Commentary

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Intergenerational Transmission of Childhood Adversity-Related Risk: Fetal Brain Programming as Potential Mechanism

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Early adversity in the form of childhood maltreatment is one of the most pervasive stressors in society and affects the lives of millions of children (1). A large body of research has shown that childhood maltreatment has devastating short- and long-term consequences for brain development (2) and is associated with an increased risk for many neuropsychiatric disorders (3). Importantly, the negative effects of childhood maltreatment are not limited to the individual, but can be transmitted across generations, even though the adverse event happened years before the child was born. Consequently, understanding how early adversity can "get under the skin" is extremely important for developing prevention strategies to limit transmission of risk for neuropsychiatric disorders across generations.

Until recently, explanations for the intergenerational transmission of early adversity and adversity-related risk focused mainly on insensitive parenting practices, arguing that early exposure to trauma impedes the capacity of mothers to nurture their children [e.g., (4)]. While parenting likely plays a role, recent reports have shown that neurobiological traces of transmission across generations can already be found in infants shortly after birth, before parenting could have had a major impact. A 2018 study by Moog *et al.* (5) found that the effects of maternal childhood maltreatment were already visible in newborns' brains. Their findings showed smaller overall brain size and less gray matter volume in neonates of mothers who were exposed to maltreatment in their childhood. In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, a novel article by Hendrix *et al.* (6) contributes to the sparse literature on the potential neural mechanisms of intergenerational transmission of early adversity. In their study, the authors included a sample of 41 African American mothers and their infants. Mothers filled out the Childhood Trauma Questionnaire-Short Form—a broadly used inventory of key types of childhood maltreatment including sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglects. At 1 month postpartum, infants were scanned during a resting-state functional magnetic resonance imaging paradigm during natural sleep. Analyses were focused on frontoamygdala functional connectivity of the neonate. The results showed that higher mother-reported childhood emotional neglect was associated with stronger positive amygdala–ventromedial prefrontal cortex and amygdala–dorsal anterior cingulate cortex connectivity in the infant. Other forms of maternal childhood adversity were not associated with infant's functional brain connectivity. Importantly, the results remained significant after controlling for prenatal stress of the mother, which was measured as a composite score of mother-reported scores for perceived prenatal stress, anxiety, and depression. Like Moog *et al.* (5), Hendrix *et al.* (6) show that the prevailing paradigm—that transmission of early adversity risk from mother to child occurs after the child's birth—is likely false and that it should be extended to include prenatal neurobiological mechanisms.

The central theory of prenatal mechanisms is that intergenerational transmission begins during intrauterine life (7). The key notion is that maternal childhood adversity poses changes to the mother's body, such as an altered stress system and immune functioning, and epigenetic changes of maternal cells and her follicles/oocytes, to which the fetus will be subsequently exposed to during pregnancy. Prenatal exposure to maternal altered stress system and immune functioning may, in turn, affect fetal brain development. After birth, these brain alterations are hypothesized to be linked to subsequent behavioral issues, including higher risk for child depression and anxiety (a conceptual overview is shown in Figure 1). The direct evidence for prenatal neurobiological mechanisms is still sparse but growing. For instance, an earlier report by Moog *et al.* (8) indicated that maternal exposure to childhood maltreatment was associated with altered placental–fetal stress physiology (i.e., placental corticotropin-releasing factor). The altered placental–fetal stress physiology may, in turn, affect fetal brain development. Further research into the placental–fetal stress physiology in the context of maternal early adversity will likely innovate our way of thinking about intergenerational transmission of risk toward a more integrated, multidisciplinary view.

A crucial question remains: is fetal brain development affected by maternal experience of childhood maltreatment? Even though the articles by Moog *et al.* (5) and Hendrix *et al.* (6) measured neonates' brain early after birth, it is still only a proxy for fetal brain development. The brain develops exceptionally rapidly in the first few weeks postpartum and is extremely sensitive to environmental cues, especially those presented by the mother. Consequently, even a few weeks postpartum may have an observable effect on the neonate's brain function and structure. In addition, there is evidence for an association between exposure to childhood maltreatment and increased risk for negative birth outcomes, such as delivering preterm (9). Isolating the effect of maternal childhood maltreatment on

SEE CORRESPONDING ARTICLE ON PAGE 470

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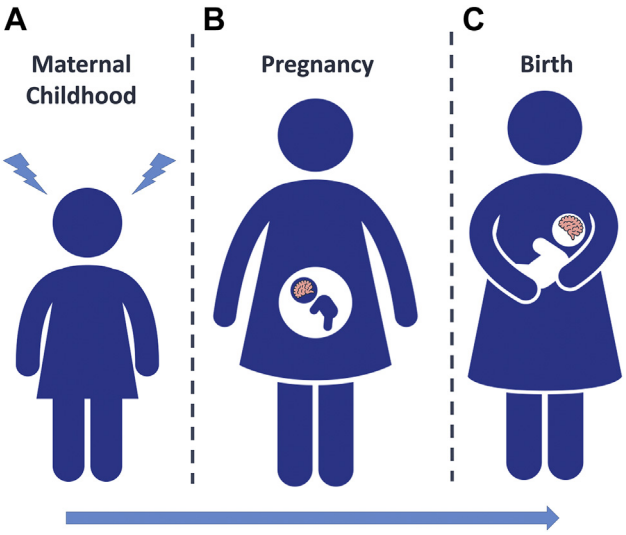

Figure 1. Theoretical overview of intergenerational transmission of childhood adversity–related risk. **(A)** Childhood adversity of the mother affects her child via various alterations to her body at times of the maltreatment, e.g., altered stress system, epigenetic changes of maternal cells and the follicles/oocytes, and immune functioning. **(B)** Subsequently, the fetus will be exposed to these alterations during pregnancy, which affect fetal brain development. **(C)** After birth, the child's brain shows alterations in brain structure and function. These alterations may be linked to subsequent behavioral issues, including a higher risk for child depression and anxiety.

brain development of the child before birth is necessary to uncover the neurobiological mechanisms of risk transmission of childhood maltreatment across generations. Measuring the fetal brain directly with the use of fetal resting-state functional magnetic resonance imaging [see (10) for a review] could therefore be a logical next step for future research.

Finally, focusing on neurobiological mechanisms may not only bring us closer to the full complexity of risk transmission, but also facilitate better prevention strategies for helping families struggling with early adversity and trauma. Implying that childhood maltreatment exposure leads to insensitive parenting may put unnecessary blame on mothers raising their children and may not provide a useful message for improving the lives of families dealing with early adversity and trauma. Instead, preconceptional or prenatal interventions targeted to correcting trauma-induced changes in maternal physiology may be another important avenue for future research.

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Article Information

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