Published in final edited form as:

Biol Psychiatry. 2016 December 01; 80(11): e85–e87. doi:10.1016/j.biopsych.2016.09.011.

Effects of Maternal Prenatal Stress: Mechanisms, Implications, and Novel Therapeutic Interventions

Amalia Londono Tobon, Andrea Diaz Stransky, David A. Ross, and Hanna E. Stevens

Yale University Child Study Center (ALT, ADS) and Department of Psychiatry (ALT, ADS, DAR), Yale University, New Haven, Connecticut, and the Department of Psychiatry (HES), University of Iowa, Iowa City, Iowa

A 30-year-old man presents to your clinic for the first time with symptoms of depression and anxiety. When would you say that his mental illness began? At the time of clinical presentation? When he first noticed the onset of symptoms? Perhaps even earlier?

As psychiatrists, we are trained not just to consider the individual's presenting problem but to delve deeper into their history so as to create an encompassing biopsychosocial formulation. To this end, we may ask about relationships, employment, education, and medical history. The astute clinician will also inquire about early experiences of trauma or neglect that may set the stage for future illness. The impact of such experiences has been made clear through seminal data from The Adverse Childhood Events study, among others; for example, the study found that individuals who experience four or more adverse childhood events had up to a 12-fold increase in their risk for alcoholism, drug abuse, depression, and suicide attempts (1). But how far back in a patient's history should we consider?

Current neuroscience is showing us that one of the most vulnerable times may be while an individual is still in utero. A range of critical neurodevelopmental processes are taking place during this time, including neurogenesis, cell migration, and synaptogenesis (Figure 1). Given the complexity of this process, it is no surprise that small perturbations can lead to significant long-term consequences, as has been shown for a wide range of medical stressors (e.g., nutritional or hormonal alterations, radiation, toxins or drugs, and infection). Here, however, we will focus more narrowly on a less commonly discussed factor: the influence of maternal stress on long-term outcomes in offspring.

Some of the earliest and most interesting data on the potential impact of prenatal stress come from epidemiologic studies of historical catastrophic events. Multiple studies have shown that offspring born to women during or soon after such events have an increased risk of developing psychopathology. For instance, increased risk of depression and schizophrenia

Address correspondence to Amalia Londono Tobon, M.D., Yale Child Study Center, 230 South Frontage Road, New Haven, CT 06520; amalia.londonotobon@yale.edu.

ALT and ADS contributed equally to this work.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

has been noted among individuals whose mothers experienced natural disasters, war, and bereavement while pregnant (2).

These observations paved the way for more definitive animal and human research exploring the impact on offspring of maternal stress. For example, depression, anxiety, and psychological stress have been strongly connected with maternal cortisol derangements and hypothalamic-pituitary-adrenal axis dysregulation in offspring (3). In fact, evidence suggests that the relationship between prenatal stress and aberrant neurodevelopment may be a harbinger of many psychiatric disorders (3). Moreover, it seems that not only the type of stressor but also the magnitude and timing of the stressor may greatly affect outcomes.

How do prenatal exposures lead to mental illness in adulthood? One key mechanism by which environmental stress may impact neurodevelopment and lead to psychiatric illness is through alterations in oxidative stress (4). In simple terms, oxidative stress refers to the balance between the production and containment of reactive oxygen and nitrogen species by mitochondria and various enzymes. This oxidative balance is fundamental to all cellular and neuronal processes, including neurogenesis, synaptogenesis, neuronal migration, and pruning. Increased presence of free radicals caused by prenatal stress may disrupt these processes, thereby possibly leading to cortical layer disorganization, such as that found in postmortem brains of children with autism (5).

A second key mechanism by which prenatal stress may affect long-term outcomes is by causing epigenetic changes in the developing brain. Epigenetics refers to modifications of DNA and histones via biochemical alterations, such as methylation and demethylation. These changes may lead to increased or decreased gene expression, either transiently or for prolonged periods of time. Multiple animal studies have identified epigenetic changes in response to in utero stress. In one of these studies, the pups of prenatally stressed mice developed behaviors reminiscent of schizophrenia and bipolar disorder. Their prefrontal cortices had increased DNA methylation in important developmental genes, including brain-derived neurotrophic factor and genes that are expressed particularly in inhibitory neurons (e.g., glutamate decarboxylase 1) (6).

In this issue of *Biological Psychiatry*, Lebel *et al.* take advantage of modern neuroimaging to explore the variability in brain morphology and connectivity of infants whose mothers experienced perinatal depression. Their research proposes that maternal depressive symptoms—constituting both a prenatal and postnatal stressor—are associated with reduced cortical thickness and gray matter changes (7). These results suggest that the stress related to maternal depression may impact brain structure through disruptions of neurogenesis, synaptogenesis, migration, and pruning—all of which may be influenced by oxidative stress and epigenetic changes.

Understanding the mechanisms by which early stress may contribute to adult psychopathology is imperative for identifying new treatment approaches. One fascinating example comes from the study of mice with the schizophrenia-like phenotype described above. When these mice were given clozapine, haloperidol, or placebo, the researchers found that only clozapine reversed the behavioral and epigenetic changes that had been

induced by prenatal stress (6). This study and others point to a potential future of “precision” psychiatry, wherein clinicians may be able to diagnose specific subtypes of syndromic illnesses and then employ customized treatment plans based, for example, on epigenetic changes that occurred prenatally.

While the prospect of individualizing treatment in this manner is appealing, an even greater aspiration would be to prevent the adverse impact of prenatal stress altogether. This may sound futuristic or overambitious, but other neurodevelopmental disorders caused by perinatal deficiencies have already achieved this goal. Spina bifida and anencephaly rates have nearly halved in the past two decades thanks to prenatal folic acid supplementation and wheat fortification (8). Similar to folate, choline plays a crucial role in brain development, serving as an essential element of cell membranes and in cell signaling. The hippocampus, an important brain region in memory processing, has nicotinic acetylcholine receptors that play a role in responses to stress. Interestingly, in healthy animals, choline fortification in the diet of pregnant rodents appears to foster hippocampal development in their offspring, thereby leading to improved memory and lower anxiety/depression (9) [with a similar effect reported in one study of humans (10)]. Of special relevance to models of psychopathology, some evidence has suggested that prenatal stress may lead to choline sequestration in the mother’s liver (10). This may induce a relative choline deficit for offspring, thereby leading to dysfunction of inhibitory neurons and impaired cerebral inhibition (similar to inhibitory deficits seen in the electroencephalograms of adults with schizophrenia). Of note, choline supplementation in the prenatal stress model with rodents reverses this deficit and leads to a healthy pattern of cerebral inhibition. This offers the tantalizing possibility that choline supplementation could do the same thing for some psychiatric conditions as folic acid has done for neural tube defects.

In summary, brain development is an extraordinary and indescribably complex process resulting in a mature brain that is composed of billions of neurons forming trillions of neuronal connections. Prenatal stress may critically affect this process, at times disrupting the fine balance required for optimal development and therefore leading to pathology. The nature, strength, and timing of the stress can cause differential responses in the developing brain, either aiding proper development or predisposing the brain to illness. Accumulating evidence suggests that psychopathology may start even earlier than is commonly acknowledged, and some psychiatric illnesses may need to be redefined as neurodevelopmental disorders. Prenatal stress may lead to pathology via various mechanisms, including oxidative damage and epigenetics. A more thorough understanding of these and other mechanisms may lead to unique therapies that can either reverse the damage of prenatal stressors or prevent the damage altogether. To advance the treatment and prevention of psychopathology, more studies investigating the complex in utero dynamics between environmental stressors and the genome are imperative.

Acknowledgments

This work was supported by National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH086466 07S1 (to DAR) and was produced in collaboration with the National Neuroscience Curriculum Initiative. DAR is co-chair of the National Neuroscience Curriculum Initiative.

We thank Dr. Ashley Walker for her contribution as National Neuroscience Curriculum Initiative editor and Amanda Wang for her role in developing Figure 1.

References

1. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med.* 1998; 14:245–258. [PubMed: 9635069]
2. Schmitt A, Malchow B, Hasan A, Falkai P. The impact of environmental factors in severe psychiatric disorders. *Front Neurosci.* 2014; 8:19. [PubMed: 24574956]
3. Kim DR, Bale TL, Epperson CN. Prenatal programming of mental illness: Current understanding of relationship and mechanisms. *Curr Psychiatry Rep.* 2015; 17:5. [PubMed: 25617041]
4. Smaga I, Niedzielska E, Gawlik M, Moniczewski A, Krzek J, Przegalinski E, et al. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. *Pharmacol Rep.* 2015; 67:569–580. [PubMed: 25933971]
5. Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, et al. Patches of disorganization in the neocortex of children with autism. *N Engl J Med.* 2014; 370:1209–1219. [PubMed: 24670167]
6. Dong E, Tueting P, Matrisciano F, Grayson DR, Guidotti A. Behavioral and molecular neuroepigenetic alterations in prenatally stressed mice: Relevance for the study of chromatin remodeling properties of antipsychotic drugs. *Transl Psychiatry.* 2016; 6:e711. [PubMed: 26756904]
7. Lebel C, Walton M, Letourneau N, Giesbrecht GF, Kaplan BJ, Dewey D. Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. *Biol Psychiatry.* 2016; 80:859–868. [PubMed: 26822800]
8. Gong R, Wang ZP, Wang M, Gao LJ, Zhao ZT. Effects of folic acid supplementation during different pregnancy periods and relationship with the other primary prevention measures to neural tube defects. *J Matern Fetal Neonatal Med.* 2016; 29:3894–3901. [PubMed: 27023398]
9. File SE, Cheeta S, Kenny PJ. Neurobiological mechanisms by which nicotine mediates different types of anxiety. *Eur J Pharmacol.* 2000; 393:231–236. [PubMed: 10771018]
10. Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry.* 2013; 170:290–298. [PubMed: 23318559]

Figure 1.
General neurodevelopment timeline: most of neurogenesis (violet), neuronal migration (magenta), and synaptogenesis (green) occurs before birth.