



Intergenerational Transmission of Maternal Childhood Maltreatment Exposure: Implications for Fetal Brain Development

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Objective: Growing evidence suggests the deleterious consequences of exposure to childhood maltreatment (CM) not only might endure over the exposed individual's lifespan but also might be transmitted across generations. The time windows, mechanisms, and targets of such intergenerational transmission are poorly understood. The prevailing paradigm posits that mother-to-child transmission of the effects of maternal CM likely occurs after her child's birth. The authors seek to extend this paradigm and advance a transdisciplinary framework that integrates the concepts of biological embedding of life experiences and fetal origins of health and disease risk.

Method: The authors posit that the period of embryonic and fetal life represents a particularly sensitive time for intergenerational transmission; that the developing brain represents a target of particular interest; and that stress-sensitive maternal-placental-fetal biological (endocrine,

immune) pathways represent leading candidate mechanisms of interest.

Results: The plausibility of this model is supported by theoretical considerations and empirical findings in humans and animals. The authors synthesize several research areas and identify important knowledge gaps that might warrant further study.

Conclusion: The scientific and public health relevance of this effort relates to achieving a better understanding of the "when," "what," and "how" of intergenerational transmission of CM, with implications for early identification of risk, prevention, and intervention.

Key words: intergenerational transmission, maternal childhood maltreatment, brain development, psychopathology

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The effects of stress on health and disease risk are well established and are known to be particularly pronounced when stress exposure occurs during sensitive developmental periods such as childhood.¹ Across the various types of early life stress, childhood maltreatment (CM) likely represents one of the most pervasive and pernicious societal stressors because of its widespread prevalence and the duration and severity of its deleterious consequences on mental and physical health.¹⁻⁷ Emerging evidence suggests that the long shadow cast by CM in women might not be restricted to their own lifespan but might be transmitted to their children.⁸⁻¹⁷ We seek to extend the prevailing paradigm that posits such intergenerational transmission likely occurs during the child's postnatal period of life. We articulate a transdisciplinary framework that integrates the concepts of biological embedding of life experiences and fetal origins of health and disease risk. Our model (Figure 1) suggests that intrauterine life represents a particularly sensitive period when the effects of maternal CM exposure could be

transmitted to the offspring; the principal mode of transmission is biological; transmission primarily occurs through the independent and/or interactive effects of the psychological, behavioral, and biophysical sequelae of maternal CM on aspects of maternal-placental-fetal (MPF) gestational biology that participate in the process of fetal programming of health and disease risk; and the developing fetal brain represents a key target of such programming. Although we focus on the intergenerational consequences of maternal CM exposure, we note that similar processes and biological mechanisms could underlie the intergenerational transmission of other forms of maternal early life stress (ELS) and trauma.¹⁸

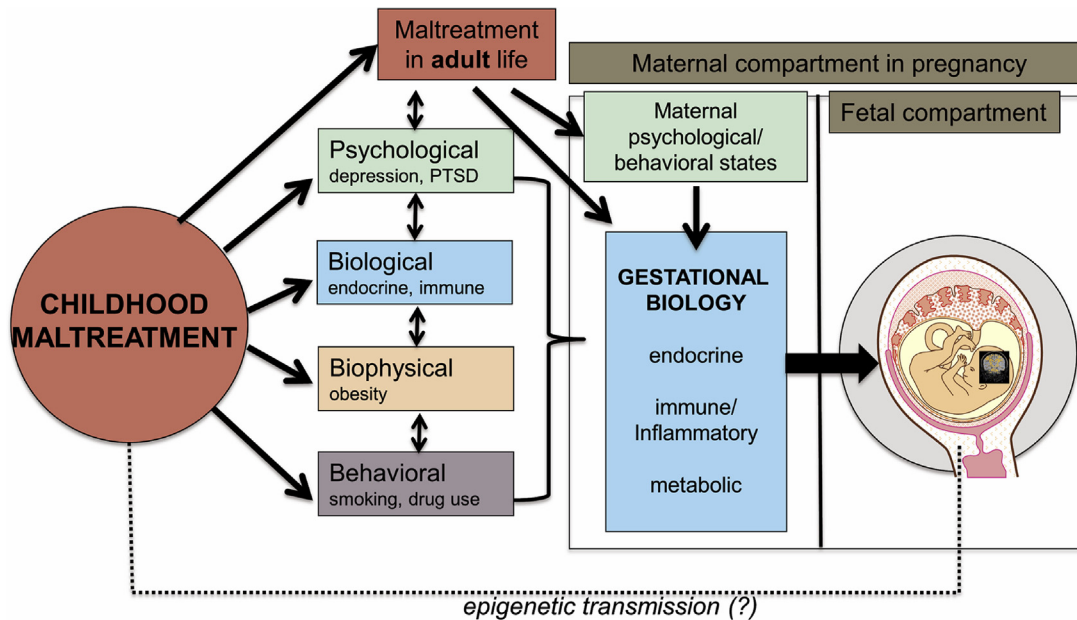
We begin with a very brief overview of the prevalence and long-term consequences of exposure to CM and the key biological pathways that appear to mediate these consequences over the exposed individual's lifespan. We proceed to review the evidence supporting the concept that these adverse sequelae of CM might not be restricted to the exposed individual's lifespan but might be transmitted across generations. We broadly discuss the genetic, epigenetic, and environmental pathways that



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FIGURE 1 Intergenerational transmission during gestation of the effects of maternal exposure to childhood maltreatment: a conceptual framework. Note: The model suggests intrauterine life representing a particularly sensitive period when the effects of maternal childhood maltreatment exposure might be transmitted to the offspring. The principal mode of transmission is biological; transmission occurs primarily through the psychological, behavioral, and biophysical sequelae of maternal childhood maltreatment on aspects of maternal-placental-fetal gestational biology that participate in the process of fetal programming of health and disease risk; and the developing brain represents a key target of such programming. PTSD = posttraumatic stress disorder.



might underlie the intergenerational transmission of acquired phenotypes and then specifically relate this discussion to the issue of intergenerational transmission of CM-related sequelae, with a review of the state of the current evidence in humans and animals. We identify stress-related MPF gestational biology as a leading candidate pathway of interest in the context of intergenerational transmission during the prenatal period of life, and we review how variation in stress-related MPF gestational biology could affect fetal brain developmental trajectories. Next, we review the major elements underlying the postnatal intergenerational transmission pathways of CM, and we raise the possibility that many aspects of these postnatal effects could be conditioned in part on the effects of prenatal factors. We conclude by articulating current knowledge gaps and discussing approaches and future research directions that warrant consideration to inform mechanism-based interventions aimed at breaking the cycle of intergenerational transmission of CM.

PREVALENCE AND LONG-TERM CONSEQUENCES OF EXPOSURE TO CHILDHOOD MALTREATMENT AND BIOLOGICAL PATHWAYS

The term *childhood maltreatment* is commonly used to refer to specific traumatic events that occur in childhood

such as different forms of childhood abuse (physical, sexual, emotional) or neglect (physical, emotional). Large population-based surveys have suggested many children in the United States are exposed to CM,^{19,20} and that 30% to 40% of adult women have experienced at least 1 and 15% to 25% have experienced more than 1 type of abuse or neglect in their childhood.²¹⁻²³ Similar estimates have been reported in other developed and developing countries, highlighting the global nature of this problem. The long-term sequelae of CM exposure are well established, and they include adverse psychological, biological, biophysical, and behavioral states and increased likelihood of developing mental and physical disorders such as depression, posttraumatic stress disorder, drug addiction, obesity, and cardiovascular, metabolic, and autoimmune diseases.^{1,7,24-29} Although these psychological, biological, and behavioral sequelae associated with CM might be adaptive from the perspective of evolutionary fitness, they can confer detrimental or unfavorable effects on health and well-being from the individual's perspective.¹⁹

The biological pathways underlying these long-term effects relate primarily to CM-induced alterations in the brain and in the endocrine and immune systems.¹ Stress-regulatory neural, neuroendocrine, and immune systems are particularly plastic during early life and are under strong environmental influence.^{2,30,31} Individuals exposed to CM commonly exhibit structural and functional changes in a network of brain regions implicated in vigilance, emotional regulation, and neuroendocrine and immune control.³²

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