been conceived as a neurodevelopmental disorder resulting from the interaction of genetic and environmental factors [24, 25], with impairments in cognitive, motor, and social functioning preceding the full manifestation of symptoms in early adulthood [26].

Several lines of research support the neurodevelopmental theory of schizophrenia [27]. First, brain imaging studies showed brain volume loss even before the onset of psychotic experience, i.e., hallucinations and delusions [26]. Second, despite its manifestation in early adulthood and its chronic course, neurodegenerative changes in postmortem human brains from patients with schizophrenia are not evident. Third, many patients exhibit early "soft" neurological signs at childhood before any psychotic symptoms. Fourth, there is a robust association between early brain trauma due to obstetric complications and later risk of schizophrenia. Maternal nutrition is another environmental risk factor that may play a crucial role in the causation of schizophrenia as epidemiological studies have shown a strong link between mothers' exposure to famine during the early pregnancy stages and later risk of schizophrenia in offsprings [28].

Emerging large-scale genetic studies suggest that other psychiatric disorders such as autism and bipolar disorder may share genetic and/or neurodevelopmental factors with schizophrenia [29]. Depressive disorders also run in families [30–32], though heritability estimates (37%) are substantially less than those for schizophrenia (83%) and bipolar disorder (85%) [33]. Actually, environmental factors seem to play a more relevant role in depression. Childhood adversity and trauma, particularly sexual abuse [34], has been linked to the later development of depression, personality features of neuroticism [35], and a more severe course of psychiatric disorders [36].

The neuropsychiatric disorders in the offspring do not necessarily replicate maternal psychopathology, reinforcing the role of mechanisms other than genetics. In the most important study of offspring of mothers with depression (STAR∗D), it was observed that nearly half of the offspring (45%) had a lifetime psychiatric disorder, including disruptive behavior (29%), anxiety (20%), and depressive (19%) disorders. The following characteristics of maternal depression were associated to specific offspring disorders: maternal comorbid panic disorder with agoraphobia and offspring depressive and anxiety disorders, maternal irritable depression and offspring disruptive behavior disorders and any disorder, and maternal substance use disorders and any disorder. Even though these associations are not specific for prenatal or postpartum depression, they emphasize the plurality of negative outcomes in the offspring. One interesting finding of this study is the concomitant improvement of mother and offspring when mothers received treatment, raising the issue of how interventions during pregnancy could impact the future generation [37, 38].

3 Inflammation: Connecting the Dots

A number of studies have investigated whether inflammatory mechanisms are involved in the pathogenesis of schizophrenia and other major psychiatric disorders [39]. In schizophrenia, for example, genome-wide association studies linked several inflammation-related genes to an increased risk of the condition [40, 41]. Postmortem prefrontal cortex samples from schizophrenic patients have shown upregulation of genes involved in inflammatory response [42]. Moreover, inflammation/neuroinflammation related to neuronal and synaptic plasticity presents a potential mechanistic role in the neurodevelopmental theory of schizophrenia [43]. A very important point is the timing of the insult to development of the neuropsychiatric disorder. One of the most accepted theories support the two-hit hypothesis. In this theory, besides the genetic background, problems that affect the mother will cause different consequences to the offspring (first hit) according to the moment of development, such as an earlier onset or a more severe disorder [44].

There are several stages of neurodevelopment from early conceptual stages to the birth of the baby and then postnatal brain development and cortical maturation that

continue for several years. Early fetal period, which extends to approximate midgestation, is critical in the development of the neocortex [45]. Differentiation of the neural progenitor cells and the formation of the neural tube are the first steps in the central nervous system development that start as early as the second week of gestation. Early fetal period is clinically important as many medications and other drugs that are taken by the pregnant woman during this period may affect brain development. For instance, sodium valproate, a widely used anti-epileptic and mood stabilizer, is not recommended in any women in childbearing age due to the risk of congenital malformations, especially neural tube defects [46]. After the formation of the neural tube, further maturation, neuronal and glial production, migration, and differentiation continue to shape the growing brain throughout the fetal gestation period until the second trimester. These are critical periods of vulnerability during brain development regulated by both genetic and environmental factors. Genetic factors provide the developing brain a template while environmental factors – through immune/inflammatory mechanisms, among others – shape and regulate the brain development and functioning. Disruption of these mechanisms (first hit) leads to the risk of development of neuropsychiatric disorders.

Most of the available studies on early mechanisms derive from experimental investigations with other species. Exposure to prenatal stress can lead to significant increase in microglial activity, the mainline of immune defense in the brain [47–49]. Maternal deprivation stress at early postnatal stage also increases inflammatory markers in the offspring brain [46]. Exacerbated immune responses were found in prenatally stressed animals that were subsequently given an immune challenge in adulthood [47–49]. These observations support the notion that early-life stress sensitizes microglial cells so that there is an exaggerated microglial response to stress in late adolescence or young adulthood, when the "second hit" usually happens, underlying the development of psychiatric disorders [47–53]. Once the condition is established, an inflammatory process might mediate progressive neuronal injury, resulting, for example, in the grey matter volume loss seen in schizophrenia and other major psychiatric disorders [49].

Maternal health, stress, and nutritional status have been long recognized to be among the most important factors in fetal neurodevelopment. Maternal depression during pregnancy is associated with decreased self-care, reduced rates of adherence to prenatal care, and increased recreational drug use [54]. These all culminate in poorer health outcomes for both mother and developing fetus. Maternal stress and depression can trigger inflammation in the brain, and studies consistently show the link between neuroinflammation and the development of psychiatric disorders in the offspring.

After childbirth, depressive symptoms can also severely impair the mother's ability to interact/attach and communicate with her child [55], exerting a detrimental effect on cognitive and emotional development of the child, leading to an elevated risk for behavioral and psychiatric disorders [49]. Actually, maternal mental illnesses create a stressful environment for infants at a vulnerable developmental stage in their life [56].

4 Conclusions and Future Perspectives

New research using animal models has been able to help psychiatry drift from previous nonempirical theories to a more mechanistic understanding of healthy development and mental disorders. Prenatal and early years of life are crucial for brain development. Minimizing the adverse impact of maternal psychopathology may lead to less brain insults and is very important to prevent long-term mental health problems. Despite the body of evidence supporting the link between prenatal/perinatal brain insults and later onset of psychiatric disorders in humans, there is a critical knowledge gap in the mechanisms involved and the strategies to improve early brain development. Current knowledge supports the participation of immune mechanisms in the onset of mental illness. Evidence-based strategies to personalize care of pregnant women and their offspring will be of great importance in the prevention of psychiatric disorders. In the meantime, early screening and intervention are pivotal in reducing the negative impact of mental health problems in the mother and the child. Embracing healthy lifestyle by cutting down smoking, drugs, and alcohol intake, managing stress, proper nutrition, and physical activity during pregnancy are attainable strategies that could have substantial impact in the prevention of neurodevelopmental and psychiatric disorders.

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