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

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Abstract

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

Method—We 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 our model is supported by theoretical considerations and empirical findings in humans and animals. We synthesize several research areas and identify important knowledge gaps that may warrant further study.

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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.

Keywords

intergenerational transmission; maternal childhood maltreatment; brain development; psychopathology

INTRODUCTION

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 among the most pervasive and pernicious societal stressors in terms of its widespread prevalence and the duration and severity of its deleterious consequences on mental and physical health.[1–7] Emerging evidence now suggests that among women, the long shadow cast by CM may not be restricted to their own life span, but also may 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 here a trans-disciplinary framework that integrates the concepts of biological embedding of life experiences and fetal origins of health and disease risk. Our model, depicted in Figure 1, suggests that: *a*) intrauterine life represents a particularly sensitive time period when the effects of maternal CM exposure may be transmitted to the offspring; *b*) the principal mode of transmission is biological; *c*) transmission primarily occurs via the independent and/or interactive effects of the psychological, behavioral, and biophysical sequelae of maternal CM on aspects of maternal-placental-fetal gestational biology that participate in the process of fetal programming of health and disease risk; and *d*) the developing fetal brain represents a key target of such programming. Although we focus here on the intergenerational consequences of maternal CM exposure, we note that similar processes and biological mechanisms may underlie the intergenerational transmission of other forms of maternal early life stress (ELS) and trauma.[18]

We begin this article 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 life span. We then proceed to review the evidence supporting the concept that these adverse sequelae of CM may not be restricted to the exposed individual's life span, but may also be transmitted across generations. We broadly discuss the genetic, epigenetic, and environmental pathways that may 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 maternal-placental-fetal (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 may impact 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 may, in part, be conditioned upon 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 suggest many children in the US are exposed to CM,[19,20] and that 30–40% of adult women have experienced at least one and 15–25% more than one 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 (PTSD), drug addiction, obesity, cardiovascular, metabolic, and autoimmune disease.[1,7,24–29] Although these psychological, biological, and behavioral sequelae associated with CM may be adaptive from the perspective of evolutionary fitness, they may confer detrimental or unfavorable effects on health and well-being from the individual 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/immune control.[32] These changes include alterations of the hypothalamic-pituitary-adrenal (HPA) endocrine axis,[33,34] decreased glucocorticoid receptor (GR) sensitivity,[35] and altered immune function.[6,36] The capacity to respond to maltreatment with temporally stable physiologic and behavioral changes may be due to epigenetic alterations.[35,37] These CM-associated alterations in endocrine and immune function have implications for responsivity to subsequent stress exposures, and they are believed to constitute a crucial link between CM exposure and adult disorders such as PTSD,[38,39] major depression,[2,40,41] and obesity.[4,42] Moreover, some studies suggest that the co-occurrence of CM-associated affective disorders is associated with exacerbation of the adverse neurobiological consequences of CM exposure.[2] For example, adult women with a history of childhood sexual or physical abuse and depression appear to exhibit markedly increased autonomic, neuroendocrine, and immune responses to stress compared to CM-exposed women without depression.[40,43–45]

INTERGENERATIONAL TRANSMISSION OF THE EFFECTS OF MATERNAL EXPOSURE TO CHILDHOOD MALTREATMENT

Growing evidence suggests that the detrimental consequences of CM exposure may not be restricted to the exposed individual alone but also may get transmitted to the next generation, thus significantly extending the long-term reach of CM. Several studies have reported that children of mothers with a history of CM exposure exhibit a higher prevalence of adverse birth outcomes,[46] neurodevelopmental and behavioral problems (*e.g.*, conduct disorders, antisocial behavior, externalizing and internalizing problems[10–14,16]), autism,[15] obesity,[17] and poorer general health.[47] This association between maternal maltreatment exposure and the child's health appears to be particularly pronounced if the maternal maltreatment occurred during her own childhood, as opposed to at a later stage in life.[48] Moreover, these effects on child health are apparent even in the absence of the child having been directly exposed to maltreatment.[8] The role of the caregiving environment as one of the potential mediators is an important consideration, and it is discussed subsequently in section "Postnatal Environmental Effects." Conceptually, it is important to distinguish intergenerational transmission (*i.e.*, transmission of the effects of an exposure from the parental [F0] to the subsequent generation [F1]), which is the focus of the present work, from transgenerational transmission (*i.e.*, transmission of the effects of an exposure from the parental [F0] across at least 2 generations [F3]). Transgenerational transmission implies there is no direct exposure of the condition of interest in the generation in which its effects are observed. Thus, a claim of transgenerational transmission of the effects of maternal CM exposure would necessitate the study of at least four generations in order to exclude the possibility of in utero exposure (i.e., the grandmaternal environment during her pregnancy may affect integrity of oocytes that her fetus develops that give rise to her grandchildren) and direct parental transmission. For a detailed discussion of this topic, the reader is referred to a recent review by Klengel et al.[49]

MECHANISMS OF INTERGENERATIONAL TRANSMISSION OF CHILDHOOD MALTREATMENT

Broadly, the intergenerational transmission of characteristics and states (phenotypes) can be mediated via genetic and/or environmental mechanisms. The independent contribution of genetic (DNA base pair sequence) variation for most complex common traits including psychopathology appears to be relatively modest.[49–54] Specifically in the context of CM-related phenotypes, intergenerational transmission of these sequelae through inheritance of genetic variants would imply the existence of a genetic predisposition that concurrently confers increased likelihood of a parent's exposure to CM and the expression of adverse neurobiological sequelae in the child. It is theoretically possible that a genetic predisposition that favors a more difficult infant/child temperament may satisfy these conditions (*e.g.*, gene-environment correlations[55]), although we are not aware of any empirical data that have substantiated this possibility. On a somewhat related note, certain genetic variants have been identified that appear to exacerbate the neurobiological consequences of CM;[33,35] if these variants are inherited by the offspring, this genetic predisposition may render this subgroup of children more susceptible to the adverse sequelae of exposure to maternal CM.

Human studies on intergenerational transmission of acquired phenotypes can broadly be categorized into those describing the influence of the postnatal environment, the prenatal environment, and/or the environment prior to conception (see [49] for examples). The majority of the scientific literature on the intergenerational transmission of the effects of CM has postulated that the mechanism is environmental in nature, and that offspring exposure after birth to suboptimal maternal care (which, in turn, is a result of maternal CM-associated depression or poor bonding) represents the primary transmission pathway.[10,12,13,48,56] We agree that this scenario likely represents an important pathway. However, we suggest that the intergenerational transmission of the effects of maternal CM exposure may start even earlier, during the highly sensitive period of gestation and fetal development. If so, how, then, can an embryo/fetus obtain information about past events and conditions going back to her or his mother's childhood, and incorporate this information into her or his own development? Theoretically, there are three broad possibilities: firstly, that the effect is inherited through the products of conception such as maternal CM-related epigenetic alterations in her germ line (oocytes) that survive the reestablishment of postconceptional epigenetic marks.[57,58] Secondly, that maternal CM may produce alterations in her oocyte cytoplasm (such as mitochondria, proteins, and RNA molecules) that, after conception, exert an influence on her developing embryo/fetus. And thirdly, that the mode of transmission is mediated via gestational biology, with the developing feto-placental unit sensing and responding to biological cues in the maternal compartment that reflect the long-term independent and/or interactive effects of the biological, psychological, biophysical, or behavioral sequelae that CM-exposed women may bring to their pregnancy and gestational state. In the following sections, the theoretical plausibility of each of these three transmission pathways is reviewed, along with any empirical evidence that is currently available.

Epigenetic Alterations in the Maternal Germ Line

CM exposure can produce persistent epigenetic alterations in certain tissues.[35,37,59] There is, however, considerable controversy surrounding the process of intergenerational epigenetic transmission, and some confusion about the difference between, on the one hand, true intergenerational epigenetic inheritance (i.e., transmission of epigenetic marks that CM may have produced in the germ line), and on the other hand, the perpetuation of intergenerational transmission via de novo production of stable epigenetic alterations in the offspring.

Epigenetic inheritance through the germ line—Before considering the plausibility of germ line-dependent epigenetic mechanisms as pathways of intergenerational transmission, some basic principles of the complex dynamics of epigenetic processes during gametogenesis and embryonic development warrant discussion and are summarized here. We note that our current knowledge of these processes and mechanisms is almost exclusively based on rodent models. Paternally- and maternally-derived methylation marks contribute unique epigenetic information to the zygotic epigenome, but these epigenetic marks are almost completely erased in the earliest stages of embryonic development (i.e., immediately after fertilization) to enable zygotic totipotency.[60] There are exceptions. Certain specific loci, such as germ line differentially methylated regions (gDMRs) responsible for imprinting and the intracisternal A particle (IAP) family of retrotransposons, appear to be largely resistant to this first wave of DNA de-methylation in the early embryo. Furthermore,

recent evidence now suggests that beyond gDMRs and IAPs, there is a considerable amount of mostly maternally derived DNA methylation that seems to play a role in gene expression in the early embryo and the placenta, giving rise to the concept of transient gDMRs.[58,61–63] Thus, certain epigenetic characteristics in the germ line do appear to be resistant to postfertilization reprogramming, which raises questions related to what information these marks carry forward to the next generation, and their functional implications with respect to offspring development.

A true intergenerational epigenetic inheritance must necessarily satisfy two conditions: first, that the exposure of interest (such as CM) must produce epigenetic alterations in the germ line of exposed individuals (i.e., oocytes in females and sperm in males); and second, that these epigenetic alterations must survive the erasure and re-establishment of epigenetic characteristics that occurs very shortly after conception. Animal data support the possibility of inter- and transgenerational transmission of ELS-induced behavioral traits mediated by epigenetic modifications through the paternal germ line.[64,65] For example, compared to non ELS-exposed controls, ELS in male mice was associated with more depressive-like behavior and altered regulation of several small non-coding RNAs (sncRNAs) in the sperm, serum, and hippocampus of the CM-exposed adult animals.[64] Intriguingly, after injection of sncRNA from ELS-exposed animals into fertilized wildtype oocytes, the male progeny of ELS-exposed sncRNA donors showed similar differences in behavior, and aberrant sncRNA regulation was also found in serum and hippocampus but not sperm.[64] However, to date, we are not aware of any such evidence for heritable ELS-associated epigenetic marks mediated by the maternal germ line. It is, however, interesting to theoretically consider the plausibility of epigenetic inheritance through the maternal germ line. The long-held belief that mammals are born with their full contingent of oocytes that are held under meiotic arrest until puberty has been questioned by some recent evidence suggesting that at least in some mammals, oocytes might be steadily destroyed and then regenerated from a small population of germ line stem cells throughout the early and reproductive years of life.[66] If this were shown to be the case in humans, it would then theoretically open the possibility of meeting at least the first condition for intergenerational epigenetic inheritance (i.e., that CM exposure can change epigenetic alterations in oocytes). The processes of oocyte maturation and potentially the accumulation of its epigenetic characteristics on histones and DNA depend, in part, on the milieu of the follicular fluid in which oocytes are suspended.[67] Just as maternal obesity and stress have been associated with altered follicular fluid composition (*e.g.*, elevated levels of intra-oocyte oxidative stress[68,69]), it also may be possible that the oocyte milieu could be altered by the biological (*e.g.*, endocrine, immune, metabolic) sequelae of CM exposure. So far, to our knowledge there is no empirical evidence substantiating this claim. And even if CM exposure was able to modify epigenetic characteristics of oocytes, it is less clear whether these alterations would survive the epigenetic reorganization that occurs after conception.[70] Hypothetically, even grandmaternal CM exposure, via its biological sequelae, could affect her grandchildren's development, if the grandmother's CM-associated biological alterations were to produce epigenetic alterations in the oocytes her daughter generates during fetal life, and if these epigenetic alterations were not erased following her grandchild's conception.

De novo **production of epigenetic marks in offspring of CM-exposed mothers**—Even in the instance when mothers and offspring may share the same or similar epigenetic alterations (that, for example, are associated in the mother with CM exposure), it is very challenging to identify the origins of these alterations in the offspring and distinguish true maternal epigenetic transmission from the reestablishment of offspring epigenetic characteristics. It is plausible that in response to the same or similar biological conditions that originally produced these epigenetic alterations in the mother's oocytes, these conditions that now constitute the intrauterine environment the embryo/fetus develops in may result in epigenetic alterations. While this has not specifically been tested, different types of prenatal risk factors, which may also result from CM, such as maternal depression and maternal body mass index (BMI), in interaction with offspring genotype best explained variation in the newborn methylome.[71] Moreover, a recent meta-analysis revealed significant associations between prenatal stress and methylation of the GR gene (*NR3C1*) promoter.[72] Thus, prenatal de novo methylation in genetically susceptible offspring exposed to an unfavorable intrauterine environment may constitute a potential mechanism by which the effects of maternal CM exposure may be propagated in the subsequent generation.

Alterations of the Oocyte Cytoplasm

The accumulation of proteins and metabolites in the cytoplasm of maternal oocytes in response to physiological stress and other conditions may also directly influence embryonic and fetal development.[73] Conditions such as obesity (which is one of the sequelae of CM exposure) have the potential to alter oocyte endoplasmic reticulum (ER) stress signaling[74] and thereby reduce mitochondrial membrane potential and increase autophagy.[75] While it is plausible that CM-associated biological alterations may affect the integrity of the oocyte cytoplasm, this, to our knowledge, has not yet been systematically studied. It is important to appreciate that intergenerational effects that are mediated by such changes in maternal oocyte cytoplasm do not meet the criteria for intergenerational epigenetic transmission.

Alterations of the Gestational Biological Environment

It is well established that most, if not all, complex traits exhibit developmental plasticity, *i.e.*, a range of different phenotypes can be expressed from a given genotype. The unfolding of developmental processes across the multi-contoured landscape from genotype to phenotype is context-dependent, wherein the developing embryo/fetus seeks, receives, and responds to, or is acted upon by, the gestational environment during sensitive periods of cellular proliferation, differentiation, and maturation. These context-dependent adaptations result in structural and functional changes in cells, tissues, organ systems, and homeostatic set points (the process of phenotypic specification). These changes may then, either independently or through interactions with subsequent developmental processes and environments, have short- and/or long-term consequences for health and disease susceptibility.[76–78] These concepts have variously been referred to as the fetal or developmental origins of health and disease risk.[79,80] Except in extreme cases, this process of phenotypic specification does not cause disease per se, but instead determines susceptibility for the development of disease(s) in later life by shaping the individual's responses to subsequent endogenous and exogenous conditions.[80]

Embryonic and fetal life represent a particularly sensitive period for the development of brain structure, connectivity, and function. Firstly, the vast majority of differentiation of major brain structures occurs during prenatal life. Secondly, because brain development entails a cascade of bidirectional interactions with the environment, even small or subtle alterations in brain integrity during embryonic and fetal life can become progressively and substantially magnified over time to produce long-lasting or permanent deficits. Thirdly, the blood–brain barrier is immature in fetal life and offers limited protection. The high degree of plasticity exhibited by the brain in prenatal life is a double-edged sword: it represents a period of increased vulnerability to potentially deleterious exposures, but it also is a time when potentially salubrious exposures may produce the greatest benefit.

Exposures during intrauterine life can result in long-term “programming” consequences by producing changes in anatomy and/or physiology such as reduced neurogenesis, altered gliogenesis, and reduced availability of neurotrophic factors and neurotransmitters during critical rapid growth periods, all of which have long-term implications for brain anatomy and connectivity.[81] These long-term physiological changes can be a consequence of environmentally-induced, temporally stable epigenetic alterations in prenatal life. We note that epigenetic alterations represent one important, but not the only, mechanism by which the consequences of gestational exposures can persist long after the exposures are no longer present. During critical periods of fetal brain development, elevated concentrations of glucocorticoids may, for example, promote glia cell formation at the expense of proliferation and neuronal differentiation, with life-long consequences for neuron numbers.[82]

The potential for in utero intergenerational transmission of the effects of maternal CM exposure would be expected to be determined by, firstly, the degree to which the developing embryo/fetus can receive biological signals or cues indicative of maternal CM-related alterations in her own peripheral (systemic) physiology during pregnancy, and secondly, the extent to which these signals or cues participate directly or indirectly in the process of embryonic and fetal development and phenotypic specification of the brain and other organ systems. We suggest that stress-responsive biological systems represent a highly attractive candidate mechanism on both counts.

Exposure to childhood maltreatment and gestational endocrine and immune/inflammatory stress biology—As summarized above (in the section “Prevalence and Long-term Consequences of Exposure to Childhood Maltreatment and Biological Pathways”), CM is known to produce long-term alterations in endocrine and immune/inflammatory physiology, including greater hypothalamic-pituitary-adrenal (HPA) axis reactivity[40] and greater pro-inflammatory state.[6] When CM-exposed women become pregnant, could these alterations spill over into gestational biology? Pregnancy itself is known to produce major alterations in maternal central and peripheral physiology, some of which result in attenuation of biological responsivity to exogenous or endogenous stimuli.[83] Nonetheless, the plausibility of our conceptual framework that CM-associated endocrine/immune, psychological, biophysical and behavioral conditions may spillover into gestational biology (see Figure 1) is supported by findings that suggest the same alterations produced by CM in non-pregnant women may also be present among CM-exposed pregnant women. For example, pregnant women with a history of childhood sexual abuse exhibit a significantly

higher cortisol awakening response (a marker of HPA axis dysregulation) compared to pregnant women without a history of sexual abuse,[84] which is further exacerbated by maternal stress during pregnancy.[85,86] Women exposed to physical and/or sexual abuse have been reported during pregnancy to have increased cortisol concentrations in hair (a measure of cumulative cortisol production).[87] Pregnant women with a history of CM also are more likely to develop conditions in pregnancy such as depression,[12,56,88] sleep disturbances,[89] and certain obstetric complications[15,90] that, in turn, are associated with altered MPF endocrine and immune/inflammatory stress biology.[91] We recently published the first study that established an association between a woman's exposure to maltreatment in her own childhood and placental-fetal stress physiology during pregnancy (the magnitude and production of placental corticotrophin-releasing hormone (CRH, a hormone directly implicated in key developmental processes in the fetal brain and other peripheral systems).[92] Moreover, irrespective of CM exposure status, there is considerable continuity between preconceptional and gestational states for many psychiatric (*e.g.*, depression),[93] biophysical (*e.g.*, obesity)[94] and behavioral (*e.g.*, smoking)[95] states. Thus, in the context of CM exposure, our proposed framework posits that during gestation the consequences of common sequelae of CM exposure such as depression or posttraumatic stress disorder (PTSD), obesity, and smoking or drug use, as well as re-victimization in adolescence and adulthood, may exert additive or multiplicative effects with gestational biological alterations on fetal development (see Figure 1).

Intrauterine endocrine and immune/inflammatory stress biology and fetal brain development—Stress-related MPF biological processes appear to play a tripartite role as key sensors, transducers, and effectors of ELS-related states and conditions on the developing fetus: they are responsive to all classes of intrauterine perturbations (sensors), they mediate communication between maternal and fetal compartments (transducers), and they play an essential and obligatory role in orchestrating key events and variation underlying cellular growth, replication, and differentiation in the brain and peripheral tissues (effectors).[91]

As reviewed in the previous section, the effects of CM exposure and its sequelae may extend during the state of pregnancy to alterations in MPF stress biology.[1,2,84] Given its crucial role in fetal development, these CM-related perturbations in MPF biology would, in turn, be expected to exert detrimental effects on fetal developmental outcomes,[81,91] specifically on the fetal brain, which may then affect the offspring's susceptibility for developing neurodevelopmental and psychiatric disorders. The neurodevelopmental consequences of exposure to elevated concentrations of endocrine and immune stress mediators include changes in cell proliferation, neuronal differentiation and gliogenesis, availability of neurotrophic growth factors, cell survival, synaptogenesis, neurotransmitter levels, myelination, and adult neurogenesis,[81,96] which can result from alterations in miRNA expression and DNA methylation in the fetal brain.[97] Moreover, the magnitude of such effects and molecular mechanisms mediating these effects may vary as a function of stage of gestation-specific alterations in the endocrine and immune milieu (*e.g.*,[98]). Such effects on neurodevelopmental trajectories may then modulate an individual's propensity for subsequently developing neurodevelopmental and psychiatric disorders. In this way,

intrauterine stress exposure may alter fetal brain development and produce cognitive deficits and anxiety and depressive-like behaviors, which are phenotypes associated with several neuropsychiatric disorders.[99] We and others have previously reviewed the pathways and mechanisms by which fetal exposure to inappropriate concentrations of glucocorticoids and pro-inflammatory cytokines may impact the development of the fetal brain and other systems,[77,78,81,98,100–104] and a detailed discussion on this topic is outside the scope of the current article.

Postnatal Environmental Effects

The quality of the child's postnatal environment may, in part, mediate the intergenerational transmission of the effects of maternal CM exposure. The brain maintains a high degree of plasticity after birth, with especially rapid changes occurring over the first year of postnatal life.[105] Although a nurturing postnatal environment may exert beneficial effects on the developing brain and even partially mitigate the deleterious effects of a suboptimal intrauterine environment,[106] it appears that the suboptimal intrauterine environment of children of CM-exposed mothers is likely to be followed by an unfavorable postnatal environment characterized by higher levels of maternal depression,[13,41,48] suboptimal parenting,[10,12,13,48,56] and by abuse experience,[10,12] all of which constitute risk factors for child neurodevelopmental and psychiatric disorders.[1,107]

Our conceptual framework suggests that CM-related intrauterine conditions may exert not only additive but perhaps even multiplicative effects to exacerbate the effects of unfavorable postnatal conditions. We postulate that the above-discussed suite of CM-related intrauterine effects may adversely impact the very same maternal and child characteristics that determine the quality of the postnatal mother–child relationship, *i.e.*, maternal sensitivity and newborn temperament. Non-human primate[108] as well as human studies[109] have provided empirical evidence for CM-related oxytocinergic dysregulation, which may mediate the observed CM-associated suboptimal parenting behavior.[10,12,13,48,56] Intriguingly, oxytocinergic adaptations in preparation for motherhood get initiated during pregnancy itself,[110] and this process may be adversely impacted by an unfavorable gestational environment, with important consequences for maternal sensitivity in the postnatal period.

In terms of mother–child interactions, it is not only characteristics of the mother but also those of her child that may have a direct bearing on the nature and quality of the interaction. In this context, infant temperament is a well-established contributor to the quality of the postnatal mother–child relationship. The adverse CM-related intrauterine environment may increase the likelihood that the newborn will have a more difficult temperament (e.g., infants of mothers with elevated cortisol concentrations and depression during gestation exhibit a more difficult temperament[111]), which, in turn, may further elicit suboptimal maternal parenting behavior. In summary, the quality of the postnatal mother–child relationship – a major determinant of child neurodevelopmental outcomes – may, in part, be conditioned upon the quality of the intrauterine environment via its effects on maternal parenting behavior and on infant temperament.

The above-discussed postnatal pathways of transmission are indirect in nature, but there also is the possibility of direct postnatal biological transmission via breastfeeding (contents of

breast milk) and/or the exchange of microbiota.[112] There is empirical evidence from animal models demonstrating an effect of maternal stress on breast milk composition (e.g., cortisol concentrations[113]) as well as on the composition and diversity of the microbiome[114] – both of which have important consequences for offspring developmental trajectories and health. However, to our knowledge, human studies have not yet examined these putative pathways in the context of intergenerational transmission of the sequelae of CM.

QUESTIONS, ISSUES, CONSIDERATIONS, AND FUTURE RESEARCH DIRECTIONS

Our framework and the above-discussed empirical findings support the plausibility that maternal CM exposure may alter the gestational environment in ways that program offspring phenotypes to increase susceptibility for psychopathology. In this context, it is apparent that the efficacy of potential interventions would be enhanced by the extent to which they can target earlier rather than later stages of brain development. Presently there are many open questions regarding the extent of modifiability of CM-associated conditions and the biological mechanisms underlying their intergenerational transmission that need to be addressed in order to develop specific and time-sensitive interventions directed towards early identification of risk and prevention of its adverse sequelae.

These open questions include the determination of how environmental exposures at specific stages of gamete development influence epigenetic characteristics in oocytes and alterations in oocyte cytoplasm, how early in development these processes begin, and whether and how such epigenetic marks survive zygotic reprogramming and are retained in the embryo. Evidence to support or refute intergenerational epigenetic inheritance will likely need to be derived from animal studies that perform specific manipulations during oogenesis and oocyte maturation.

Animal studies have and will continue to provide important insights into the biological mechanisms underlying intergenerational transmission, but they also have some limitations. There is considerable across-species variation in gestational physiology. For example, placental CRH production and activity is observed only in humans and great apes, which is why many of the commonly used animal models of gestational stress may not be optimal for this purpose. Moreover, there are no appropriate animal models for certain abuse experiences in young girls such as sexual abuse. Thus, human studies are warranted that systematically characterize the gestational environment in which offspring of CM-exposed mothers develop. In this context, CM-associated changes in MPF stress biology, maternal microbiota, and placental/fetal exosomes could provide some important and much-needed information on the gestational biology pathways of intergenerational transmission of the effects of maternal CM.

Additional questions relate to whether infants of CM-exposed mothers differ from those of non-exposed mothers in neurophenotypes that are associated with increased risk for neurodevelopmental disorders and psychopathology, and the extent to which such differences trace back to the prenatal as opposed to postnatal environment. To address these issues, we suggest that infant neurodevelopmental assessments, including but not limited to

multimodal magnetic resonance imaging assessments, be performed at or very shortly after birth in order to obtain baseline measures of brain structure and function that are not yet confounded by postnatal influences. Because it has been established that children born to mothers exposed to CM may also be exposed subsequently to a suboptimal environment in infancy and childhood, it is critical to separate the potential effects of the prenatal environment from those of the postnatal environment, examine their interactions, and track developmental trajectories over time.

Based on the consideration that some studies of CM sequelae[33] and also some studies of intrauterine influences[115,116] report sex differences in effects, we suggest that future studies consider whether the intergenerational effects of maternal CM exposure vary as a function of offspring sex.

In these ways, a better understanding of the independent and interactive contribution of specific maternal CM-associated alterations in the preconceptional, prenatal and postnatal developmental periods will set the stage for clinical and translational research, with important implications for early identification of at-risk/vulnerable populations and prevention aimed at breaking the vicious cycle of intergenerational transmission of the adverse sequelae of CM.

The perspective that the effects of maternal CM exposure can be biologically transmitted across generations via the process of fetal programming to perpetuate intergenerational cycles of unfavorable health outcomes may have broad implications for public health and policy in the United States and elsewhere. The approach articulated in this article has implications for risk identification and the subsequent development of interventions directed toward prevention. If the hypothesis of in utero transmission of maternal CM is substantiated, one important public policy implication would be the incorporation of recommendations for screening for CM among women who intend to become pregnant or are in the early stage of their pregnancy. The fetal origins perspective places a particular emphasis on the health and well-being of girls and women of reproductive age, and attending to the preconceptional and gestational health of women could be of vital importance for risk identification and the development of interventions aimed at prevention to break the cycle of perpetuation and ultimately stem the intergenerational cascade of poor health among women exposed to childhood maltreatment and their children.

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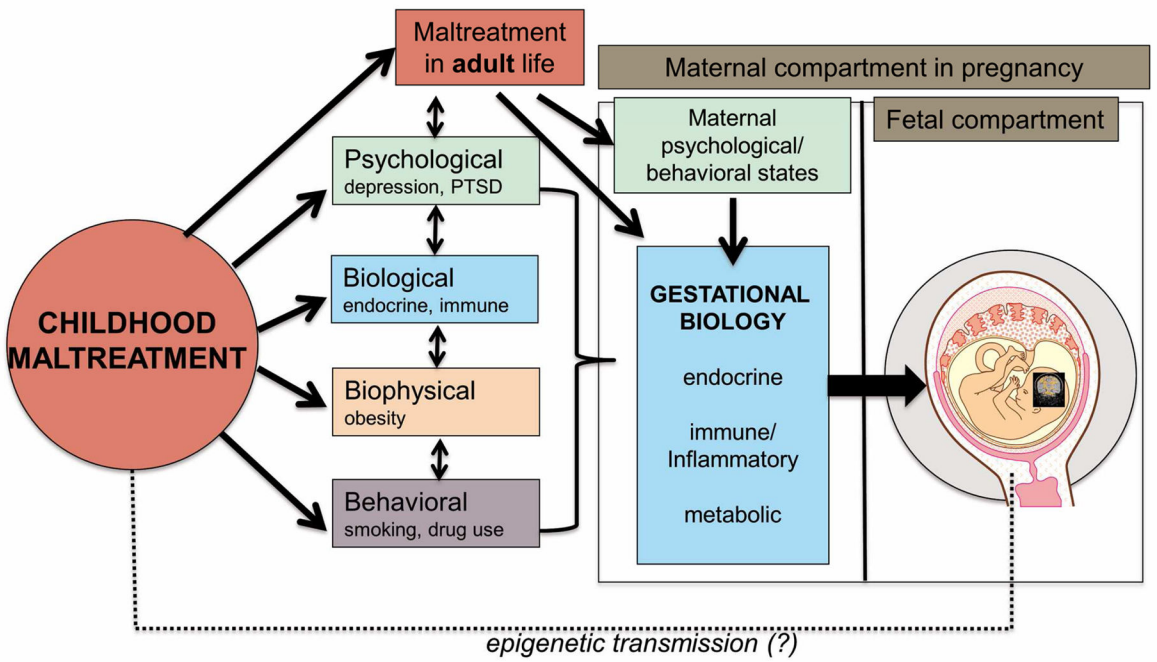

FIGURE 1.

Intergenerational transmission during gestation of the effects of maternal exposure to childhood maltreatment (CM): a conceptual framework. Note: The model suggests intrauterine life representing a particularly sensitive time period when the effects of maternal CM exposure may be transmitted to the offspring; the principal mode of transmission is biological, transmission primarily occurs via the psychological, behavioral, and biophysical sequelae of maternal CM 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.