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Epigenetics, maternal prenatal psychosocial stress, and infant mental health

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ABSTRACT

This paper provides a summary of literature on epigenetic effects and infant health outcomes of maternal psychosocial stress during pregnancy. A search of literature yielded a large body of publications between 2008 and 2018. Relevant articles were selected, and additional sources were located from ancestry searches of reference lists. Results implicate maternal prenatal stress as a source of epigenetic mechanisms that affect fetal brain development and program risk for emotional dysregulation and mental disorders over a lifetime and across generations. Implications for nursing practice are explored at multiple levels of policy advocacy, public education, primary prevention, screening and intervention.

The perinatal period has long been recognized as a critical developmental window to intervene in infant health and influence outcomes over the life course (Kitzman et al., 2010). The neurodevelopmental foundations for complex behaviors such as language, cognition, and emotional regulation are formed during the perinatal period, setting the stage for vulnerability or resilience in responding to life stress (Klengel & Binder, 2015). A call to action is coming from organizations such as the International Society for Developmental Origins of Health and Disease (DOHaD) to reduce the burden of disease by promoting healthy development from conception through childhood (Gluckman, Hanson, & Buklijas, 2010). Likewise, "The First 1000 Days" is a governmental and foundation-supported initiative launched in 2010 to improve nutrition for healthy brain development from conception through infant age two (https://thousanddays.org). Programs of research are seeking to determine how early development and adversity affect disease risk throughout life and across generations. Research findings consistently draw upon epigenetic mechanisms to explain these relationships (Bowers & Yehuda, 2016).

The purpose of this paper is to summarize literature regarding the effects of maternal prenatal psychosocial stress on epigenetics and infant mental health and identify implications for nursing practice. Maternal prenatal psychosocial stress is defined as maternal exposures to stressful life events, maternal perceptions of stress, and/or physical manifestations of the stress response during pregnancy. A ProQuest academic search was undertaken using the search terms "infant mental health", "prenatal development", "epigenetic", and "maternal psychosocial stress" and yielded 292 peer-reviewed scholarly journal articles published in the English language during the past decade, 2008 to 2018. Given the magnitude of this body of literature, this paper represents a selective rather than comprehensive review of literature. An ancestry review of reference lists from particularly relevant articles provided additional sources for review.

The "three hit model" of susceptibility to mental illness

Predisposition to mental health or illness begins before conception and is based in part on the genetic profiles of an individual's parents. Estimates of genetic heritability vary from approximately 40% to 70% across mental disorders. Genome-Wide Association Studies (GWAS) point to complex combinations of genetic polymorphisms that underlie clusters of mental disorders that share similar genotypes but are expressed with different phenotypes and symptoms (Demkow & Wolanczyk, 2017; Lee et al., 2013). According to Bale (2014), genetic predisposition is the first "hit" in a "three-hit model" of susceptibility to mental illness. In this model, stress during the prenatal period is the second hit for a genetically predisposed individual. Subsequent exposure to stress during postnatal life contributes the third hit that can "tip the scale" and trigger symptom onset (Bale, 2014, p. 298). Programs of research are exploring each of these areas of impact. Some researchers argue the "second hit" imposed by stress during pregnancy is a critical vulnerability factor because it can derail the development of organ systems and brain structures that regulate emotions and behavior (Buss, Entringer, & Wadhwa, 2012). Research on prenatal factors affecting infant mental health has focused attention on maternal stress during pregnancy and its role in programming the fetal stress response system (Lewis, Galbally, Gannon, & Symeonides, 2014).

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Prenatal programming of the stress response

The epigenetic and neurobiological effects of exposure to high levels of maternal stress during prenatal development can alter the architecture of the fetal brain and "program" a more reactive stress response system in the newborn (Bock, Rether, Groger, Xie, & Braun, 2014; Gluckman, Hanson, Cooper, & Thornburg, 2008; Shonkoff, Boyce, & McEwen, 2009). According to Erhuma (2012), "fetal programing" is defined as "the physiological, metabolic, or behavioral adaptation resulting from exposure to or lack of hormones, nutrients, stress, and other agents at critical periods during embryonic and fetal development" (p. 460). Originally described by David Barker (1995), the concept of fetal programing of adult disease refers to adaptive responses on the part of the fetus to perturbations in the intrauterine environment (Talge et al., 2007). Not all such fetal adaptations are harmful, but when adaptations occur in response to a stressed intrauterine environment, they typically involve a trade-off in terms of future growth, development or health potential. For example, a stressed intrauterine environment during the third trimester of pregnancy can signal risk for premature birth, stimulating accelerated brain maturation at the expense of abdominal organ growth. This adaptive response may increase the survivability of a premature infant but also results in "reprogramming" of liver functions, altering endocrine system set-points and increasing risk for cardiovascular disease, insulin resistance, and metabolic syndrome later in life (Barker, 1995; Beijers, Buitelaar, & de Weerth, 2014; Lewis et al., 2014).

During pregnancy, the developing infant shares the mother's physiological and emotional environment mediated through the placenta. The placenta is a complex neuroendocrine organ with many functions including the transport of nutrients and oxygen from mother to fetus (Beijers et al., 2014). Any restriction in placental blood flow that affects fetal oxygen and nutrition engenders a stress response (Lewis et al., 2014). Maternal anxiety, depression and stress affect placental blood flow and can thereby influence fetal growth and development (Arabin & Baschat, 2017). Increased weight of the placenta at birth is an indicator of a compromised intrauterine environment, revealing compensatory growth of the placenta in an attempt to safeguard the developing fetus from a number of maternal risk factors, including stress (Tegethoff, Greene, Olsen, Meyer, & Meinischmidt, 2010).

A placental enzyme, 11-beta hydroxysteroid dehydrogenase-2 (11b-HSD2), is a protective mechanism of the placenta. This enzyme regulates the amount of stress hormones that pass from mother to fetus by converting maternal cortisol into an inactive substance, cortisone. Levels of this enzyme are typically highest and most protective of fetal development during early pregnancy. Conditions that affect the health of the placenta, such as maternal hypertension or high levels of stress, have been shown to alter levels of this protective enzyme (Bowers & Yehuda, 2016; Erhuma, 2012).

Organs of the fetal stress response system are developed by 20 weeks gestation, including the hypothalamus, pituitary and adrenal glands that make up the HPA axis (Lewis et al., 2014). By the third trimester of pregnancy, the fetal HPA axis is functional and responsive to levels of circulating stress hormones. Glucocorticoid receptors (GRs) that detect levels of circulating cortisol are present in the hippocampus and hypothalamus of the fetal brain and act as a negative feedback loop to turn down the fetal HPA axis when levels of cortisol get too high (Lewis et al., 2014). During the third trimester, levels of the protective placental enzyme (11b-HSD2) normally drop, allowing greater circulation of maternal cortisol across the placenta, thereby stimulating development of the fetal lungs in preparation for birth (Erhuma, 2012). When levels of maternal cortisol remain high for long periods, the fetus can be exposed to toxic levels of circulating cortisol that alter the fetal stress response system and program stress reactivity (Palma-Gudiel, Cordova-Palomera, Eizarch, Deuschle, & Fananas, 2015; Shonkoff et al., 2009).

An extensive amount of research has linked prenatal stress exposure to DNA methylation as a means by which infant stress reactivity is programmed by exposure to maternal stress during pregnancy (Palma-Gudiel et al., 2015). Methylation of DNA is an epigenetic mechanism that changes gene expression without altering the individual's DNA sequence (Turecki, Ota, Belangero, Jackowski, & Kaufman, 2014).

Epigenetic mechanisms

Epigenetic mechanisms confer enduring as well as dynamic epigenetic signatures on the genome. Enduring epigenetic effects occur during the differentiation of cell lines in embryonic development (Srinageshwar, Maiti, Dunbar, & Rossignol, 2016). These biologically "hardwired" mechanisms induce relatively stable epigenetic signatures that distinguish cell types over a lifetime (Gluckman et al., 2008). In the past two decades, researchers have also identified dynamic epigenetic mechanisms that respond to environmental conditions and life experiences. Exposure to environments and experiences that induce epigenetic modifications continue over the lifespan and help explain how individuals with similar genotypes can express different phenotypes, behaviors, and disorders (Szyf, Tang, Hill, & Musci, 2016).

Epigenetic modifications in response to environmental conditions are increasingly recognized as contributing to individual health potential and disease risk. Epigenetic mechanisms are of particular interest in understanding how exposure to stress early in development affects risk for disease over a lifetime and across generations (Anda et al., 2006; Meaney, 2001). The methylation of DNA is an epigenetic mechanism linked to environmental stress and adversity. It involves the addition of methyl groups to the promoter region of genes, thereby altering transcription factor access to this region and changing gene expression (Szyf et al., 2016). Methyl groups generally suppress or "turn off" gene expression by blocking transcription factors from accessing the promoter region of the gene (Nestler, Pena, Kundakovic, Mitchell, & Schahram, 2016). Exposure to toxic stress early in development changes the methylation patterns of genes (Turecki et al., 2014). Among the most studied genes in developmental research is the NR3C1 gene that codes for glucocorticoid receptors (GRs). Methylation of the NR3C1 gene silences the expression of GRs in the hippocampus, thereby damaging the negative feedback loop that turns down the HPA axis when cortisol levels remain too high for too long (Braithwaite, Kundakovic, Ramchandani, Murphy, & Champagne, 2015). High levels of circulating cortisol are neurotoxic to the developing brain, resulting in smaller limbic and prefrontal brain structures and altered connectivity among neural circuits that regulate emotions and behavior (Bock et al., 2014).

Epigenetic modifications of genes in reproductive gametes (ova and sperm cells) are thought to play a role in the transgenerational inheritance of an epigenetic stress signature, affecting risk for metabolic, cardiovascular, and psychiatric disorders across as many as four generations (Gonzales-Ochoa, Sanchz-Rodriguez, Chavarria, Gutierrez-Ospina, & Romo-Gonzalez, 2018). Severe stress exposure in pre-pubescent males and females may be transmitted through epigenetic scars on genes within reproductive cells, present long before the offspring of the next generation are conceived (Bale, 2014).

Infant outcomes of maternal prenatal stress

Some stress and anxiety during pregnancy is normal and facilitates adaptation to this significant developmental transition. A study conducted in a diverse urban community identified 78% of pregnant women with low to moderate psychosocial stress and 6% with high psychosocial stress (Woods, Melville, Guo, Fan, & Gavin, 2010). Following the definitions of Shonkoff et al. (2009), "positive stress" temporarily increases stress hormones, which return to baseline through healthy coping. Even moderate to severe stress may be "tolerable" when it is time limited and buffered by supportive relationships. In contrast, stress that is "toxic" to health and development is characterized by

increased intensity, frequency and duration in the absence of a supportive context (Shonkoff et al., 2009).

Evidence from animal and human research generally links high levels of maternal psychosocial stress during pregnancy to adverse health outcomes for offspring. Animal research has been a dominant source of this evidence, reporting outcomes of impaired learning and attention, behavior problems, anxiety and depression-like behaviors in offspring (Beijers et al., 2014). There is an increasing body of human research examining differences in infants born to mothers exposed to disasters or mass trauma (Malaspina et al., 2008) and prospective studies that recruit pregnant women, assess their stress during pregnancy, and follow their infants longitudinally through stages of development (Andersson et al., 2016). Researchers differ in how they measure maternal prenatal stress; some quantify the number of exposures to stressful life events, others rely predominantly on maternal perceptions of stress, and still others elicit information about both stressful life events and mothers' perceptions (Tarabulsy et al., 2013).

Preterm birth and low birth weight

Preterm birth and low birth weight are among the most studied outcomes of high levels of psychosocial stress during pregnancy (Dunkel-Shetter & Tanner, 2012). Severe psychosocial stressors that occur early in pregnancy, such as death of a family member or exposure to extreme trauma, are significantly correlated with preterm birth. Maternal trait anxiety and pregnancy-specific anxiety are also associated with infant prematurity (Dunkel-Shetter & Tanner, 2012). Low infant birth weight is associated with chronic maternal stress during pregnancy and can be compounded by maternal depression for women living in conditions of poverty, unemployment, crowding, and/or discrimination (Dunkel-Shetter & Tanner, 2012). Preterm birth and low birth weight are leading causes of infant mortality and predict poorer outcomes for child health, including increased risk for cognitive, behavioral, and emotional problems (Beijers et al., 2014).

Dysregulation of the HPA axis and stress reactivity

Oberlander et al. (2008) tested umbilical cord blood to assess DNA methylation of the NR3C1 gene that codes for glucocorticoid receptors (GRs) in infants born to mothers with depression and anxiety during pregnancy. Infants of prenatally depressed and anxious mothers had increased methylation of NR3C1 genes at birth and elevated salivary cortisol at three months of age (Oberlander et al., 2008). Following these findings, another research group tested salivary cortisol and NR3C1 methylation in children ages four to 16 years who were diagnosed with externalizing and internalizing disorders (Dadds, Moul, Hawes, Mendoza Diaz, & Brennan, 2015). While Dadds et al. did not study maternal prenatal stress per se, their findings help establish the relationship between increased methylation of NR3C1, higher cortisol levels, and increased internalizing symptoms in children and adolescents (Dadds et al., 2015).

Braithwaite et al. (2015) also focused on maternal depression during pregnancy as a source of stress and tested methylation patterns in infant DNA through buccal swabs acquired at one to three months of age. Findings included increased DNA methylation of the NR3C1 gene in male infants and decreased DNA methylation of the brain derived neurotrophic factor (BDNF) gene in both male and female infants. BDNF stimulates neuronal growth and development. In this study, increased expression of the BDNF gene in response to maternal depression was hypothesized to be a compensatory epigenetic mechanism, stimulating rapid brain development in preparation for challenges in the postnatal environment (Braithwaite et al., 2015).

Davis, Glynn, Waffarn, and Sandman (2011) examined the effects of maternal stress during pregnancy on newborn responses to stress within the first 24 h after birth. Maternal psychosocial stress was measured with standardized instruments including the Perceived Stress Scale (PSS), the Center for Epidemiological Studies Depression Inventory (CESD), and the anxiety subscale of the State-Trait Personality Inventory. Newborn stress reactivity was evaluated in response to a heel-stick procedure. Infants of mothers with elevated psychosocial stress during the second and third trimesters of pregnancy demonstrated a greater salivary cortisol response and prolonged behavioral recovery from the heel-stick procedure (Davis et al., 2011).

Longer term effects of maternal stress during pregnancy on DNA methylation patterns of the NR3C1 glucocorticoid receptor genes in offspring were examined by Radtke et al. (2011). An analysis of blood drawn from children, ages 10 to 19, of mothers exposed to intimate partner violence (IPV) during pregnancy revealed increased DNA methylation of a specific area (NGF1-A) in the promoter region of the NR3C1 gene. The researchers described the significance of this finding as “evidence of a transgenerational effect that may exert a lifelong influence on HPA-axis regulation” (Radtke et al., 2011).

Phelan, Dibenedetto, Paul, Zhu, and Kjerulff (2015) examined the effects of maternal stress during the third trimester of pregnancy on infant outcomes at one, six and 12 months (Phelan et al., 2015). The Psychosocial Hassles Scale developed by Misra, O'Campo, and Strobino (2001) was used to measure maternal stress. Outcomes of high levels of maternal stress during pregnancy included increased newborn respiratory and gastrointestinal symptoms and more emergency department visits during the infant's first year of life. The researchers attributed these infant outcomes to effects of prenatal stress on HPA axis dysregulation and compromised immunity. They also postulated indirect effects mediated postnatally through maternal perceptions and behaviors. Mothers with high levels of stress during pregnancy may continue to experience stress during the postpartum period, affecting their perceptions of parenting, vigilance to their infant's distress, and anxious interactions with their newborns (Phelan et al., 2015).

The Stress in Pregnancy (SIP) study is examining effects of maternal perceived stress during pregnancy (MPSP) on infant and child health over time. Similar to findings by Phelan et al., SIP researchers linked prenatal maternal stress to altered fetal immune system development. Examination of umbilical cord blood from high stress mothers yielded evidence of increased inflammatory cytokines in fetal circulation (Andersson et al., 2016). Other outcomes from the SIP study include evidence of complex associations between MPSP, fetal HPA axis dysregulation, epigenetic modifications in mitochondrial gene expression, and more irritable infant temperaments (Lambertini, Chen, & Nomura, 2015). In this study, mitochondria genes from postdelivery placental tissue were analyzed. Lambertini et al. explain, “the placenta shares the genetic and epigenetic profile of the developing fetus” (p. 3), thus analysis of placental tissue provides insight into fetal epigenetic modifications in response to stress and HPA axis dysregulation. Findings from this study associated MPSP with increased mitochondrial gene expression in the placenta (an indicator of heightened stress-related energy demands) and irritable temperament in six-month-old infants (Lambertini et al., 2015).

Altered cognitive skills and brain development

Sandman, Davis, Buss, and Glynn (2012) conducted research on both maternal and child outcomes of maternal stress during pregnancy. Maternal psychosocial stress was assessed at multiple points from 20 to 36 weeks of pregnancy using measures of pregnancy stress and state anxiety. Infants were assessed at multiple points from birth to age 8 years. Results of this study identified effects of maternal prenatal stress on several infant and child outcomes, including a more fearful temperament, impaired emotional regulation, and differences in cognitive skills depending on the timing of the prenatal stress exposure. Prenatal stress early in pregnancy was associated with compromised cognitive skills in infants assessed between three months and two years of age. Early prenatal stress exposure also contributed to structural differences in child brain development observed through neuroimaging

at 5 and 8 years of age, including decreased gray matter volumes in the prefrontal cortex, temporal lobe, and cerebellum. These brain regions are implicated in numerous cognitive functions such as attention, problem-solving, memory, learning, and language development. Mothers with higher psychosocial stress during pregnancy also had poorer health outcomes, including greater risk for postpartum depression (Sandman et al., 2012).

Attention deficit hyperactivity disorder and conduct problems

A prospective study of maternal anxiety assessed at multiple points from 12 weeks to 40 weeks of pregnancy reported a significant correlation between maternal prenatal anxiety and ADHD symptoms in offspring at 8 and 9 years of age after controlling for other risk factors such as smoking during pregnancy and low infant birth weight (Van den Bergh & Marcoen, 2004). In this study, maternal anxiety was measured with the State Trait Anxiety Inventory (STAI). Child ADHD was evaluated by the child's mother and teacher using the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF), and the Groninger Behavior Observation Scale (GBO) administered by an external observer blinded to maternal anxiety status.

Similar results confirming an association between high maternal stress during pregnancy and child ADHD and conduct problems were reported from the Avon Longitudinal Study of Parents and Children in the United Kingdom (MacKinnon, Kingsbury, Mahedy, Evans, & Colman, 2018). This cohort study of over 10,000 mother-child pairs assessed maternal prenatal stress at 18 weeks gestation and child behavior at ages 6, 9, 11, 13 and 16 years. At 18 weeks of pregnancy, mothers rated a list of 42 stressful events, indicating if they had experienced the event and their level of distress associated with the event. The Strengths and Difficulties Questionnaire (SDQ) was used to measure child internalizing and externalizing symptoms. After controlling for other risk factors and child internalizing symptoms, the researchers reported a significant relationship between high maternal stress ratings at 18 weeks of pregnancy and child symptoms of hyperactivity at ages 7, 13 and 16, and conduct disorder symptoms at all measurement points (MacKinnon et al., 2018).

Major mental illness

Exposure to extreme adversity early in pregnancy has been linked to increased risk for schizophrenia in offspring. Khashan et al. (2008) followed infants born to Danish mothers who experienced death of a first-degree relative during pregnancy. After controlling for family history of mental illness, infants of mothers who experienced death of a relative during the first trimester of pregnancy were at higher risk of developing schizophrenia as adults (Khashan et al., 2008).

Malaspina et al. (2008) reported similar findings from research on data from the Jerusalem Prenatal Study of pregnancies during the Arab-Israeli war of 1967. The children of mothers exposed to the trauma of war during their first trimester of pregnancy were at increased risk of developing schizophrenia in adult life, with greater risk for females compared to males. Researchers speculate this female gender effect may in part be due to fewer live male births due to unsurvivable effects of early extreme prenatal stress on male fetuses.

These studies point to the first trimester of pregnancy as a particularly vulnerable period for alterations in neurodevelopment that increase susceptibility to major mental illness later in life. Wide-spread DNA methylation of genes has been detected in research on schizophrenia, offering a possible epigenetic explanation for how extreme stress early in prenatal development contributes to greater lifetime risk for this disorder (McGowan & Roth, 2015).

Other outcomes that limit life expectancy

Early adiposity

Adipocytes, also known as lipocytes or fat cells, differentiate from embryonic stem cells and predominantly form during the third trimester of pregnancy and in early postnatal period (Berry, Stenesen, Zeve, & Graff, 2013). Childhood and adult obesity has been linked to conditions that compromise the intrauterine environment, including maternal stress. A study by Entringer et al. (2017) collected maternal cortisol at multiple points during pregnancy to examine the relationship between maternal prenatal stress (evidenced by elevated cortisol) and infant adiposity during the first six months of life. Mothers' third trimester cortisol levels were significantly and positively correlated with gains in infant adiposity (percent body fat) from birth to six months of age (Entringer et al., 2017). This study is one of many examining the relationship between childhood obesity, maternal prenatal stress, and restricted fetal growth. As early as 1995, Barker published evidence of fetal programming of risk for cardiovascular disease and metabolic syndrome related to maternal prenatal stress, particularly in the third trimester.

Shortened telomere length

Multiple studies have examined the effects of prenatal stress on shortened telomere length in newborns as a predictor of lifetime morbidity and mortality risk (Entringer et al., 2013; Marchetto et al., 2016). Telomeres are the protective end-caps on chromosomes that promote chromosome stability. Telomeres become shorter with each cycle of cellular replication and the process is accelerated under conditions of stress, unhealthy lifestyle practices, and advancing age (Shammas, 2011). Shorter telomeres in infants and children are markers of accelerated cellular aging and predict increased risk for a host of age-related diseases and premature death.

Complex gene × environment interactions

There is empirical evidence linking high levels of maternal prenatal stress to adverse health outcomes for infants and children. Reported outcomes include premature birth and low birth weight, increased stress reactivity and irritable temperament in newborns, altered brain development affecting cognitive functions and emotional regulation, hyperactivity and conduct problems during school age and adolescence, and risk for major mental illness in adulthood. Evidence points to stress-induced epigenetic modifications such as DNA methylation and reduced expression of the NR3C1 glucocorticoid receptor gene as a source of these adverse outcomes. Epigenetic modifications “program” a reactive stress response system, altering an individual's baseline of emotional and behavioral reactivity and increasing vulnerability to psychiatric disorders.

Researchers acknowledge the difficulty of parsing the unique effects of maternal prenatal stress from the broader context of early developmental influences on infant health (Monk, Spicer, & Champagne, 2012). Mothers' exposures to experiential and environmental stressors often continue from pre-conception through pregnancy and into the postnatal period. Those who report high levels of stress during pregnancy often report high levels of stress in the postnatal period and may be more likely to engage in health risk behaviors such as smoking and/or alcohol use, which can independently exert negative effects on infant health and development (DiPietro, 2012; Lewis et al., 2014). Impoverished living conditions during pregnancy often continue through postnatal development, imposing a host of stressors affecting the health of mothers, infants, and children (Dunkel-Shetter & Tanner, 2012; Luby et al., 2013).

From a positive perspective, the infant's brain and epigenome remain highly responsive to experience and the environment during postnatal development (McGowan & Roth, 2015). While high levels of prenatal stress confer an increased susceptibility to psychopathology in

offspring, this susceptibility may itself be epigenetically modifiable. Meaney's landmark study of high lick-groom versus low lick-groom rats was first to reveal the ameliorating influence of early caregiving on the stress susceptibility of offspring. In Meaney's research, nurturing maternal care modified the epigenetic scars on offspring glucocorticoid receptor (GR) genes, mobilized the expression of GR receptors in their hippocampi, and decreased their reactivity to stress; effects that were sustained through cross-generational transmission of maternal caregiving behaviors in the female offspring (Weaver, Meaney, & Szyf, 2006).

Evidence of the ameliorating effects of parenting has also been reported in human research. Schechter et al. (2017) recruited a sample of pregnant women from a mental health treatment center and followed them through pregnancy and their children's early development. Over 90% of recruited women met criteria for a psychiatric diagnosis. In addition to clinical scales such as the Clinical Global Impressions Scale (CGI), the Hamilton Rating Scale for Depression (HRSD), and the Beck Depression Inventory (BDI), the pregnant women in this study completed the Perceived Stress Scale (PSS) as a measure of prenatal psychosocial stress. The cognitive abilities of their children were evaluated with the Differential Ability Scale (DAS) during a follow up visit at an average child age of 44 months. During this visit, mother-child parenting interactions were recorded and coded by trained researchers using the Dyadic Parent-Child Interaction Coding System (DPICS). Children in this study were exposed to prenatal psychosocial stress as well as clinical levels of maternal psychiatric symptoms. Higher levels of maternal prenatal stress were significantly and negatively correlated with child cognitive abilities for mothers with poor parenting behaviors. However, the relationship between cognitive impairment and high prenatal stress did not remain significant for children of mothers with positive parenting behaviors. It was concluded that positive parenting moderated the detrimental impact of maternal prenatal stress on child cognitive abilities (Schechter et al., 2017).

Implications for practice

According to Szyf et al. (2016), we are currently "moving from bench to bedside" in translating epigenetic research into practice. We are in early stages of identifying, implementing and evaluating healthcare interventions based on scientific discoveries in this field. As we wait for translational research to discover effective models for reversing stress-induced epigenetics, we can envision implications for nursing practice at multiple levels, from universal public health initiatives to specialty practice interventions with high risk populations. Nurses are in key roles to disseminate information and promote maternal and infant mental health at every level of policy advocacy, public education, primary prevention, screening and intervention.

Nursing as a profession has a powerful, trusted voice in formulation and advocacy of national public policies to address stress associated with poverty and discrimination as sources of epigenetic modifications transmitted from generation to generation. Public education is needed to draw attention to the health implications of multi-generational stress and the health benefits of providing healthy, supportive contexts during pregnancy and early infant development. Education about stress during pregnancy and outcomes for infant health can be provided by school nurses in middle school and high school health classes, community health nurses, and nurses in obstetric and pediatric primary care practices. Routine assessment of psychosocial stress can be performed by nurses in any setting and especially with women of child-bearing age. Assessment tools such as the "Psychosocial Hassles Scale" (Misra et al., 2001) and the "Perceived Stress Scale" (Cohen, Mermelstein, Kamarck, & Hoberman, 1985) are screening tools that can provide a basis for teaching about the impact of stress, ways to manage stress exposures, and lifestyle practices that downregulate the stress response.

Effective parenting education and intervention programs already exist and can integrate new information about the ameliorating effects of positive parenting on epigenetics and health potential. A simple parenting intervention such as "prescribed maternal stroking of their infants" has demonstrated effectiveness in lessening the influence of maternal prenatal depression on infant mental health (Palma-Gudiel et al., 2015, p. 896).

Nurse home-visiting programs, such as the "Nurse Family Partnership", which begin in the first trimester of pregnancy and continue through infant age two have an established record of evidence-based interventions and improved infant outcomes, including mental health (Kitzman et al., 2010; Olds, 2012). Another example of an effective pregnancy intervention is "Centering Pregnancy", a prenatal program that provides education and group emotional support with demonstrated effectiveness in reducing preterm births (Phelan et al., 2015).

Psychiatric nurses are taught the value of three-generational genograms in identifying family processes across generations. With minor adaptations, a "Generational Stress Genogram" could be completed during nurse-patient encounters, providing a framework for discussing the impact and generational transmission of the epigenetic signatures of stress. Epigenetics has been described as a framework for integrating a relationship-based practice with psychoeducation, psychotherapy and psychopharmacology in advanced practice psychiatric nursing (DeSocio, 2016). Research is needed to achieve this level of translation from science to integrated evidence-based practice. However, promising indications are already appearing in the literature. A pilot study of the effects of prolonged exposure therapy for veterans with PTSD is among the first to evaluate stress-induced epigenetic markers, such as methylation of the NR3C1 glucocorticoid receptor gene, as indicators of symptom severity and response to treatment (Yehuda et al., 2013). Klengel and Binder (2015) also report on the future of pharmacological agents that reverse stress-induced epigenetic modifications, currently being tested in animal research. These reports foretell an exciting evolution in epigenetically-informed, evidence-based practice for nursing and other healthcare disciplines.

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