9 Epigenetic Mechanisms Linking Prenatal Maternal Stress to Developmental Outcomes in Infants and Children

Frances A. Champagne, Laura H. Dosanjh, and Morgan Firestein

Introduction

Epigenetic mechanisms have emerged as a critical biological interface between genes and the environment that accounts for both developmental plasticity and the lasting impacts of early life experiences (Meaney, 2010). During the prenatal period, there are dynamic molecular and neurobiological changes that shape the fetal and infant brain and predict neurobehavioral outcomes (Glynn & Sandman, 2011; Miller et al., 2014). At a molecular level, changes in gene expression are regulated through multiple factors, including epigenetic mechanisms. These epigenetic mechanisms include molecular modifications either directly to DNA (i.e. DNA methylation) or to surrounding proteins and gene transcripts (i.e. histone modifications, noncoding RNAs) (Jenuwein & Allis, 2001; Razin, 1998; Sato et al., 2011). DNA methylation has been explored extensively, due to the role of this chemical modification in gene silencing and due to the plasticity of this epigenetic mechanism in response to a broad range of experiences. The emerging literature within this field suggests that DNA methylation can shape developmental trajectories particularly in response to experiences that occur in early life (Szyf & Bick, 2013). Though plasticity in DNA methylation can be observed across the lifespan, variation in DNA methylation in the fetus and infant may establish the foundation for neurobehavioral functioning that persists into childhood, adolescence, and adulthood.

Prenatal maternal stress has been established as a significant predictor of obstetric and developmental outcomes in humans (Liou et al., 2016; Preis et al., 2021). Though the causal role of prenatal maternal stress in shaping development has primarily been established in animal models, the parallel between these lab-based studies and epidemiological studies in humans is evident (Monk et al., 2012; Weinstock, 2008). Exploration of the mechanisms linking prenatal maternal stress to developmental outcomes is increasingly incorporating analyses of epigenetic mechanisms such as DNA methylation. In this chapter, we will explore this literature, with a particular focus on the placenta and the association between prenatal maternal stress and preterm birth. Though the factors contributing to maternal stress are vast and include the early life experiences of mothers, there are potential interventions during the post-

F. A. Champagne (✉)
Department of Psychology, University of Texas at Austin, Austin, TX, USA
e-mail: fchampagne@utexas.edu

L. H. Dosanjh
Steve Hicks School of Social Work, University of Texas, Austin, TX, USA
e-mail: laurados@utexas.edu

M. Firestein
Columbia University Irving Medical Center, Department of Psychiatry, Division of Developmental Neuroscience, New York, NY, USA
e-mail: mrf2138@cumc.columbia.edu

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natal period that may interrupt the intergenerational transmission of prenatal maternal stress. Understanding of epigenetic mechanisms within this context may generate novel approaches to fostering healthy development in infants and children.

Epidemiological Studies Exploring the Impact of Prenatal Maternal Stress

Maternal exposure to psychosocial stressors before and during pregnancy increases the risk for suboptimal birth and infant outcomes (Ding et al., 2021; Lima et al., 2018). A recent meta-analysis of studies published in the United States, Europe, Asia, Africa, and Australia found that prenatal stressful life events were associated with a 20% higher risk of preterm birth, 23% increased risk for low birth weight, and 14% higher risk of babies being born small for gestational age (Ding et al., 2021). In addition, maternal prenatal stress has been associated with obstetric complications, spontaneous abortion, delayed intrauterine growth, heightened infant stress responsivity, and delayed motor and cognitive development (Bussières et al., 2015; Davis & Narayan, 2020; Wainstock et al., 2013; Weinstock, 2008). Within this literature, the type of maternal stressors associated with fetal and infant outcomes is broad and includes exposure to intimate partner violence, poverty, racism, discrimination, insecure housing, incarceration, natural disaster or other trauma, death of a family member, and mental health problems, including depression, anxiety, and post-traumatic stress disorder (PTSD) (Blumenshine et al., 2010; Collaer & Hines, 1995; Cutts et al., 2015; Ding et al., 2021; Laelago et al., 2017; Liou et al., 2016; Liu & Glynn, 2022; Menclova & Stillman, 2020).

Though explorations of the impact of prenatal maternal stress have focussed primarily on stressors occurring during gestation, there is also evidence that the lifetime stress of mothers, particularly stressors occurring in early life, can impact birth outcomes (Kern et al., 2022; Souch et al., 2022). The impact of childhood adversity on birth outcomes has been investigated through analyses of single forms of adversity such as sexual abuse or through a limited range of types of adversity. These studies have demonstrated mixed findings in relation to birth outcomes. For example, Wosu et al. (2015) surveyed research examining the relationship between childhood sexual abuse (CSA) and preterm birth. Only 50% of their final sample demonstrated that CSA had a statistically significant effect on the odds of preterm birth (Wosu et al., 2015). In a sample of female nurses, analyses of the relationship between type, timing, and severity of maltreatment (sexual abuse, physical abuse, and harsh parenting) on preterm birth found that that forced sexual activity in childhood or adolescence was linked to a 22% increase in odds of preterm birth (Selk et al., 2016).

The impact of childhood adversity on birth outcomes has also been examined through the Adverse Childhood Experiences (ACEs) model (Christiaens et al., 2015; Hemady et al., 2022; Kern et al., 2022; Mersky & Lee, 2019). The ACEs screen captures several types of adversity and creates a total score based on the number of adversity categories reported. The ACE score includes direct forms of maltreatment such as physical abuse, sexual abuse, verbal abuse, physical neglect, and emotional neglect in addition to several categories of household dysfunction such as parental divorce, incarceration of a parent, parental mental illness, substance use in the home, and domestic violence (Felitti et al., 1998). It has been suggested that because forms of maltreatment often co-occur (i.e. individuals exposed to one form of maltreatment are more likely to be exposed to additional types of maltreatment), results from studies measuring only singular types of maltreatment may be limited by the confounding (albeit unmeasured) effects of other adversities (Dong et al., 2004; McLaughlin et al., 2020). For this reason, it has been asserted that the ACEs model supports a more thorough assessment of the impact of ACEs on numerous outcomes across the lifespan (Hamby et al., 2021). Consistent with this assertion, studies examining birth outcomes using an assessment of total ACEs have shown more consistent results.

In a recent systematic review, studies investigating the link between total ACEs and preterm birth were surveyed with seven of nine studies demonstrating a significant effect of ACEs on preterm birth (Sulaiman et al., 2021).

Psychological, Behavioral, and Social Risk Factors Linking Early Life Stress and Infant Outcomes

Early life adversity has been associated with many prenatal stressors that are linked to suboptimal birth and infant outcomes, such as prenatal depression, anxiety, and PTSD (Davis & Narayan, 2020). For example, a study with a sample of 636 pregnant women found that participants with four or more ACEs had a 2.5-fold increase in the odds of prenatal depression (Wajid et al., 2020). Similarly, a study of low-income racially diverse pregnant women found that the total number of ACEs predicted elevated levels of depressive and PTSD symptoms (Atzl et al., 2019). In a recent study, a dose–response relationship was found between the total number of ACEs and the odds of prenatal depression and anxiety (Racine et al., 2022). Taken together, these studies demonstrate the wide-ranging psychological impacts of childhood adversity across the lifespan. While these experiences affect maternal psychological well-being during pregnancy, they also affect the development of the fetus and subsequent infant outcomes. Maternal depression and anxiety have been associated with preterm birth as well as delayed social-emotional, cognitive, language, motor, and self-regulation skills in infants and children (Rogers et al., 2020; Staneva et al., 2015). A recent systematic review and meta-analysis demonstrated that prenatal maternal PTSD is associated with increased risk of low birth weight, preterm birth, and gestational age (Sanjuan et al., 2021). Maternal PTSD has further been associated with delayed fine motor and adaptive behavior development in infants (Koen et al., 2017).

Childhood adversity has also been associated with maternal health risk behaviors and exposure to current life stressors during pregnancy. Early adversity has been linked to higher rates of substance use and smoking during pregnancy, which may mediate the effects of adversity on birth and infant outcomes (Chung et al., 2010; Davis & Narayan, 2020; Smith et al., 2016). While ACEs are associated with risky health behaviours, they are also associated with life circumstances that increase risk for poor fetal and infant outcomes. Early childhood adversity in mothers is associated with exposure to traumatic and stressful life events such as intimate partner violence (IPV), exposure to neighborhood violence, and food insecurity (Buehler et al., 2022; Castro et al., 2003; Mahenge et al., 2018). IPV has been associated with low birth weight and preterm birth (Hill et al., 2016; Laelago et al., 2017) as well as increased odds of language delay in toddlers (Udo et al., 2016).

Biological Mechanisms Impacted by Prenatal Stress

Maternal exposure to stress, such as the experience of early childhood adversity, has neurobiological consequences that are transmitted to the fetus during pregnancy resulting in the intergenerational transmission of adversity (Davis & Narayan, 2020) though disruption to neural, endocrine, immune, and metabolic physiology (Deighton et al., 2018). In particular, the experience of chronic stress in childhood can impact the function of the hypothalamic–pituitary–adrenal (HPA) axis resulting in long term hyper- or hyporeactivity of the sympathetic and parasympathetic branches of the nervous system. This dysregulation may manifest in abnormal peripheral and central glucocorticoid activity, reduced or unmodulated immune function, and increased inflammatory markers (Berens et al., 2017; Deighton et al., 2018). During gestation, the HPA axis and placenta form a feedback loop that stimulates production of corticotropin releasing hormone (CRH) from the placenta. The maternal HPA and placental axis plays a vital role in the process of fetal maturation and timing of delivery and it has been demonstrated that early life adver-

sity of mothers is associated with elevated CRH levels during pregnancy (Moog et al., 2016). Elevated levels of maternal placental CRH (pCRH) in late pregnancy have been associated with early life adversity of mothers (Steine et al., 2020). Elevated pCRH during pregnancy has also been linked to preterm birth (Lee, 2014), fetal growth restriction (Wadhwa et al., 2004), and maternal psychiatric and medical outcomes such as postpartum depression, preeclampsia, and pregnancy-induced hypertension (Glynn & Sandman, 2014; Laatikainen et al., 1991). Long-term consequences of elevated pCRH on the development of infants and children include heightened levels of fear and distress, depression, anxiety, and externalizing symptoms (Davis et al., 2005; Howland et al., 2016). Thus, the HPA axis and placenta serve as a critical pathway linking maternal childhood adversity to intergenerational outcomes.

Placental Regulation of Stress Transmission and Exposure

The role of the placenta in regulating the transfer of nutrients and waste between the mother and fetus has long been recognized as a critical process for healthy fetal development (Burton & Jauniaux, 2015; Godfrey & Barker, 2001). In recent decades, more nuanced functions of the placenta, such as epigenetic and hormonal responses to environmental factors have become the focus of emerging areas of research (Shallie & Naicker, 2019). The placenta is a temporary endocrine organ that plays a critical role in regulating the hormonal milieu of the mother, the fetus, and the intrauterine environment more broadly. Early in embryonic development, the blastocyst forms and is composed of two primary layers, the inner cell mass, which will develop into the fetus, and the trophoblast, which will form the placenta, emphasizing the genetic overlap between the fetus and the placenta (Boss et al., 2018). As the trophoblast continues to develop, mononuclear cytotrophoblast cells fuse together and form the highly specialized syncytiotrophoblast cells, which are responsible for the production, synthesis, regulation, and transfer of many hormones between mother and fetus (Gore et al., 2014; Gude et al., 2004; Kliman et al., 1986, 2021). Notably, the placenta has the potential to modulate the synthesis and transfer of maternal hormones, such as glucocorticoids and androgens, which in turn may impact maternal mood and behavior, fetal brain development, and the quality of mother–infant interactions postnatally (Firestein et al., 2022; Gore et al., 2014; Jensen Peña et al., 2012; Mann & Bridges, 2001; Monk et al., 2012, 2016; Siiteri & MacDonald, 1966). Placental function as an interface between mother and fetus is dependent on transcriptional changes that are regulated by epigenetic mechanisms (Maltepe et al., 2010; Novakovic & Saffery, 2012).

To further understand the intergenerational transmission of stress and impacts on fetal and infant development, two primary epigenetic mechanisms within the placenta have been investigated: differential DNA methylation (gene-specific and genome-wide) and epigenetic aging.

Placental Epigenetic Modifications Associated with Prenatal Maternal Stress

Research spanning human and nonhuman species has evaluated the role of epigenetic modifications to specific genes, especially those within the HPA axis, in the relationship between exposure to prenatal stress and offspring behavioral outcomes (Monk et al., 2012). Prenatal maternal stress is associated with changes in DNA methylation and expression of corticosteroid 11-beta-dehydrogenase 2 (*11β-HSD2*) in both human (Capron et al., 2018; Conradt et al., 2013; Monk et al., 2016) and rodent (Jensen Peña et al., 2012) placentas. This gene is of particular interest as it encodes the 11β-hydroxysteroid dehydrogenase 2 enzyme, which converts cortisol into the biologically inactive cortisone and is highly expressed in placental tissue (Bronson & Bale, 2016; Limumpornpetch & Stewart, 2019; Monk et al., 2012). Interestingly, perceived psychological distress in humans has been found to be more

strongly associated with changes in DNA methylation of *11β-HSD2* than direct measures of maternal cortisol (Monk et al., 2016). Maternal depression occurring in early pregnancy is associated with broad changes in DNA methylation within the placenta, particularly within genes that regulate neural development (Lund et al., 2021). Further, *11β-HSD2* methylation within the placenta has been found to moderate the association between prenatal maternal depression and infant cortisol levels (Stroud et al., 2016) and reduced expression of this enzyme in the placentas of women who were depressed during pregnancy results in elevated fetal cortisol exposure (Nemoda & Szyf, 2017). Socioeconomic stress during pregnancy is associated with low levels of placental DNA methylation within *11β-HSD2*, particularly within the male placenta (Appleton et al., 2013). Exposure to chronic stress or trauma during pregnancy has been associated with altered placental DNA methylation in several genes within the HPA axis, particularly at transcription factor binding sites, which may be predictive of low birth weight (Kertes et al., 2016). Differential methylation of HPA axis genes within the placenta, particularly *NR3C1*, is associated with greater infant cortisol reactivity and self-regulation, suggesting prenatal epigenetic programming of infant development (Conradt et al., 2015).

Prenatal Stress Impacts on Epigenetic Aging

DNA methylation-based (DNAm) age estimators have emerged, which may provide insight into the impact of stress on biological aging (Horvath & Raj, 2018). These DNAm age estimators, or 'DNAm age' measures, have a robust linear relationship with chronological age and DNAm age, even in pediatric populations where infant gestational age at birth (in weeks) and DNAm age correlations are assessed using cord blood or blood spots at birth (Knight et al., 2016; McGill et al., 2022). Despite the overall linear relationship, DNAm age can exceed chronological age, a state referred to as DNAm age acceleration or epigenetic age acceleration (Simpson & Chandra, 2021). It has been proposed that this biological aging acceleration is the consequence of lifetime stress burden and may reflect the process by which this burden impacts physical health (Jain et al., 2022; Roetker et al., 2018). This process may also have intergenerational consequences. For example, elevated maternal anxiety during pregnancy is associated with greater DNAm age acceleration in children at 6–10 years of age, especially among male children (McGill et al., 2022). Epigenetic age acceleration is also associated with childhood adversity, which may then impact maternal mental health during pregnancy as well as infant development (McKenna et al., 2022; Rampersaud et al., 2022). While epigenetic age acceleration may reflect greater exposure to stress in utero, it may also confer protective benefits to the preterm neonate. Among extremely preterm infants, those with heightened epigenetic age acceleration were less likely to require surfactant or postnatal corticosteroid treatment for lung immaturity, required fewer days of assisted ventilation, and were less likely to be diagnosed with bronchopulmonary dysplasia (Knight et al., 2018).

Epigenetic Variation in Preterm Birth

The prenatal adversity that may emerge as a consequence of maternal stress can result in further intrauterine and gestational complications leading to premature birth. Preterm birth includes any delivery that occurs prior to 37 weeks gestational age and accounts for approximately 10% of all births in the United States (Frey & Klebanoff, 2016) with global estimates ranging from 8.7% to 13.4% of births (Chawanpaiboon et al., 2019). Infants who are born preterm are at increased risk for neurodevelopmental conditions, including autism, attention-deficit/hyperactivity disorder, language delays, and deficits in executive function and other cognitive domains (Welch et al., 2015), with risk modulated by a broad range of variables, including gestational age at birth, birth weight, childhood adversity, and sociodemo-

graphic variables (Hee Chung et al., 2020). Several gestational factors have been implicated in the etiology of premature delivery and it is generally categorized into three subtypes: medically indicated preterm birth, spontaneous onset of labor resulting in preterm birth, and preterm premature rupture of membranes resulting in preterm birth (PPROM) (Frey & Klebanoff, 2016; Goldenberg et al., 2012; Horta et al., 1997). Elevated DNA methylation has been found in postpartum blood samples of mothers who deliver preterm vs. term in the cytohesin 1 interacting protein *(CYTIP)* gene, which is normally highly expressed in the myometrium during labor (Hong et al., 2017). The presence of risk factors for preterm birth may be important considerations in predicting the epigenetic profiles associated with this outcome. For example, many pregnancies that result in preterm birth are complicated by preeclampsia, a gestational condition leading to maternal hypertension that is thought to arise due to inadequate formation of the spiral arteries of the placenta (Herzog et al., 2017; Perez-Sepulveda et al., 2015). In cases of early-onset preeclampsia compared to spontaneous preterm birth, there are thousands of differentially methylated sites within the genome of white blood cells from the umbilical cord blood and the placenta (Herzog et al., 2017). Compared to healthy controls, only placentas from cases of early-onset preeclampsia differ epigenetically. These findings suggest that infants who are delivered prematurely due to preeclampsia may experience epigenetic programming that differs from that of infants who are born preterm for other reasons such as PPROM or an intrauterine infection.

Altered DNA methylation within genes in the placenta have been observed in cases of preterm birth. A large meta-analysis reported that several genes (*UNC, OXTR, DLLI, RUNX*) are hypomethylated in placentas of preterm infants (Toure et al., 2017). This hypomethylation is even more pronounced in male placentas, which may be linked with the male bias in the incidence of preterm births (Martin et al., 2017). Using data from the extremely low gestational age newborns study (ELGANS) cohort, 2745 genomic sites from 578 genes were found to be differentially methylated between male and female placentas (Santos et al., 2019). All but 13 genes were located on the X-chromosome and were hypermethylated in male placentas compared to female placentas. Genes within the major histocompatibility complex, a genomic region critical for immune reactivity, tend to be hypomethylated in women who deliver prematurely and increased expression of immune factors could result in maternal rejection of the fetus (Ribeiro de Andrade Ramos & da Silva, 2017). Taken together, these findings suggest that there may be sex-specific susceptibility to environmental insults that could result in further alterations to fetal and maternal immune responses during pregnancy that could shorten the length of gestation.

During the postnatal period, differential DNA methylation in infants has been found associated with preterm birth and this epigenetic variation is predictive of neurobehavioral outcomes. Both hypomethylation and hypermethylation have been observed in the *NR3C1* gene in saliva samples from preterm infants compared to full-term infants (Kantake et al., 2014). These epigenetic effects are influenced by several factors, including intrauterine growth, mode of delivery, and the infants' Apgar scores at 1 minute after delivery. Hypermethylation of the *NR3C1* gene is associated with poor neurodevelopmental outcomes as measured by the NICU Network Neurobehavioral Scale (NNNs) (Lester et al., 2014, 2015). Specifically, hypermethylation of the *NR3C1* gene in placentas of preterm infants was inversely correlated with the quality of physical movements and attention to external social and nonsocial stimuli. Similarly, increased DNA methylation of the *SLC6A4* gene in neonates is associated with a shortened duration of orienting toward social stimuli (Montirosso et al., 2016). Seven year-old children who were born preterm exhibit increased DNA methylation of the *SLC6A4* gene in salivary samples that is associated with behavioral difficulties in mid-childhood, suggesting that the epigenetic effects of preterm birth persist well beyond NICU discharge (Chau et al., 2014). Finally, hypomethylation of the

IGF2 antisense transcript (*IGF2AS)* has been measured in blood samples from 18- to 27-year-old adults who were born prematurely at very low birth weights, which may account for lifespan health outcomes as a consequence of preterm birth (Wehkalampi et al., 2013).

Preterm Birth, Postnatal Adversity, and the Epigenome

Following exposure to the intrauterine and gestational complications that lead to premature birth, preterm infants are born into an environment for which their central and autonomic nervous systems are not yet prepared. The environment of the neonatal intensive care unit (NICU) may be particularly adverse for the developing preterm infant (Provenzi et al., 2017). During NICU hospitalization, infants are exposed to sensory stimulation that is qualitatively different than what they would ordinarily be exposed to in utero at that gestational time point. Given the relatively immature neurodevelopmental state of the preterm brain, these infants exhibit extreme sensitivity and reactivity to external stimuli, including routine NICU procedures like diaper changes, which have the potential to elicit a stress response (Spittle et al., 2016). Infants who are hospitalized in the NICU are also exposed to high levels of pain and discomfort as part of standard NICU care. In a sample of 137 preterm infants, the average number of skin-breaking procedures during NICU stay was 121 (Grunau et al., 2009). Critically, infants who were neonatally exposed to a greater number of painful procedures had poorer neurodevelopmental functioning during toddlerhood (Grunau et al., 2009). Moreover, DNA methylation within the *SLC6A4* gene increases significantly from birth to NICU discharge in preterm infants who are classified as having had high-pain exposure while hospitalized (Provenzi et al., 2015). An additional consequence of NICU hospitalization is prolonged and repeated maternal separation and there is a substantial literature illustrating that interactions with caregivers can have profound and long-lasting effects on epigenetic, social, and emotional development of the offspring (Hane et al., 2015; Peña et al., 2013; Weaver et al., 2004).

Postnatal Interventions to Foster Healthy Development in Preterm Infants

In the NICU, several interventions, including Kangaroo Mother Care (KMC), the Newborn Individualized Developmental Care and Assessment Program (NIDCAP), and Family Nurture Intervention (FNI), have been implemented with the goal of improving the health and neurodevelopment of preterm infants (Lawhon & Hedlund, 2008; Tessier et al., 2003; Welch et al., 2012). These interventions increase parental engagement with newborns, particularly though increased tactile interactions and skin-to-skin contact. At 1 year of age, preterm infants who received KMC have improved performance on personal–social, hearing and speech, and executive functioning tasks (Tessier et al., 2003). KMC is associated with accelerated brain maturation in neonates and long-term improvements in cerebral-motor functioning (Kaffashi et al., 2013; Schneider et al., 2012). Preterm infants within NIDCAP interventions have improved motor regulation and self-regulation scores, increased brain maturation and improved overall health relative to premature controls (Als et al., 2012). Preterm infants who receive FNI have improved cognitive and language scores, reduction in attention problems, decreased socioemotional problems resulting in reduced risk of autism, and similar to KMC and NIDCAP exhibit advanced brain maturation (Welch et al., 2015, 2017). FNI also has lasting effects on maternal mental health and maternal caregiving behavior, resulting in decreased maternal depression and anxiety as well as improved mother–infant face-to-face communication at 4 months of age (Beebe et al., 2018; Welch et al., 2016). Though the epigenetic impact of these interventions has yet to be elucidated, increased frequency of neonatal tactile stimulation is associated with global changes in DNA methylation and altered epigenetic age (Moore et al., 2017). Moreover, the increased

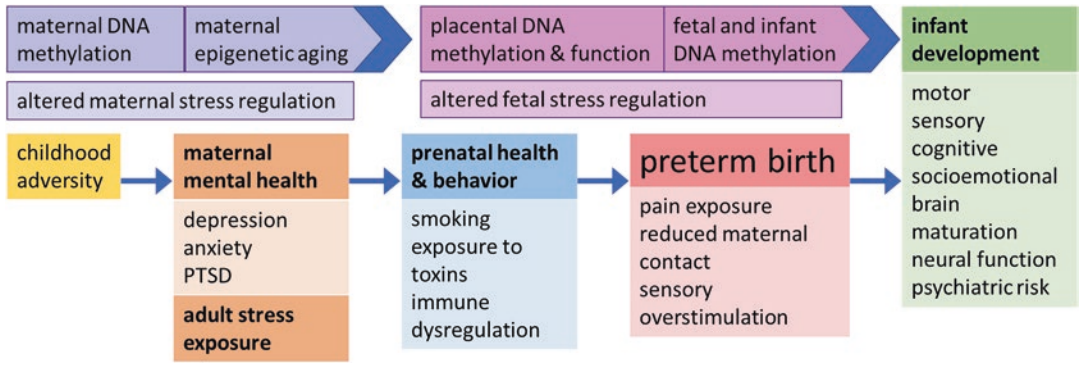

Fig. 9.1 Cascade of maternal experiences that are associated with mental health during pregnancy, risk behaviors, and stress exposure that contribute to prenatal maternal stress and risk of preterm birth. Preterm birth is associated with additional exposures that may confer vulnerability. Cumulatively, these experiences impact infant development via dysregulation of maternal and fetal stress systems, and altered DNA methylation in mothers, the placenta, and fetus

maternal responsivity associated with these interventions may lead to decreased DNA methylation of the *NR3C1* gene and more regulated stress responses in infants (Conradt et al., 2019).

Summary and Key Points

Prenatal stress is a reflection of the life experiences of mothers and can result in the intergenerational transmission of health risks. This transmission is characterized by a cascade of biobehavioral effects that impact the fetal environment, the timing of birth, and exposure to variation in the quality of the postnatal environment (see Fig. 9.1). Integration of analyses of epigenetic effects within this cascade reveals the critical importance of placental function, the multifaceted risk associated with preterm birth, and potential avenues for dynamic epigenetic and developmental change associated with postnatal interventions that focus on the experiences of mothers and infants. Though DNA methylation variation within genes that regulate the response to stress (i.e. *NR3C1*, *11β-HSD2*) and mood (i.e. *SLC6A4)* have emerged within this literature, broader epigenome-wide associations are increasingly apparent that suggest a global impact of stress and potential impacts on immune function and biological aging. Importantly, though DNA methylation is highly stable, the ability to target the plasticity of this mechanism and shift developmental trajectories is being increasingly explored. Future work in this field should continue to explore this plasticity and integrate this more dynamic notion of the epigenome within intergenerational studies. Understanding of this plasticity may also be enhanced through integration of emerging findings regarding the impact of pre-conceptional paternal stress on developmental trajectories and the interplay between maternal and paternal stress on gestation and the offspring epigenome (Day et al., 2016; Mashoodh et al., 2018).

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