Commentary

Impact of Prenatal Stress on Offspring Psychopathology and Comorbidity With General Medicine Later in Life

Jill M. Goldstein

Stress affects every chronic disease we know, and psychiatric disorders are prime examples of this phenomenon. However, “stress” may likely be one of the most overused and sometimes loosely defined concepts in medicine and in other fields. The term has been used to describe both the stimuli causing a reaction (or “stressors”) and the responses to stimuli/stressors. It includes a multitude of modalities (either noxious or positive) that can be physical, chemical, social, and/or psychological, including perception of the stressor alone. The notion of “stress” in relation to human biology was defined by an adrenal response and coined more than 80 years ago by Hans Selye (1). In fact, Selye, a basic scientist, endocrinologist, and biochemist, described stress as a physiologic hypothalamic-pituitary-adrenal (HPA) response, inducing hormonal, autonomic nervous system (ANS), immunologic, and blood pressure outcomes that impacted multiple organ systems, including cardiovascular, pulmonary, and renal systems driven by the brain. In addition, he first described the nature of stressors as physical, chemical, or psychological in nature.

Selye was ahead of his time. He defined all sorts of stressors that could produce similar effects on the body involving different tissues and organs. He coined the term “general adaptation syndrome” and observed that people with different diseases experienced similar symptoms (the “triad of stress” involving the adrenal gland, thymus and lymph nodes, and gastric ulcers), although he studied only rats. He discovered the impact of glucocorticoids as critical in the HPA axis response, including their anti-inflammatory role, which led to new ideas about the crosstalk between stress and immunity. Thus, he extended Walter Cannon’s notions of stress on human illness (2) by discovering the role of glucocorticoids.

Stress and the Brain

The middle of the 20th century saw a substantial growth of studies on the biology of stress on illness, defining stress, akin to Selye, as a physiologic HPA response, implicating steroid and pituitary hormones, ANS regulation, immune responses, and blood pressure. Brain regions driving the HPA axis (or stress response) circuitry provide inputs through numerous routes to the paraventricular nucleus of the hypothalamus (PVN), the final common motor output for the neuroendocrine hypothalamus. These brain regions include central and medial amygdala subregions, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and the anterior cingulate cortex. Central to the HPA axis are a group of neurons found in the PVN that synthesize and secrete corticotropin-releasing hormone. Secretion of corticotropin-releasing hormone from these neurons and cosecretion of arginine vasopressin into the hypothalamo-hypophyseal portal capillaries of the median eminence regulate secretion of adrenocorticotropic hormone from the anterior pituitary. In turn, adrenocorticotropic hormone drives the secretion of cortisol in humans and corticosterone in many other mammals from the zona fasciculata of the adrenal cortex. Preautonomic neurons in the PVN activate the sympathetic nervous system to stimulate the rapid release of epinephrine from chromaffin cells in the adrenal medulla. Glucocorticoid release also drives adrenal medullary synthesis of phenylethanolamine *N*-methyltransferase, which is responsible for transforming norepinephrine to epinephrine.

The combination of glucocorticoids and epinephrine secreted into the bloodstream generates diverse responses throughout the body in addition to a glucocorticoid-mediated negative feedback response at the pituitary and brain levels. A major role for the HPA axis is to integrate potentially stressful stimuli and respond with the neuroendocrine signals (described above) that coordinate homeostatic responses throughout the body. Threatening physical or psychological stressors are sensed at many levels of the central nervous system, and this information is passed to the hypothalamus after processing in limbic regions.

Although Selye’s emphasis was not on the impact of stress on brain, his contributions are quite relevant as we think about the impact of “prenatal stress” models for understanding the etiologies of psychiatric disorders across the lifespan. Prenatal stress programming of psychiatric disorders (i.e., disorders that primarily do not emerge until postpuberty and into adulthood) is a relatively new notion. For example, it was not until the early 1980s that schizophrenia was considered a neurodevelopmental disorder rather than being thought of as a disorder that occurred after the brain developed (a so-called adult lesion model of disease). However, psychiatry has a long history of focusing on the early origins of psychopathology, ranging from adverse childhood experiences (e.g., Freud) to the impact of social class and other early life environmental exposures on notions of later mental illness by investigators such as Hollingshead and Redlich (in the 1950s) and Bruce and Barbara Dohrenwend (in the 1980s and 1990s). These notions of early life stressful events on psychopathology laid the foundation for our understanding of the impact of prenatal early life stressors on the development of psychopathology. Our ideas about the early origins of psychiatric disorders

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blossomed in the decade of the brain in an increasing literature on fetal brain development and later psychopathology, the importance of which will be underscored here.

The cascade of physiologic stress responses, particularly when they are chronic or sustained, are now understood to take a potentially long-term toll on human health across the lifespan. When these responses occur during pregnancy, they have yet an additional toll—that is, on the developing fetus. Prenatal stress models refer to the disruption of the HPA axis response in mothers during pregnancy that impacts the developing fetal brain, laying the vulnerability for the risk for numerous psychiatric disorders in the offspring later in life. Previously, this was only investigated in animal models. However, prenatal cohorts following offspring into adulthood and aging have provided windows of opportunity for prospectively investigating the impact of prenatal exposures on risk for human psychopathology [see Goldstein *et al.* (3)]. These models have included numerous types of exposures during pregnancy, including obstetric complications (e.g., preeclampsia and other conditions resulting in fetal growth restriction), bacterial and viral infections, nutritional deprivation (e.g., early work derived from the Dutch Famine Birth Cohort Study by Susser and Stein), oxygen deprivation, and social and psychological exposures, such as chronic social disadvantage, physical/sexual trauma, and death of a spouse (e.g., early work by Brown and Harris). Although defined variously, the final common pathway of the impact of these noxious stressors involves disruption of the maternal HPA axis, causing maternal overexpression of glucocorticoids, immune dysregulation, changes in blood pressure and vascular function—elements of which, in part, affect placental function or cross the placenta and impact the development of HPA circuitry, physiology, and the vasculature in the offspring.

Impact of Maternal Prenatal Stress on Fetal HPA Circuitry and Psychopathology

Central nervous system brain regions that regulate the HPA axis (PVN, central and medial amygdala subregions, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and the anterior cingulate cortex) are also implicated as abnormal, both structurally and functionally, in a number of psychiatric disorders, including major depressive disorder and anxiety disorders, schizophrenia, attention-deficit/hyperactivity disorder, and autism. Thus, at the human level, fetal programming studies have primarily focused on these disorders. Studies suggest that abnormalities in the fetal development of HPA axis regions are associated with the fact that they are dense in glucocorticoid and sex steroid hormone receptors (4) and cytokine receptors. Further, these regions relay information that regulates cardiac function through the ANS, suggesting, as we have previously, a pathway through which a psychiatric disorder, like major depressive disorder, is highly comorbid with cardiovascular disease and metabolic syndrome with shared fetal origins (3,5).

In fact, at the preclinical level, prenatal stress programming studies demonstrated the impact of maternal stressors or stress-responsive hormones on a host of HPA-related outcomes, including hypothalamic and hippocampal structure and function, with lasting effects on the HPA axis by programming a "hyperactive" system vulnerable to mood and anxiety symptomatology, ANS deficits, hyperglycemia and hypertension (6), and metabolic dysregulation (7,8). Thus, preclinical studies, along with human studies, provided compelling evidence of maternal prenatal stress impacting multiple organs and systems, as did Selye and Cannon many years ago, suggesting final common pathways for understanding comorbidity of psychiatric disorders with general medical disorders, such as cardiovascular disease and metabolic syndrome.

Impact of Sex: Timing is Critical

It is important to underscore that prenatal stress programming studies need to incorporate designs that evaluate the impact of sex. Gestational development is a critical, sensitive period of the sexual differentiation of the brain. The primary drivers of sexual differentiation are gonadal hormones, although there are direct effects of genes on sexual differentiation before gonad differentiation. From the gonadal hormone point of view in humans, at the beginning of the second trimester, the testes begin to secrete testosterone, and testosterone has direct effects on masculinizing the male human brain and potential indirect effects through its conversion into estradiol by the enzyme aromatase. Testosterone and estradiol have major effects on brain development at every level of neuronal growth and development, beginning with neurogenesis to apoptosis (neuronal death). Given key critical gestational periods of sexual differentiation, importantly, the impact of stressors on the development of sexually dimorphic brain regions will depend on the timing of exposure of the stressors. In fact, we and others have demonstrated in multiple studies that depending on the timing of gestational exposure, the impact of maternal HPA axis disruption during pregnancy results in sex differences in the offspring's HPA axis brain circuitry development and stress and vascular physiology, creating vulnerability for sex differences in the onset of psychopathology later in life (3), comorbidity with general medical disorders impacted by HPA axis dysregulation [such as cardiovascular disease (3) and metabolic syndrome (5)], and vulnerability for sex differences in disorders of brain aging that are associated with stress, immune, and cardiac physiology (7,9,10).

It is not possible in this commentary to provide all of the evidence for making an argument for the importance of taking a lifespan perspective, beginning in fetal development, for understanding psychopathology that primarily emerges much later in life. However, a long history of research at both human and animal levels supports the notion that noxious stressors are associated with multiple illnesses of the brain and body. They can be defined in a variety of ways, be they physical, chemical, social, or psychological. Regardless of type, they impact the body and brain, in part, through common physiologic and anatomic pathways that cross tissues and organ systems and are regulated by the brain. When they occur during prenatal development, they can have a lifelong impact on the risk for psychopathology and comorbidity with general medical disorders, particularly in the face of genetic risk for the disorders. Further, depending on the timing of exposure, they contribute to understanding sex differences in the risk for numerous psychiatric disorders. Of course, the impact of prenatal stress on psychopathology refers to a limited, albeit critical, window of time—i.e., 9 months of gestation. We know that stressful exposures in infancy and early childhood can extend this toll. The Romanian orphan deprivation studies conducted by Charles Nelson provide an extreme example, as do studies of childhood abuse and neglect and childhood poverty, toxic stressors that contribute to effects on later psychopathology. We believe that applying a life-span perspective will identify exactly what is disrupted, how, and the timing in early development to provide critical clues to target for early interventions that are sex-dependent and in the service of the development of precision therapeutic medicine.

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Article Information

From the Departments of Psychiatry and Medicine, Harvard Medical School, and the Departments of Psychiatry and Obstetrics and Gynecology, Massachusetts General Hospital, Boston, Massachusetts.

Address correspondence to Jill M. Goldstein, Ph.D., Massachusetts General Hospital, Founders Building, 5th floor, Room 514B, 55 Fruit St., Boston, MA 02114; E-mail: jill_goldstein@hms.harvard.edu.

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