Maternal Influences on Fetal Neurodevelopment

Andrew W. Zimmerman · Susan L. Connors
Editors

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Clinical and Research Aspects

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Preface

Novel Approaches into the Origins of Neurodevelopmental Disorders: The Fetal Physiology Foundation

Over the past two decades, *autism*, a neurodevelopmental disorder that is defined by behavior and was once believed to be rare, became recognized in increasing numbers of children and recently received distinction as an "epidemic" [1]. While numbers of affected children have steadily increased, our knowledge is still insufficient to explain autism's diverse causes and broad range of presentations. Despite remarkable progress in research, available medical diagnostic testing applies only to a small minority of affected children. Thus, scientifically based explanations with which physicians can diagnose and treat the majority of children with autism and advise their parents are quite limited.

Our society and scientific community were unprepared for the rise in autism, which explains our present inability to understand most of its causes. Researchers in neurodevelopmental disorders have long been aware of other disorders that, despite extensive efforts, have not yielded clear genetic or environmental origins, and autism has become symbolic of the need for new approaches to research into these complex conditions. Although autism has captured our attention in recent years, the prevalence of other neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and bipolar disorder, among others, also has been increasing [2–4]. Several of these conditions share some symptoms with autism, and ADHD, bipolar disorder, OCD, Tourette syndrome and schizophrenia occur more frequently than expected in the extended families of children diagnosed with autism. Similar to autism, none of these disorders is likely to have singular genetic or environmental causes, even though both genes and environmental factors have been implicated in their origins [5].

Further evidence for relationships among these neurodevelopmental disorders can be observed in their overlapping symptoms (Fig. 1). Hyperactivity is present in ADHD and frequently, in autism. Problems with mood regulation are seen in bipolar disorder, ADHD and autism. Thought disorder occurs in schizophrenia and often in bipolar disorder, and difficulty relating to others is common in autism, and may be seen in individuals with ADHD and bipolar disorder. Clinicians have long

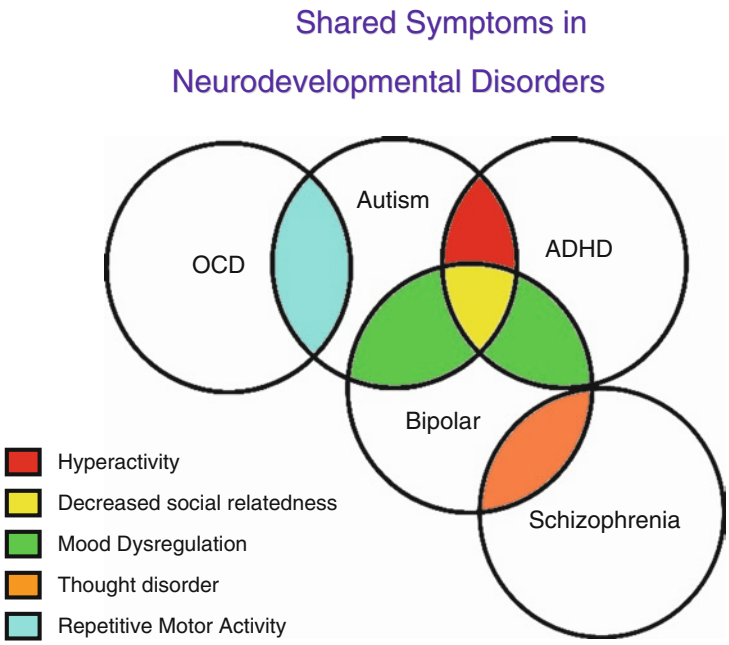

Fig. 1 Several neurodevelopmental disorders have symptoms in common that may result from shared cellular mechanisms during fetal life which may lead to abnormal brain development

observed that family members of affected individuals frequently display traits of these disorders, although they are usually milder and not disabling. They also noted that this group of neurodevelopmental disorders shares a high level of comorbidity; for example, up to 38% of patients with a diagnosis of autism also fulfill criteria for other developmental disorders, such as bipolar disorder, ADHD and OCD [6, 7].

Seven years ago, when many believed that postnatal factors, such as vaccines, were probable causes of autism, a number of researchers hypothesized that prenatal origins were more likely. Data from existing twin studies and an increased incidence within families showed that autism had genetic components. However, the prevalence of this disorder was increasing at an accelerated rate, faster than could be explained by genetic mutations alone. Furthermore, postmortem brain studies showed abnormalities in structures that develop before birth, and extensive epidemiologic research did not support causation by vaccines. It is now apparent that autism – as well as other related neurodevelopmental disorders – may involve multiple causal factors, and that their origins are, in most cases, prenatal.

Until several years ago, only a small number of studies suggested that prenatal interactions between genes and the environment might cause autism, schizophrenia, and other neurodevelopmental disorders. There were relatively few researchers taking this approach, and they were working in disciplines that were historically disconnected from one another. This was a new concept, and important questions arose from this idea and included *when, how and for how long* interactions between

genes and the environment could occur, to result in a neurodevelopmental disorder such as autism. It became clear through the existing scientific literature and clinical observations that the *fetal environment* should be explored as the staging ground for neurodevelopmental disorders.

Historically, research in neurodevelopmental disorders has focused on single genes and biomarkers. In 2003, a small group of investigators envisioned shared elements and complex prenatal origins in causation of these disorders and perceived that environmental influences at multiple levels can act on genetic vulnerabilities to disrupt normal brain development. They predicted that epigenetics and normal gene variants (polymorphisms) would be important contributors to neurodevelopmental disorders. Further, they understood that numerous abnormalities of brain development that occur in neurodevelopmental disorders are not abnormalities of *form*, but rather, disorders of *function* in neurons, neuroglia and their circuitry that affect *future* responses and performance in these tissues. Therefore, dysfunctions that result will often not affect parameters measured at birth, such as Apgar scores or the standard neonatal exam, but will later reveal themselves in symptoms of neurodevelopmental disorders during early childhood, adolescence, or young adulthood. They also believed that changes that occur during fetal life could not only affect the brain, but could also cause system-wide changes in cellular physiology during postnatal development.

The Fetal Physiology Foundation was started to support the concept that the prenatal origins and biological complexity of neurodevolopmental disorders are results of environmental factors acting on genetic susceptibility. This broad new approach was proposed in order to create dialogue among researchers across disciplines, and was based on exploration of development at the cellular level during fetal life. Through the vehicle of this nonprofit research organization, investigators could find both the forum and financial support they needed for small, novel projects centered on fetal neurodevelopment that would lead to larger basic and translational studies.

In 2006, the Fetal Physiology Foundation held its inaugural symposium entitled *Fetal Mechanisms in Neurodevelopmental Disorders* at The Kennedy Krieger Institute in Baltimore, Maryland. Participants identified and discussed both recognized and hypothetical prenatal cellular mechanisms responsible for abnormal neurodevelopmental trajectories. Topics in the symposium illustrated the innovative research the Fetal Physiology Foundation plans to facilitate and support [8].

Since then, research has continued to suggest that the fetal environment is the staging ground for neurodevelopmental disorders and that these disorders result, in part, from genetic susceptibility influenced by various factors during prenatal life. It is likely that the overlapping symptoms among these disorders result from shared fetal mechanisms that interfere with normal cell programming at critical periods during gestation, and that this process is due to multiple environmental, genetic, maternal, and even transgenerational factors. A number of these influences can affect the *intrauterine environment*, such as maternal stress, endocrine alterations, immune responses to infection or a foreign (e.g., paternally determined) protein expressed in the fetus, as well as exposure to pesticides and medications.

Because gene-environment interplay has its most significant effects on brain development within the intrauterine environment, the Fetal Physiology Foundation believed that maternal influences on the fetal environment would be an important topic of investigation. This genre of research, though expanding, was a relatively new approach to the causes of neurodevelopmental disorders. In 2008, the Fetal Physiology Foundation held its second symposium: *Maternal Influences on Fetal Neurodevelopment*, at The Johns Hopkins University School of Medicine, supported by Kennedy Krieger Institute and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and moderated by Tonse Raju, M.D. Participants included both practicing physicians and researchers from diverse disciplines whose work involves maternal–fetal interaction. The chapters of this book, written by invited speakers at the symposium, represent the relevant research presented and discussed. They characterize ongoing efforts of The Fetal Physiology Foundation to foster understanding and support research into maternal and fetal mechanisms that lead to neurodevelopmental disorders.

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Chapter 1
Brave New World: The Intrauterine Environment as the Biological Foundation for the Lifespan

Tonse N.K. Raju

Keywords Developmental origins of adult diseases • Fetal behavior • Fetal programming • Maternal hypothyroxinemia • Maternal–fetal interface • Perinatal encephalopathy

It is widely recognized that Sir Joseph Barcroft (1872–1947) laid the modern methodological foundation for the study of the mammalian fetus. After studying high-altitude physiology for decades, Barcroft, at age 60, turned his attention to the physiology of the mammalian fetus to learn how it develops in an environment of extremely low oxygen tension, or as he put it, "while living on Mt. Everest in-utero." Although his focus was on fetal physiology, he never lost sight of the fact that "…one day, the call will come and the fetus will be born. Not only has the fetus to develop a fundamental life… [to withstand] the shock of birth, but to [also survive in] its new environment [1]." Thus, he implied that physiological processes in the fetus need to be interpreted with a perspective for long-term survival.

More than six decades since the publication of his book, "Research on Prenatal Life" [1], the study of the mammalian fetus and its environment has grown into a robust, multidisciplinary science that confirms Barcroft's visionary statement. The intrauterine environment not only prepares the fetus to withstand the "shock of birth," but also shapes the life course of the infant and his or her mother. In fact, bidirectional developmental programming prepares the maternal–fetal dyad for its interactions and life journey together.

Knowledge in this field has grown rapidly, largely due to unprecedented advances in technology and research methods, and collaboration among scientists from diverse disciplines previously considered "unrelated" fields. Adaptation of research methods from physiology, developmental neuroscience, child psychology,

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molecular biology, population genetics, biomedical imaging, evolutionary biology, and epidemiology was essential to gain insight into the complex world of the intrauterine environment.

The chapters in this volume present a brief overview of the state of the science on this topic. Some major themes addressed by the authors are summarized below.

The Developing Brain

Medical and biology students for generations were taught that the newborn infant's brain is essentially a blank slate onto which, gradually, new knowledge is "filled-in [2]." Some students and teachers may hold such views even now.

The collective evidence, however, seriously contradicts the notion that the mammalian newborn is no more than a "brainstem creature." Within seconds after birth, the newborn infant unleashes a large set of sophisticated neural processing pathways to collect and evaluate, collate and assemble, prune and consolidate neurosensory inputs, constantly remodeling his or her own brain [2]. The infant continues to observe, explore, imagine, and learn more than we ever thought possible. It has been said that a newborn infant is a "scientist in the crib [2]."

In fact, preparations for sculpting the infant brain start long before birth. In addition to the continuous supply of nourishment to the fetus from the mother, there is constant interaction between the two throughout pregnancy. The routes for such interactions include the placenta, the fetal membranes, the amniotic fluid and the uterine wall. The mediators for such intense interplay might be a rich array of hormones, biochemical substances, and cellular intermediates. There may be other channels and mediators yet to be explored. In a large sense, these efforts are geared to assure that the infant launches successfully into this noisy world of light, ambient air, and atmospheric pressure, and to prepare its mother for the role of continuing caregiver.

In Chapter 3, DiPietro summarizes the evidence from several sources on how maternal psychological functioning modulates fetal neurobehavior and evokes responses from the autonomic nervous system. Maternal mood and anxiety states have been shown to elicit responses in fetal motor activity, changes in heart rate and its variability, and breathing. It is remarkable that fetal responses, in turn, influence the mother's biology, often without reaching the level of her conscious perception. In DiPietro's studies, maternal heart rate and skin conductance responses to fetal motor activities at different stages of pregnancy were remarkably similar, whether the mother was from Baltimore, or from Lima, Peru. This apparent universality implies that the phenomenon is biological, rather than cultural. The reasons behind the evolutionary need for such a response are yet to be understood.

Glynn describes an integrated approach to appreciating the complex interrelationships within the maternal–fetal dyad. By means of maternal and fetal programming, both the fetus and the maternal prenatal milieu constantly influence each other, and affect the development of the fetal brain. In addition, we learn of animal studies in which permanent alterations in maternal brain structure and function

take place during pregnancy. Such changes facilitate and strengthen maternal–offspring bonding, perhaps through hormonal mediators.

Disorders in the Offspring and the Intrauterine Environment

In Chapter 5, Rovet and Willoughby review the role of maternal thyroid function in promoting fetal brain development. During the first half of gestation, the human fetus depends entirely upon the mother for thyroid hormones, as shown by measurable concentrations of T4 in the fetal brain long before the fetal thyroid gland begins secreting these hormones. Deprived of the neurodevelopmental effects of maternal thyroxine during gestation, children treated for congenital hypothyroidism secondary to untreated maternal hypothyroidism do not develop full intellectual function, even when therapy is started soon after birth [3].

However, controversy exists concerning the value of universal thyroid screening during pregnancy and the antenatal treatment of subclinical hypothyroid states. Some reasons for this uncertainty are as follows. The serum concentrations of thyroid hormones fluctuate in a somewhat unpredictable manner during pregnancy. Thus developing a standard definition for "subclinical" hypothyroidism is difficult. The laboratory methods and standards for measuring thyroid hormones vary greatly, thus a given blood sample tested in two laboratories may report different results. Perhaps due to the above reasons, no clinical trial to date has shown benefits from intervention for subclinical maternal hypothyroidism during pregnancy.

The US Clinical Trials registry lists many ongoing and recently completed clinical trials on this topic. In one such trial [4] (scheduled to end in 2015), the Maternal–Fetal Medicine Network of the *Eunice Kennedy Shriver* National Institute of Health and Human Development (NICHD), is testing the effect of thyroxine therapy for subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy. In a double-masked[1] randomized controlled trial, 1,000 women have been enrolled and the IQ of the child at 5 years of age is the primary outcome. Recruitment is complete and infant follow-up is continuing.

Ennen and Graham review the complex topic of perinatal asphyxia and neonatal brain damage. Recent demonstration of the beneficial effects of mild therapeutic hypothermia for infants with severe perinatal encephalopathy [5], and the reduced incidence of cerebral palsy in preterm infants with antenatal exposure to magnesium sulfate are two encouraging advances in this field. Magnesium sulfate is the first pharmacological agent with a potential for preventing cerebral palsy.

In Chapters 7 and 8 Smith et al. and Yolken et al. address some of the most perplexing questions in neurobiology, namely, what is the role of intrauterine infections on later development of schizophrenia, and does an altered or "activated"

[1]Previously referred to as "double-blind."

maternal immune system lead to autism spectrum disorders during childhood? The microbial culprits implicated in the etiology of schizophrenia include *Toxoplasma Gondii*, herpes, rubella, polio, measles, and influenza viruses. Activation of the maternal immune system by prenatal maternal infections, and the adverse effects of inflammatory mediators may be causally related to poor neuropsychiatric outcomes in offspring in this situation.

Johnson and colleagues describe the role of maternally acting gene alleles in causing neurodevelopmental disorders – a novel and rapidly expanding field of science. At least 35 distinct neuropathological conditions have been identified in which the mother is the "patient," and her offspring develop abnormally as a result of her maternally acting alleles. The conditions include autism, Down syndrome, rheumatoid arthritis, schizophrenia, and spina bifida among others. This field of genetics is new in neurodevelopmental disorders. In addition to the mother, maternal grandparents may contribute "teratogenic alleles" responsible for such conditions as schizophrenia and autoimmune disorders that develop years later in the children.

Future Research

The state-of-the-science reviews in this volume also identify gaps in our knowledge and suggest further research to fill them. A few additional proposals are discussed below.

What, How and Why? Most studies in this field have been exploratory. Studies designed to "*see what happens when …*" help generate hypotheses to be tested. "How" and "why" may be the obvious next type of questions that need to be asked. At present, genetic and molecular models have been used to seek mechanistic explanations for the observed responses to changes in the intrauterine environment. However, to address the more difficult "why" questions, one needs to design long-term prospective studies. Imaginative techniques may need to be developed by integrating research methods from biomedical and bioengineering sciences, as well as from anthropology and evolutionary biology.

Developmental, Not Only Intrauterine, Environment

Development is nonlinear and each system follows its own trajectory while interacting with other systems. The intrauterine period is one of many phases in the lifespan from an embryo and fetus to adulthood and old age. There are critical phases of growth and maturation, and of vulnerability and plasticity. Thus, a broader approach to understanding "developmental" environmental influences on adult phenotypes may be the next frontier in this field of research.

Public Health Implications of Developmental Programming

The emerging science of developmental origins of adult diseases (DOAD) has fundamentally altered our approach to adult onset disorders, such as type II diabetes, coronary artery disease (CAD), stroke, hypertension, and obesity. What are the public health implications of the evolving knowledge of DOAD? Can we develop interventions based on what we have learned? For instance, low birth weight has been associated with adult onset CAD. To reduce the risk of CAD, therefore, should we implement interventions to optimize fetal growth? Is there a risk of increasing childhood obesity by such an approach? Similarly, if maternal infections are proximate etiological "causes" for neuropsychiatric conditions, should one develop methods to diagnose them early and treat the fetus? These are but two examples in this rapidly growing field.

Manipulating the Environment to "Optimize" Outcomes

This field opens up a new world of possibilities and questions. As an example, can one manipulate the intrauterine environment to improve or modify maternal–infant bonding, or prevent damage from adverse environmental pollutants? Are there ethical limits to such approaches?

Intrauterine Environmental Deprivation

Preterm infants will be deprived of the full complement of intrauterine environmental influences compared to their term-born counterparts. The negative consequences from such deprivations, if any, could impact a large segment of the population, since the preterm birth rate has been increasing in the USA, reaching an all time high of 12.8% in 2006 [6].

Depending upon the extent of prematurity, preterm infants are at two- to tenfold higher risk than term infants for cerebral palsy, sensory motor impairments, seizures, learning and behavioral problems, and cognitive and psychological dysfunctions, many of which persist into adulthood [7]. The proportion of such morbidities attributable to the early termination of the influences of the intrauterine environment are unclear.

Kinney et al. showed that brain weight increases by about 35% between 35 and 40 weeks of gestation [8]. What are the intrauterine forces that trigger the rapid rate of synaptogenesis and dendritic arborization necessary for the late gestational surge in brain growth? Might an early termination of the intrauterine environment be responsible for disrupting those processes and the brain's growth spurt, leading to

a higher proportion of developmental and learning disabilities, and psychiatric dysfunctions in late preterm infants born between 34 and 36 weeks of gestation? Answers to these and related questions remain to be addressed in future studies.

Fetal Learning

The legend of Abhimanyu in the Indian epic *Mahabharata* may be the first reference to fetal learning (or programming?). While he was still in his mother's womb, Abhimanyu learned from his father Arjuna, the secret art of penetrating the deadly *Chakravyuha*, or circular formation of infantrymen, archers, horse-drawn chariots, and elephants in battles. Arjuna was describing this secret to his pregnant wife, and midway through the narration she dozed off. Thus the fetus could not learn how to get out of the Chakravyuha. Years later, this half-knowledge would cost young Abhimanyu his life. In the Great Battle, Abhimanyu penetrates the circular formation, but, not knowing how to get out of it, he is trapped and killed by the enemy.

Although a legend, Abhimanyu's story raises interesting questions: can maternal learning during pregnancy help program the fetus to learn, too? What is the nature of such knowledge?

There may be a risk, however, in taking the notion of fetal learning too far. As a recent article in *The Washington Post* describes, dozens of products have flooded the market as "prenatal learning systems," enticing pregnant women to enroll their unborn children in womb-schooling [9]. None of these products has been tested for efficacy, and none has received the approval of the Food and Drug Administration as a medical device. As well as being ineffective, there is potential that they may cause harm. The processes for in-utero learning (or conditioning) might have evolved through natural selection for reasons yet to be understood. Thus, it is premature for us to become "fetal teachers," and to develop devices for enhancing fetal learning systems. It may be wise to follow the dictum "not to fool Mother Nature."

Conclusions: View from Mt. Barcroft

Our current knowledge about the intrauterine environment could not have materialized without the groundbreaking work of Barcroft and his contemporaries in the early- to mid-twentieth century [1], along with technological advancements during the past 20 years. Barcroft began writing his book in 1939 as Great Britain entered World War II [1], and had plans to write Part II devoted to the developing nervous system. Unfortunately, a few weeks after receiving the printed copy of Part 1, Barcroft died of a heart attack on March 21, 1947.

In 1954, the US Board on Geographic Names christened a 13,040-ft peak on California's White Mountains, *Mt. Barcroft* [10]. Several laboratory facilities have been built by the University of California on these mountain peaks to conduct