Maternal and Environmental Influences on Perinatal and Infant Development

Alexandra O'Sullivan and Catherine Monk

Summary

Mother and child wellbeing are intimately connected during pregnancy and the first 12 months of the infant's life. The fetus and child directly experience the mother's life and are shaped by it. A mother's environmental experiences, physical health, and psychological distress affect her interactions with her infant, which in turn have physiological, neurological, and psychological consequences that extend far into the future.

In this article, Alexandra O'Sullivan and Catherine Monk explore the biological and behavioral pathways through which the physical and psychological toll of environmental experiences such as poverty, trauma, pollution, lack of access to good nutrition, and systemic disadvantage is transmitted from mother to child, thus impairing fetal and infant neurobiological and emotional development.

Fortunately, there are ways to buffer these risks and reorient both the child and the mother-child pair toward a strong developmental trajectory. The authors examine promising avenues for policy makers to pursue. Chief among these are policies that increase access to health care, including mental health care, and those that reduce family stress during pregnancy and the postpartum period, for example, by boosting family income or allowing parents to take paid leave to care for their newborn children.

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Child development begins before birth, and the womb is an influential first home. The perinatal period, which spans pregnancy through the first nine months of an infant's life, is characterized by dramatic physical and neurobiological development. The mother also experiences significant physical, mental, biological, and social changes, all of which may affect the child. Mother and infant wellbeing are intimately connected. Research demonstrates that the fetus experiences the mother's life and is shaped by it. Through biological and social pathways, factors such as her emotional and physical health or experiences of discrimination and poverty influence infant brain-behavior development and contribute to long-term child psychiatric and social-emotional outcomes. Accordingly, clinical and policy interventions that aim to improve maternal health care and ease stress during the prenatal and postpartum periods—such as increased access to behavioral health screening and treatment, paid parental leave, and extended insurance coverage—can have positive downstream effects on child development. These are early first steps that can help to prevent the intergenerational transmission of psychiatric illness and disadvantage.

Developmental Origins of Health and Disease

In the 1980s, epidemiologist David Barker hypothesized that long-lasting health effects flow to a child from early environmental influences, even those experienced prenatally. Now known as the Barker hypothesis or prenatal programming, this concept of the developmental origins of health and disease (DOHaD for short) has more recently been applied to the study of maternal mental health and children's neurobehavioral and neurocognitive development and long-term psychiatric outcomes, highlighting a third, potentially preventable pathway for the familial transmission of risk for future mental illness. That is, pregnant women's psychological and physical health may impact fetal brain development, with significant consequences for the child's future wellbeing. Using evolutionary theory as a framework, the DOHaD model describes the fetus as adapting to the in utero environment based on signals from the mother that foreshadow the postnatal environment to come, thereby promoting survival in the postnatal world. As the fetal brain continues to develop, these biological adaptations become programmed (and therefore long lasting), potentially placing the child at risk for psychological or developmental challenges if the prenatal and postnatal environments are misaligned.

The Brain's Beginnings: Fetal Neurodevelopment

The transformation of a cluster of cells into a nascent brain occurs in a mere nine months. Over this time, inherent genetic patterns and variations interact with characteristics of the fetus's environment to organize the different elements of the brain into one complex and remarkable organ. While the fetal brain is developing, it is learning. The fetal brain's plasticity allows it to learn from and adapt to environmental experiences. Though this dynamic process continues throughout a person's life, the fetal brain's heightened responsiveness to new experiences makes the prenatal period a time of great opportunity—but also vulnerability.

Fetal brain development is typically divided into three distinct phases: embryonic (from conception to the eighth gestational week), the early fetal period (up to mid-gestation), and the late fetal period (lasting until birth). By the end of the embryonic period, the basic structures of the brain and central nervous system, including the neural tube (responsible for future neuron production), are established—long before obvious signs that a woman is pregnant and often before even she knows. Because inadequate folic acid and vitamin B intake can cause neural tube defects leading to risks of serious birth malformations, vitamin supplementation is important for all women of childbearing age, as is a healthy lifestyle. During the early and late fetal periods, brain development centers on producing, connecting, and differentiating neurons. Fetal exposure to environmental toxins that influence the speed and accuracy of communication between neurons (such as drugs of abuse or prescription medications), inadequate nutrition, the effects of preterm birth, and maternal infection and inflammation all may impact the development of neural circuits and neurotransmitter systems, contributing to risk for poor neurobehavioral development. Fetal alcohol exposure is also linked to increased cell death in the developing brain.

Throughout this extensive period of brain development, fetal learning occurs. For example, by late in pregnancy, fetuses can distinguish different sounds, including music and their mother's voice. However, the communication of information from mother to fetus also includes biological signals related to aspects of the mother's life, such as relatively high levels of the stress hormone cortisol. Pregnancy is thus a period of dramatic fetal brain growth as well as developmental vulnerability during which the genetic blueprint of the brain is altered through qualities in the mother's life that make up the fetus's environment.

Environmental Influences on Fetal Neurodevelopment

The phrase environmental exposures readily conjures adverse factors, such as pollution or physical illness, that affect the mother and her health. In DOHaD research, the concept of environmental exposures also extends to mothers' psychological distress, including depression, anxiety, and perceived stress, all of which are associated with biological changes in the mother that alter the fetus's environment.

Maternal Mental Health

In 2015, the World Health Organization declared maternal mental health a major public health concern, calling it one of the most overlooked aspects of pregnancy care. In the United States, the prevalence of depressive disorders and anxiety disorders during the perinatal period is estimated to be between 18 and 19 percent and 12 and 13 percent, respectively. These rates are more than twice as high in low-income and minority populations. An estimated 30 percent of pregnant women report some kind of stress in their daily lives. These statistics matter. Substantial evidence demonstrates that elevated maternal distress during pregnancy increases the future child's risk for mental health disorders, including anxiety, depression, attention deficit/hyperactivity disorder (ADHD), and schizophrenia.

For example, a study of nearly 8,000 British children found that children exposed to higher prenatal maternal anxiety were at

greater risk for overall behavioral problems (for example, ADHD and conduct problems) at age seven. These effects persisted: exposure to high levels of prenatal anxiety doubled the risk of having a mental health disorder at age 13. This influence on children's health was evident even when researchers also considered other adverse prenatal influences, such as maternal smoking and drinking, medical conditions during pregnancy, socioeconomic status, and the mother's mood postpartum. Similar outcomes were identified for prenatal maternal depression. This association between maternal distress during pregnancy and children's increased risk for social-emotional problems has been corroborated by research groups in many other countries.

Although these associations have been found in both male and female children, research suggests that male fetuses are more vulnerable. In a recent study comparing psychologically stressed, physically stressed, and healthy mothers, researchers found that the secondary sex ratio (in the general population, 105 male infants are born for every 100 female infants, for a ratio of 1.05:1) became 4:9 for physically stressed mothers, and 2:3 for mothers experiencing psychological distress; that is, highly stressed women were less likely to give birth to a male infant. This apparent heightened male vulnerability to adverse prenatal environments may be an evolutionary response to natural selection pressures—relatively few but healthy men are needed for species survival, whereas many women are needed to carry single pregnancies to term.

More recently, DOHaD researchers have turned their attention to the brain itself. Magnetic resonance imaging studies have identified differences in newborns, older children, and even adults associated with prenatal exposure to maternal distress. A study that followed children from the prenatal period until they were six to nine years old found that higher maternal prenatal anxiety was associated with reduced gray matter volume (an indication of fewer neurons) in the brain's prefrontal cortex, a region integral to cognitive abilities such as reasoning, planning, attention, and working memory. Similar reductions have been found in adults exposed to maternal stress in the prenatal period, emphasizing the enduring nature of these changes. Other studies have related maternal prenatal depression to greater cortical thinning (a characteristic of people with depressive disorders) at age seven and child depressive symptoms at age 12. Each of these studies controlled for other possible influences, such as the mother's physical health in pregnancy. A recent imaging study confirmed that the prenatal environment is responsible for these brain changes: researchers found that resting state connectivity between the amygdala and the prefrontal cortex—a neural circuit that's key to regulating emotions—was different in the brains of newborns exposed to untreated prenatal depression compared to the newborns of healthy women. This suggests that the fetus adapts in anticipation of the unfavorable postnatal environment indicated by the mother's depression.

The association between maternal mental state and fetal neurodevelopment has even been shown in real time in studies that demonstrate fetal responsiveness to acute laboratory-induced stress at the moment the mother experiences it. These studies show that the fetuses of distressed women are more reactive to the biological cues of maternal acute stress,

with the magnitude of mid- to late-term fetal response varying based on maternal depression or stress levels, providing evidence that in the latter part of pregnancy the fetus is experiencing and being shaped by its mother's life. The public health significance of pregnant women's psychological wellbeing is thus clear. Pregnant women's mental health matters both for them and for their future children. Without access to timely and effective interventions to alleviate mothers' distress, the intergenerational cycle of psychiatric illness continues.

Other Environmental Factors Influencing Fetal Neurodevelopment

Pregnant women don't live in a vacuum. Every day, women are exposed to environmental and psychosocial sources of stress that impact both their own psychological and physical wellbeing and that of their unborn child.

Poverty and psychosocial factors. Major adverse life events, such as death or illness in the family or pregnancy-related health problems, can occur during any woman's pregnancy. However, chronic psychosocial stress factors such as poverty aren't randomly distributed throughout society. Poverty is associated with reduced access to prenatal care and to increased exposure to cigarette smoking, poor nutrition, and distressed, environmentally hazardous, or insecure housing, each of which contributes to compromised pregnancy outcomes, such as small size for a fetus's gestational age, preterm birth, and low birthweight.

In each case, factors such as reduced access to healthy food, transportation, and health care contribute to these negative birth outcomes. Opportunities to promote maternal health and reduce stress in this context may include better access to medical facilities and public transport and adjustments to built environments, such as support for developing green spaces, which have been associated with increased infant birth weight.

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Systemic racism in the United States also produces significant discrimination-related stress during pregnancy. A recent study compared stress related to discrimination experienced by non-Hispanic white and black pregnant women of similar socioeconomic level. Non-Hispanic black women reported higher levels of discrimination (and worry about discrimination); their blood samples, taken over the second and third trimesters, contained significantly higher levels of adrenocorticotropic hormone (produced in response to stress), suggesting biological differences as a result of cumulative racial disadvantage.

Nutrition. The quality of a mother's diet can have long-term implications for her child's future health. Pregnant women with inadequate nutrition often experience symptoms of depression or stress. Thus high distress and poor nutrition are highly interrelated and associated with similar adverse neurobehavioral outcomes in children.

Financial and geographical barriers to the fresh foods and vitamins required for a healthy pregnancy often limit pregnant women's options, especially when they live in disadvantaged environments.

Although macronutrient deficiencies (such as reduced overall caloric intake) pose risks to the developing fetus, relatively easy access to processed foods in the United States today has meant that most pregnant women consume sufficient calories. Yet too often this increase in calories isn't associated with a corresponding increase in intake of micronutrients (such as zinc, iron, copper, or vitamins including choline, folate, and vitamin A). Both macro- and micronutrient deficiencies during pregnancy are associated with greater risks of neurobehavioral developmental outcomes, such as cognitive delays, ADHD, autism spectrum disorder, and schizophrenia. A lack of dark leafy greens, legumes, and oranges during pregnancy can have particularly devastating consequences for fetal neurodevelopment. These foods contain high amounts of the B vitamin folate, which plays a key role in DNA synthesis and function. Research relates varying levels of prenatal folate to subtle differences in brain development; low levels correlate with future developmental challenges. Further still, inadequate levels of folate during pregnancy, and even in the month before conception, dramatically increase the risk of neural tube defects, which can lead to severe physical disabilities such as spina bifida. Prenatal folate deficiency has also consistently been linked with infant and child emotional and behavioral problems, particularly social withdrawal, poor attention, and aggression.

Nutrition also plays a key role in mothers' mental health. Deficiencies of folate, vitamin B12, calcium, iron, selenium, zinc, and magnesium have been associated with symptoms of depression. Studies have shown that people experiencing stress and depression are more likely to choose processed, high-fat, high-sugar foods at the expense of fresh, nutritious options. During pregnancy, poor nutrition affects two generations.

Research into the effects of prenatal nutrition underpinned the most effective pregnancy-related public health campaigns to date. Beginning in the 1990s—based on clinical trials demonstrating the benefits of dietary supplementation of folic acid, a synthetic form of folate—pregnant women were told about the relationship between their own health and their child's development. Since approximately half of US pregnancies are unplanned, the US Preventive Services Task Force now recommends that all women of childbearing age take a daily folate supplement. In addition, the US Food and Drug Administration approved folate supplementation for foods such as cereals and, more recently, corn masa flour. The effects of this campaign have been significant. From the early 1990s to the 2000s, the rate of neural tube defects dropped from 11 to seven cases per 10,000 live births. It's estimated that food fortification prevents about 1,300 neural tube defects a year. Nevertheless, rates of daily folate supplementation today are still low and falling. Between 2006 and 2016, daily vitamin supplementation decreased in women of childbearing age, falling from 32.7 to 23.6 percent. One reason for this decrease may be a lack of patient understanding of

the risks of neural tube defects; another might be the cost of daily multivitamins. Clearly, work remains to be done in both public education and increasing access to affordable prenatal vitamins and fortified foods.

Chemicals and pollution. The developing fetal brain is affected by maternal environmental exposure to chemicals and air pollution. Researchers who've collected mothers' blood, urine, and hair samples have revealed widespread exposure throughout pregnancy to numerous chemicals, many of which are known to have adverse health effects. For example, easily metabolized chemicals (such as the phthalates, parabens, and bisphenol A, found in plastics and personal care products) and heavy metals (such as lead and mercury, found in contaminated water or paint particles) are known to affect fetal growth and lead to poor birth outcomes, including low birthweight, preterm birth, and associated developmental delays.

Understandably, pregnant women diagnosed with a high risk-pregnancy complication are often anxious or suffer from depression.

Air pollution increasingly affects maternal and fetal health as large US cities continue to become more congested. Air pollutants commonly inhaled by pregnant mothers, such as nitrogen dioxide, carbon monoxide, sulfur dioxide, and ozone, pose risks to fetal and infant health and have been associated with low birthweight, preterm birth, and future respiratory illnesses. Studies have shown that these adverse outcomes are heightened in more socially disadvantaged women. Policies to reduce traffic congestion and carbon emissions positively impact all citizens, including those not yet born.

Maternal physical health. Mothers' psychological distress in the form of anxiety, depression, or perceived stress is both a risk factor for and a consequence of chronic maternal diseases, such as diabetes and preeclampsia, a disorder causing sudden high blood pressure in pregnant women. Both diseases cause pregnancy complications and can affect infants' neurodevelopment.

Understandably, pregnant women diagnosed with a high risk-pregnancy complication are often anxious or suffer from depression related to the uncertainty surrounding their pregnancy and the associated risks to their child's future health. This distress is not unfounded. One studied showed that the babies of "physically stressed" mothers (for example, pregnant women with elevated daily blood pressure or high caloric intake) are more than twice as likely than the babies of unstressed mothers to be born preterm (22 percent compared to 8 to 10 percent). Hypertensive disorders during pregnancy are also linked with higher risk for child behavioral problems, ADHD, mood disorders, and schizophrenia. Moreover, psychological distress and psychosocial stress factors can themselves induce gestational diabetes mellitus, which is associated with an increased risk for autism spectrum disorder.

Finally, many drugs of abuse cross the placenta and so reach the fetus. Prenatal drug exposure is related to prematurity,

low birth weight, and neonatal abstinence syndrome, a condition in which the baby goes through withdrawal. In the past two decades, neonatal abstinence syndrome diagnoses have increased nearly fivefold in the United States, resulting in estimated neonatal hospital costs in excess of $1 billion per year. In addition to contributing to serious pregnancy complications, prenatal exposure to drugs of addiction is associated with severe behavioral dysregulation and cognitive impairment. For example, prenatal opiate exposure has been related to poor neurocognitive development from age six months on, worsening by school age and into adolescence. Similar neurocognitive deficits have been found in infants and toddlers exposed prenatally to cocaine, alcohol, tobacco, and marijuana, independent of risks associated with premature birth and socioeconomic status.

The Growing Mind: Neurodevelopment in Infancy

Birth brings considerable environmental change for the infant, yet continuity remains in the neurodevelopmental processes that commenced nine months earlier. The learning that began in the womb continues and accelerates significantly over the first 24 months as the infant becomes familiar with his or her new environment and the people in it. At birth, the neonatal brain weighs 400 grams, approximately 25 percent of its eventual adult size; by age two, the brain has grown to 75 percent of its adult size, indicating the importance of infancy and toddlerhood as developmental periods. During this further period of neural plasticity, the brain is highly malleable and constantly evolving, as it is custom built to reflect the child's experiences in the world.

Maternal Mental Health in the Infant's First Year

An infant's neurobehavioral development in the first year is exquisitely sensitive to the postnatal environment, including the mother's mood. In the United States, an estimated 20 percent of mothers will experience an episode of depression in the first three months after giving birth. Women with a history of depression, anxiety, or prenatal depression or anxiety are at significantly greater risk for postpartum depression. As we've noted, the incidence more than doubles in at-risk maternal populations, such as women in poverty. One study looking at young, low-income African American mothers between two weeks and 14 months after delivery found that 56 percent of the mothers met the criteria for either major (37 percent) or minor (19 percent) depressive disorders. These mothers' experiences play a significant role in early infant development. Maternal depression undermines mother-infant emotional communication and dyadic reciprocity (the sharing of emotional affect between mother and infant) and has profound consequences for an infant's social-emotional development. Laboratory studies show that infants are stressed when their mothers display a withdrawn affect. Using the well-established still face paradigm, in which the caregiver plays with and then emotionally withdraws from the infant—a simulation of the experience of maternal depression—studies demonstrate that infants of depressed mothers respond to the unpredictability of maternal engagement with reduced activity, greater behavioral dysregulation, and withdrawal.

The effects of maternal depression on child neurodevelopmental processes don't end in

infancy. Maternal postpartum depression is also associated with reduced social competence and compromised language development in early childhood. These effects are long lasting and stark. A large, recently published study followed the course of maternal depression and child outcomes for 18 years. The study found that mothers with severe postpartum depression at both two and eight months after delivery were more likely to still be depressed 11 years later, compared to mothers with nonpersistent depression. Their children, in turn, were four times more likely to exhibit behavioral problems when they were between three and four years old, twice as likely to have lower math scores at 16, and seven times more likely to have depression themselves at 18. These intergenerational effects of maternal depression show how important it is to screen for depression at all life stages and to promote a dyadic approach to identifying and treating maternal mood disorders.

However, maternal sensitivity—the mother's ability to interpret and effectively respond to the infant's signals—can mediate maternal depression's effects on infants. On the one hand, insensitive maternal behavior during caregiving tasks is associated with increased infant neurobehavioral responsiveness to stress and child psychopathology. Maternal distress associated with depression and social disadvantage can diminish a mother's ability to provide sensitive caregiving and a responsive home environment that stimulates early cognitive and language development. On the other hand, sensitive maternal behavior in infancy predicts better social-emotional outcomes in children. In addition—and importantly for intervention purposes—sensitive maternal caregiving can buffer the neurobehavioral effects of prenatal distress. For example, only when the quality of postnatal care at age four months was low did the four-month-old infants of mothers diagnosed with anxiety or depression in the second trimester of pregnancy show significantly higher cortisol levels (a biomarker of stress) than the infants of healthy women. In short, sensitive maternal caregiving in the infant's first year can enhance the developmental trajectories of infants exposed to maternal distress in the womb.

Biological Pathways for Transmission of Risk

How does maternal distress shape fetal and infant neurobiological and emotional development? Through which biological and behavioral pathways are environmental experiences transmitted from mother to child?

Mechanisms during Pregnancy

Several pathways have been associated with increased risk of autism spectrum disorder, schizophrenia, mood disorders, and ADHD in children. One is the hypothalamic–pituitary–adrenal (HPA) axis, which plays a central role in releasing stress hormones. Atypical functioning of the mother's HPA axis is associated with maternal distress and increased circulating levels of the stress hormone cortisol. Cortisol can readily cross the placenta and thereby reach the fetus, affecting the development of the infant's own HPA circuitry and brain development, which increases the risk of psychological distress in the future child. Another pathway is alterations in the mother's immune system that can affect brain connectivity. Maternal immune activity—part of a stress experience

and/or response to infection—may cause placental inflammation or the release of cytokines (signaling molecules that affect the survival and differentiation of neurons in the brain) into the mother's system, where they can cross the placenta and affect the developing fetus.

Environmental influences also may alter fetal neurodevelopment by modifying the functioning of the placenta through a process called *epigenetics*, which can result in heritable modifications to gene expression (whether a particular gene is activated or suppressed). The most commonly studied epigenetic mechanism, DNA methylation, can change the activity of DNA without changing the underlying sequence itself. For example, the placenta regulates fetal exposure to cortisol in part by DNA methylation of certain genes. Changes to this placental function can lead to high arousal and poor self-regulation in newborns, each of which is an indicator of risk for future behavioral problems. Considerable research is under way to determine whether epigenetic processes in the placenta and other tissues that are key to development contribute to the intergenerational transmission of environmental experiences, such as poverty, trauma, and systemic disadvantage.

The maternal microbiome offers another possible way for prenatal maternal stress to influence fetal neurodevelopment. Prenatal distress is known to alter mothers' gut microbiota, and research shows the infant microbiome is developed perinatally during birth (for example, infants born vaginally show gut microbiota that resemble their mother's vaginal microbiome) and even prenatally via transmission through the placenta. The microbiota that colonize the infant gut affect important processes such as metabolism and nutrient extraction. And because infant brain development exerts a high metabolic demand, microbial colonization may influence brain maturation in a long-lasting way. Animal studies that have found evidence of this pathway have suggested that probiotic supplementation, which alters gut microbiome, may reduce the symptoms of some psychiatric disorders, including autism spectrum disorder and depression. However, neither animal nor human studies have yet considered whether prenatal maternal stress, along with accompanying changes to the infant microbiome, have long-term behavioral and psychiatric implications.

But what of the role of shared genes? How can genetic traits shared between mother and child be disentangled from the mother's prenatal lifestyle factors and negative child outcomes, particularly for characteristics such as depression, known to run in families? Studies that consider the influence of both genes and environmental factors, such as maternal mood, have found that maternal distress remains a significant independent factor. For example, one study identified an independent effect of prenatal maternal distress on children's risk for behavioral problems and anxiety in both related children and unrelated children that were conceived with the egg of another woman via in vitro fertilization (that is, the risk was found in both related and unrelated children with prenatal exposures to their mothers' lives). Another study, which controlled for parental history of psychiatric symptoms as a marker for genetic predisposition, also found an independent effect of prenatal stress on children's psychiatric outcomes. Researchers are currently trying to learn more about the unique interactions between

prenatal maternal stress and infant genes and to identify how these interactions shape children's risk profiles for future psychopathology.

Mechanisms Extending beyond Pregnancy

Sensory experience, which is common to both the prenatal and postnatal periods, is another way that risk for future neurodevelopmental and social-behavioral problems is transmitted. Researchers in one animal study found that pig fetuses learned to associate a particular human voice with a negative (for example, painful) maternal experience; once born, the piglets emitted more distress calls upon hearing that voice. This suggests that the fetal brain may learn in the womb to associate maternal experiences (experienced by the fetus via maternal hormones or cardiorespiratory activations) with external sounds, including voices. One question for future research is whether children who are primed to associate their mother's angry or upset words with biological stress cues may be more sensitive to their mother's (or others') distress. Another is whether children be can primed to respond with similar sensitivity to sounds associated with intimate partner violence, learned before birth.

Studies have also shown that consistency in fetal and infant sensory experiences is important. Mere unpredictability of sensory signals (for example, disjointed maternal emotional states during pregnancy or unpredictable postnatal maternal care) may be a form of chronic stress to the offspring that affects the structural and functional development of the brain during a vulnerable period. In this context, "unpredictability" doesn't refer to how sensitive the mother is, but rather the consistency of her behavior. Remarkably, some researchers have found greater positive mental development in one-year-old children whose mothers experienced consistent pre- and postnatal depressive symptoms than in children with mothers whose emotional state improved postnatally. Scientists have since shown that the neurodevelopmental effects of unpredictable sensory experiences (including visual, auditory, and tactile signals) are associated with long-term emotional difficulties, poor cognitive outcomes, and immature executive function (associated with vulnerability to future mental illness) in both early and late childhood.

The fetal brain may learn in the womb to associate maternal experiences with external sounds, including voices.

Opportunities for Intervention

A considerable body of evidence has established that the foundational experiences of the fetus during pregnancy and the infant postpartum are critical to early development. In particular, untreated maternal prenatal distress and poor mother/infant attachment can lead to long-term adverse cognitive and behavioral outcomes. Interventions aimed at easing maternal distress and improving maternal health care in both the prenatal and postpartum periods have downstream positive effects on child development. Here we review promising avenues for intervention and treatment; most of them focus on addressing maternal mood because stress, depression,

and anxiety independently affect outcomes or accompany other adverse experiences that affect mothers and their offspring.

Cognitive behavioral therapy and interpersonal psychotherapy are first-line behavioral treatments consistently found to reduce the symptoms of perinatal depression and anxiety. In 2019 the US Preventative Task Force recommended that at-risk pregnant and postpartum women be referred to these types of counseling.

In-home visiting programs have proven particularly successful as a means of reaching at-risk women during the perinatal period, and adding a cognitive behavioral therapy component to the home-visiting model has helped prevent perinatal depression. One such program is Mothers and Babies, a prenatal and postpartum cognitive behavioral therapy program that gives mothers a "toolkit" that encourages them to take part in enjoyable activities, gives them access to increased social support, and promotes healthier ways of thinking. A recent randomized controlled trial (RCT) found that adding the Mothers and Babies model to a regular perinatal home-visiting service for primarily single, low-income Latina or African American women reduced women's depressive and anxiety symptoms at six months after birth compared to women who received only the home visit.

Other in-home programs, such as Minding the Baby (MTB), are directed toward young first-time parents (ages 14 to 25) who are at heightened risk for difficulty adjusting to the postnatal period. These programs use an interdisciplinary, attachment-focused approach that aims to improve mothers' mental health and strengthen the mother-infant relationship. An initial RCT of the MTB program demonstrated a range of beneficial health and attachment outcomes, including more child immunizations at one year, fewer reports to child protective services, an increased likelihood of secure attachment, and less likelihood of infant behavioral disorganization at 12–14 months. Follow-up studies have found significantly fewer externalizing behavioral problems in MTB mothers, and lower levels of obesity in Hispanic MTB toddlers relative to control groups. Recently, the second phase of the RCT found that the ability of mothers in the MTB group to understand their child's mental state (a mental process called "reflective functioning," which is often impaired in stressed mothers but is essential for secure mother-infant attachment) increased over the course of the program compared to control mothers.

Recent work from our group has also shown that prenatal social support for the mother from family, friends, or community is important. A physically or psychologically stressed mother's social support can act as a protective factor against adverse birth outcomes, including preterm birth and younger gestational age at birth. Thus enhancing a mother's social support—for example, through home visits or mothers' group programs—may be an effective clinical intervention.

Finally, although much research on the developmental origins of health has focused on identifying the causes of negative outcomes and how to prevent them, researchers are increasingly exploring the beneficial consequences of positive maternal mental health. For example, the Growing Up in Singapore Towards Healthy Outcomes

project has established that self-reported maternal positive mood and sense of self is uniquely and positively associated with better cognitive, linguistic, and socioemotional development among two-year-olds. The potential beneficial downstream effects, for both the individual and society, of such adaptive developmental processes in early childhood should make positive maternal mental health a top public health priority.

Psychotherapy for Mother and Child

Despite the progress researchers have made in developing interventions to alleviate maternal distress, too few studies consider maternal and child outcomes together. Because improvements in pregnant women's mood and wellbeing can have a beneficial effect on the developing child, prenatal interventions can aim to treat at least two patients, the mother and her child. This kind of dyadic approach to treatment would take advantage of the profound bidirectional psychological and biological influences between them: as the infant brain develops before birth, so too does the parental brain.

It would be a grave perversion of science if research into the consequences of maternal experience were used to blame women for their children's development.

Increasingly, clinical researchers point to two factors that impact infant neurodevelopment: maternal depression (with associated risks via prenatal programming of poor mother-infant attachment) and related dysfunctional parenting behaviors, which may be easier to target in the short term. RCTs in progress of two innovative programs—one of which offers women resources for effective parenting in the postpartum period and the other of which offers interpersonal therapy—ask the key question about prenatal parenting interventions, namely, whether reducing pregnant women's depression positively affects infants' neurobehavioral development, thus reducing the risk of later psychopathology. These trials will function as an experimental test of the fetal programming hypothesis, and the results will have direct implications for programs that seek to improve pregnant women's behavioral health and treat maternal distress.

How Not to Blame the Mother

It is clear that mothers' experiences are crucial to children's outcomes. Yet it would be a grave perversion of science if research into the consequences of maternal experience were used to blame women for their children's development. Women already feel intense pressure regarding the mothering role, particularly in the era of social media. DOHaD researchers and other developmental researchers therefore must stress that maternal health is one of a complex patchwork of factors that influence children's brain-behavior development. Others include shared genes, as well as paternal factors such as the quality of the father's sperm and his support for the mother's wellbeing during pregnancy. Broader social factors are also relevant. The maternal distress and exposures frequently associated with poor child outcomes, such as air pollution, lack of nutrition, and inadequate housing, are in many cases the products of

systemic disadvantage and discrimination. Such stress factors take a particularly heavy toll on racial minorities and low-income populations. Poverty is the magnet that attracts risk factors for toxic stress and other social determinants of health, thus perpetuating the cycle of disadvantage. Policy interventions to improve these psychosocial risk factors, as well as women's mental health, must be a priority if we are to make substantial progress in improving the lives of women and future generations.

Policies for Perinatal Success

Chief among policy proposals that mesh with the aims of clinical interventions are those that emphasize increasing access to health care, including mental health care, and reducing family stress during pregnancy and the postpartum period.

Improving Access to Behavioral Health Care

Complex issues of family, stigma, cost, and availability are common obstacles to women accessing mental health care services. Following recommendations from the American College of Obstetricians and Gynecologists, prenatal care increasingly includes mental health screening, particularly for anxiety and depression. Yet screening alone doesn't mean women will receive treatment. By helping women access the care they need, perinatal home-visiting programs have significantly improved family and child outcomes. But given their high cost, these programs should be reserved for the most vulnerable families. One proposal for increasing access is to embed cost-effective mental health care in primary obstetric offices. Pregnancy represents a unique period in which nearly all women, including women from underserved communities, are both motivated and, via Medicaid for pregnant women, able to regularly see health care professionals for prenatal checkups. Even low-risk pregnancies typically involve 12–15 visits to obstetrics practices in less than a year. This increased contact offers an opportunity to screen for and treat prenatal psychological distress. Embedding behavioral health professionals in primary obstetric care reflects the collaborative care model developed at the University of Washington as part of its Advancing Integrated Mental Health Solutions program, which is designed to treat common but chronic mental health conditions such as anxiety and depression requiring systemic follow-up. RCTs in the United States and other countries have consistently found that collaborative care leads to better patient outcomes, greater patient and provider satisfaction, and reduced health care costs: in short, it works.

The Massachusetts Child Psychiatry Access Program for Moms (MCPAP for Moms) offers another approach to increasing access to mental health services. This program builds obstetrics practices' capacity to care for perinatal women's mental health by providing resources and training on depression screening and treatment, telephone access to perinatal psychiatric specialists, and the means to link women with individual psychotherapy and support groups. This low-cost model, funded by the Massachusetts legislature, was piloted in 2016. Since then, MCPAP for Moms has enrolled 145 obstetric practices and served 3,699 women and has received positive feedback from health care providers. The same group has recently designed a practice-specific program, the

Program In Support of Moms (PRISM), which incorporates MCPAP for Moms but aims to help obstetrics practitioners provide stepped care treatment for perinatal depression. In pilot trials, both programs reduced depressive symptoms, and a five-year RCT is now under way to further assess their effectiveness.

In 2018, following MCPAP for Moms' success, the Health Resources and Services Administration of the US Department of Health and Human Services announced a five-year grant program that aims to scale up this model in other states, with a focus on rural and medically underserved communities; Florida, Kansas, Louisiana, Montana, North Carolina, Rhode Island, and Vermont were awarded funds. It remains to be seen whether the MCPAP for Moms model can succeed in these states, which, unlike Massachusetts, lack enhanced state-based health care. We also need further research to see whether placing the management of perinatal behavioral health in the hands of time-poor obstetricians—as opposed to embedding behavioral health professionals in obstetrics practices—will result in an unwarranted emphasis on pharmacology. Evidence shows that the best model for mild to moderate depressive symptoms is psychotherapy, while a combination of psychotherapy and pharmacology works well for moderate to severe symptoms.

One successful example of embedded interdisciplinary care focuses on the crucial period from birth to toddlerhood. HealthySteps, a program of nonprofit Zero to Three, offers embedded behavioral health services in conjunction with standard primary care well-child visits. In pediatric practices that include HealthySteps, a behavioral health professional can address common but complex family concerns such as sleeping, attachment, and parental depression, and social determinants of health such as insecure housing and lack of social support. A great deal of evidence supports the model's effectiveness. Select outcomes include substantial improvements in timely developmental assessments, continuity of care, and children's nutrition (including breastfeeding), along with reductions in children's emergency room visits.

Finally, economic policy can help to alleviate the psychological and biological effects of maternal stress. Researchers have found that the increased income from the dramatic expansion in the Earned Income Tax Credit (EITC)—a refundable tax credit providing cash payments to low-income families with children—after passage of the Omnibus Reconciliation Act of 1993 helped to protect mothers' health. Specifically, mothers who received higher EITC payments reported better health and fewer poor mental health days; their biomarkers of stress also decreased, particularly blood pressure and inflammation. Thus public policies that put more money in low-income families' pockets represent one clear way to address the intergenerational transmission of psychiatric illness. Although such redistributive programs are expensive, the public health costs of inaction on perinatal maternal distress may be higher. In the United States, research firm Mathematica recently estimated that over the six years from the beginning of pregnancy until children reach age five, the cost of untreated maternal mental health disorders for all US births is $14.2 billion, or $32,000 for every untreated but affected mother-child

pair. Most of these costs are incurred in the first year postpartum.

Improving Access to All Health Care

Financial barriers frequently impede adequate prenatal and postpartum health care, either directly through a lack of sufficient insurance coverage or indirectly through lack of time to attend medical appointments once family finances or lack of job security require the mother to return to work. Health insurance during pregnancy is essential to ensure that all women and their children have access to sufficient prenatal care. However, affordable access to health care before conception and during the postpartum period is also required to guarantee timely treatment of maternal conditions, such as diabetes, hypertension, and psychiatric illness, that put children's development at risk. In the United States, even women with insurance often lack coverage for mental health care, forcing a choice between forgoing treatment altogether or costly out-of-network care.

Today nearly 50 percent of births in the United States are covered by Medicaid, the government program for low-income families without health insurance, which has offered safety-net coverage for pregnant women since the 1980s. A recent study found that women receiving Medicaid during pregnancy had attended 75 percent fewer well-woman visits before conception than did privately insured women. They were also 18 percent more likely to receive late prenatal care and three times more likely to visit an emergency department for a pregnancy-related problem. Other comparable nations provide comprehensive health insurance for women before, during, and after pregnancy, but Medicaid pregnancy coverage ceases 60 days after delivery. Without private insurance (often financially unrealistic) or Medicaid recertification (unavailable to many women due to family income levels, particularly in states that haven't expanded Medicaid), many women lose coverage altogether only two months after their child is born. The reform that would do the most to improve postpartum access to care, then, is the extension of pregnancy Medicaid coverage from two to 12 months postpartum. Proposals to extend Medicaid coverage are currently being advocated at both the state and federal level; one such proposal is contained in a bill—S.1343, or the MOMMIES Act—introduced by a number of US senators in May 2019. The 2020 Democratic presidential nominee, Joe Biden, has also released a proposal to expand Medicaid coverage to low-income individuals who are otherwise uninsured. Losing health care not only deprives new mothers of screening and treatment opportunities but also increases the risk that their children will suffer neurodevelopmental problems related to maternal health.

Problems with access to health care are also compounded by race, ethnicity, and citizenship status. In the United States, Black women are three to four times more likely to die of pregnancy-related causes than are non-Hispanic white women; they are also more likely to suffer life-threatening complications during pregnancy and childbirth. In addition to patient, community, and system-level factors that pregnant women may contend with, health care providers may have entrenched implicit or unconscious bias against minority groups that significantly affect patient-provider interactions, treatment decisions, and health outcomes. Implicit bias education and training for providers could

make culturally competent maternal health care more widely available.

Paid Parental Leave

Another way to reduce maternal stress and depression would be to build in a longer period of adjustment to the postpartum period for parents through a federal paid family leave policy. Parents need time to learn their infant's signals, facilitate breastfeeding (recommended until at least six months of age by the American Academy of Pediatrics and the World Health Organization), and attend well-child medical visits, while infants need time to learn their caregiver's voice, face, and smell. Close parental monitoring of infants in the early months also increases the likelihood that developmental delays, estimated to affect up to 13 percent of infants and toddlers, will be noticed and addressed early, preventing long-term impairments to social-emotional, cognitive, and language capabilities. Research supports these arguments. Studies of policies in California and New Jersey have found that paid family leave increases the likelihood of exclusive breastfeeding at six months and reduces hospitalizations for infections and illnesses that an infant with good preventative care is less likely to contract. Other outcomes include improved health in school-aged children through reductions in ADHD and hearing and weight problems, all of which improve the long-term bottom line of public health budgets.

Over four million babies are born in the United States each year, and almost 60 percent of mothers with infants are in the labor force. A comprehensive federal paid family leave policy of at least 12 weeks' duration would improve outcomes for these mothers and their children. Studies show an inverse relationship between maternal depressive symptoms and leave duration up to six months postpartum. Although the Family and Medical Leave Act (FMLA) allows 12 weeks of unpaid, job-protected parental leave, 40 percent of workers are ineligible for the federal program because they work for employers with fewer than 50 employees, work part time, or have spent insufficient time on the job to qualify. And even among eligible employees, nearly half are unable to take it because it is unpaid. A welcome development is the Federal Employee Paid Leave Act, signed into law in December 2019 and effective as of October 2020, which provides 12 weeks' paid parental leave for federal employees eligible under the FMLA. But families that fall outside the reach of these laws need more help. The United States is the only country in the Organisation for Economic Co-operation and Development that doesn't provide paid leave for mothers employed in the private sector. Although corporate America has begun to recognize the benefits of strong family leave policy—many leading Fortune 500 companies, including Apple, Amazon, and Bank of America offer plans ranging from six to 16 weeks' paid leave—this progress often exclusively benefits relatively well-off, highly educated women rather than low-income, hourly employees. A national 12-week paid leave policy, such as that reflected in legislation introduced in the United States Senate in March 2019 (S.463, or the FAMILY Act), could reduce anticipatory and actual distress during pregnancy and the postpartum period and alleviate systemic racial disparities in maternal and child health outcomes (both of which, research suggests, can lead to reduced rates of preterm birth and low birthweight infants). Parents need time needed to build the foundational relationships and skills essential for developmental success.

Conclusions

The four trimesters that make up the perinatal and early postpartum period and the following nine months of a baby's life represent a time of both great vulnerability and opportunity for the mother and child. Almost one American woman in four will experience psychological distress during these periods, and increased exposure to health care providers would provide more opportunities to help women get mental health care, parenting help, and social services. Similarly, though biological pathways for the transmission of risk for psychiatric illness emphasize the importance of the womb as the infant's influential first home, qualities of the mother's life, experiences of optimal early-infancy childcare, and other reinforcing social factors can buffer risks and reorient both the child and the mother-child pair toward a strong developmental trajectory. Maternal health and life experiences matter not just for the mother but for the health of the generation that follows.

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