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Exploring the Link Between Chronic Stress and Substance Abuse Among Public Health Workers: Neuroendocrine Pathways

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Abstract

Aim: This review examines how early life stress, particularly during the prenatal and perinatal periods, impacts the neuroendocrine and immune systems, increasing the risk of substance use disorders (SUDs) across generations.

Methods: A synthesis of animal and human studies was conducted, focusing on the effects of maternal stress, glucocorticoid administration, and prenatal drug exposure on offspring. The role of the hypothalamic-pituitary-adrenal (HPA) axis and immune system was also explored.

Results: Evidence suggests that maternal stress and drug exposure during pregnancy can biologically embed risks for SUDs through alterations in HPA axis function and immune responses. Increased cortisol levels and gene expression changes in offspring are observed, linking prenatal stress to heightened susceptibility to addiction. Animal studies consistently show a pattern of increased drug sensitivity and preference in those exposed to prenatal stressors.

Conclusion: Understanding the biological mechanisms by which early stressors contribute to addiction vulnerability is crucial for developing effective prevention and intervention strategies. Future research should further explore the interplay between various stressors and their cumulative effects on neurobiological pathways related to substance abuse..

Key Words: *Substance use disorders, prenatal stress – Neuroendocrine system – HPA axis – Addiction – Fetal programming.*

Introduction

SUBSTANCE abuse and addiction are major public health concerns since almost 21 million adults in the US suffer from a substance use disorder (SUD) (US Department of Health and Human Services, Office of the Surgeon General, 2016). Reducing the effects of SUDs and addiction on people and communities requires an understanding of the underlying causes of these conditions. Notably, stress in early childhood has been found to be a major risk factor for alcohol and drug abuse (Enoch, 2011; Stone et al., 2012). Thus, bettering preventative and treatment strategies requires examining the neurobiological pathways that connect early life stress with substance dependence.

Stress can have an impact on behaviors that put health at risk even in the pre- and perinatal phases, which include the time from implantation to pregnancy and the first six months of life. Due to its rapid fetal brain development and increased biological plasticity, this phase is especially sensitive to external stimuli (Lupien et al., 2009; Provençal and Binder, 2015). There is clear evidence of a complex cycle of intergenerational transmission, where mothers who struggle with substance use are more likely than mothers without such problems to expose their children to similar stressors during the prenatal and perinatal period. These mothers also frequently have higher rates of childhood abuse, neglect, and substance exposure. According to Cash and Wilke (2003), this cycle raises the likelihood of substance use disorders later in life. Translational neuroscience has begun to shed light on how early adversities can become "biologically embedded," with the help of both animal and human research. This has revealed the mechanistic pathways that link pre/perinatal stress to subsequent maladaptive outcomes, like substance misuse (Miller et al., 2011). Crucially, it is thought that during the prenatal and perinatal phases, the neuroendocrine and immune systems are critical in transmitting risks for addiction and psychological disorders resulting from acute and chronic stressors (Enoch, 2011; Koob and Le Moal, 2001; Mayes and Suchman, 2006). According to Ei-

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den et al. (2016), most current etiological theories of substance abuse and addiction have not considered the early stages of development, when immunological and endocrine processes may be the basis for future susceptibility to addiction. A proposed conceptual model demonstrates how immunological and neuroendocrine pathways can increase the susceptibility to addiction caused by prenatal and perinatal stress. In order to demonstrate how stress exposure during pregnancy and infancy affects neuroendocrine and immunological systems, which raises the risk for substance abuse and addiction, this study synthesizes data from studies conducted on humans and animals. First, we review the literature on three main types of prenatal stress: stress caused by the mother (which includes psychosocial stress and psychopathology), stress created in the lab by glucocorticoid administration, and stress brought on by prenatal drug exposure. We include evidence about the function of the hypothalamic-pituitary-adrenal (HPA) axis in these topics. The relationships between stress during pregnancy and the postpartum period, substance use in offspring, and immune function are then examined. Relevant animal research on immunological activation, viral infections, and prenatal drug exposure is included, as are human studies that establish a connection between stress, prenatal drug use, and inflammation.

We also touch on the importance of perinatal HIV infection as a practical background for comprehending immune-related stresses and their possible influence on the vulnerability of offspring to substance abuse. In each section, we begin by examining the relationships between prenatal and perinatal stressors and the likelihood of substance dependence, and then we discuss the research on the role of the immune system or the HPA axis in these processes. Stressor types have been compiled due to the paucity of material that has been written about these subjects. Moreover, a thorough analysis of all the literature on each chemical was outside the purview of this work. We approach the problem of intergenerational transmission of substance use and addiction in this review from a translational neuroscience perspective. According to Fisher and Berkman (2015), this method promotes a nuanced knowledge of the networks that link early developmental stress to lifetime substance dependence. With a focus on prevention and intervention measures, translational neuroscience especially looks for biological components that are both causative and moderating (Fisher and Berkman, 2015). Such research aims to shed light on the different effects of early life stress on the distinct processes that confer the risk of addiction while also investigating the interplay between these mechanisms. We wrap up by talking about the ramifications for addiction prevention and intervention programs.

In conclusion, early life stress plays a pivotal role in the development of substance use disorders, with implications that span across generations. The evidence indicates that stressors encountered during the pre- and perinatal periods can biologically embed risks through neuroendocrine and immune pathways, ultimately influencing the likelihood of substance abuse later in life. By understanding the mechanisms linking early adversity to addiction vulnerability, researchers can better inform prevention and treatment strategies aimed at mitigating these risks. A translational neuroscience perspective highlights the importance of identifying the biological factors involved in these processes, which may lead to targeted interventions that address both individual and intergenerational impacts of stress. Future research should continue to explore the interplay between various types of stress and their effects on the HPA axis and immune function, paving the way for comprehensive approaches to addiction prevention. Addressing these foundational issues will not only enhance our understanding of addiction but also contribute to the development of effective public health strategies aimed at reducing the burden of substance use disorders across populations.

Pathways to Substance Abuse:

Early Experiences, the HPA Axis, and High levels of maternal stress and associated physiological changes in the neuroendocrine and immune systems might impact the fetal environment due to the semi-permeable nature of the placenta (Barrett et al., 2017). Fetal programming is the term used to describe this occurrence (Glover et al., 2010; Kapoor et al., 2008). Fetal programming may have historically enabled advantageous adaptations, such as resource saving in difficult circumstances, even though it can have negative implications in modern contexts (Seckl and Holmes, 2007). It is believed that exposure to such programming may set children up for a variety of physical and mental health problems, including drug use disorders. Glucocorticoids (GCs), particularly cortisol in humans, are essential for HPA axis programming and play a pivotal role in the transition from fetal development to adult diseases (Davis and Sandman, 2010). Because of their wide-ranging effects on key regulatory systems, such as the immunological, gastrointestinal, autonomic nervous, and neurological systems, GCs have a particularly significant impact (McEwen, 2013). Research on animals indicates that GC pathways play a primary role in mediating the neuroendocrine and immunological responses to extreme

stress (Lupien et al., 2009), whereas human studies are still limited in scope.

In order to preserve homeostasis and control the mobilization of biological resources in response to acute stress, the neuroendocrine system is essential. It works by causing the pituitary to release more adrenocorticotropic hormone (ACTH), which in turn causes the adrenal cortex to produce cortisol. This is accomplished by the release of hypothalamic corticotrophin-releasing hormone (CRH). According to de Weerth et al. (2003), infants who are two months old show signs of a diurnal cortisol pattern, which is marked by lower cortisol levels at night and a progressive increase during the day. Between 12 and 24 months, a more noticeable adult-like pattern with a peak soon after awakening appears (Saridjan et al., 2010). These patterns may also be indicative of transient increases in cortisol brought on by acute stressors, which can include both physical (like injuries) and psychosocial (like scary or unpredictable circumstances) occurrences. Since newborns rely on primary caregivers for basic requirements like nutrition and security, separations from them during infancy indicate acute psychosocial stress (Gunnar and Donzella, 2002).

Although animal studies account for a large portion of the research on prenatal and perinatal stress, fetal HPA activity, and substance use, there is growing evidence from human studies as well. According to research on animals, fetal programming from prenatal and perinatal stress exposure influences adult behavior in three primary ways: learning impairments, elevated anxiety and depressive symptoms, and heightened susceptibility to substance abuse (Lupien et al., 2009). Studies conducted on a range of animal species, including rodents, guinea pigs, and primates, have shown that a single or repeated exposure to maternal stress raises the mother's GC levels. This, in turn, increases the fetal HPA activity through the placenta, as indicated by higher levels of corticosterone in the offspring (Henry et al., 1994; Kapoor and Matthews, 2005; Seckl, 2007).

Fetal Programming and the HPA Axis:

Given the effects of the growing fetal HPA axis, the intrauterine environment, and maternal HPA function, pregnancy is a particularly sensitive time for the development of the HPA axis (Davis and Sandman, 2010). According to the "fetal origins of adult disease" theory, a number of prevalent adult illnesses, including mental health issues like substance use disorders and physical afflictions like diabetes, have their roots in fetal development (Hellemans et al., 2010). A positive feedback loop happens during pregnancy when cortisol stimulates placental CRH production, leading to concurrent increases in CRH, ACTH, and cortisol levels throughout gestation. This is in contrast to the negative feedback mechanisms that are normally found in the brain and pituitary gland (King et al., 2001; Wadhwa, 2005). During a typical gestation, maternal cortisol levels can rise two to four times (Brown et al., 1996), but too much cortisol can be harmful to the developing fetus. The placental barrier is not completely impermeable, especially during periods of prolonged or extreme maternal stress, which can result in increased GC exposure for the fetus, even if a placental barrier enzyme reduces fetal exposure to maternal stress hormones (O'Donnell et al., 2012). The developing blood-brain barrier in the fetus makes it especially susceptible to this kind of GC exposure (Wadhwa, 2005). We suggest three possible mechanisms by which HPA axis function and prenatal and perinatal stress may raise the risk of substance abuse: postnatal stress exposure, prenatal exposure to drug usage by mothers, and prenatal exposure to stress and GCs in mothers.

Prenatal Stress Exposure, Substance Abuse Risk, and the HPA Axis:

Prenatal Exposure to Maternal Stress:

Studies on Animals: Studies on Animals have looked at a variety of prenatal and postnatal stressors, such as feeding restriction, administering synthetic glucocorticoids, using restraint methods, separating mothers from their babies, and medication exposure. A variety of substances, including amphetamines (Deminière et al., 1992; Diaz et al., 1995; Henry et al., 1995), MDMA (Morley-Fletcher et al., 2004), ethanol (Biggio et al., 2018; Rodrigues et al., 2012), opioids (Deroche et al., 1992, 1995; Rodrigues et al., 2012), and cocaine (Kippin et al., 2008; Pastor et al., 2018). Nevertheless, the precise mechanism by which neuroendocrine activity causes these effects has not been well studied. Remarkably, Deroche et al. (1992) showed that adrenalectomy, which lowers corticosterone levels, prevented amphetamine sensitivity in children whose mothers had experienced stress. Further research is required to elucidate the neuroendocrine systems involved.

Clinical Studies: There is a dearth of human studies on the relationship between prenatal stress, HPA axis function, and substance dependence later in life. Depression and anxiety in expectant mothers are the two main forms of stress that have been researched. Offspring exposed to prenatal stress have been shown to have altered GR gene expression and HPA functioning (Sosnowski et al., 2018). For example, regardless of postnatal mother mood, higher methylation of the GR gene (NR3C1) and heightened cortisol responses in three-month-old new-

borns were connected with maternal anxiety and depression in the third trimester (Oberlander et al., 2008). Furthermore, increased basal cortisol levels in babies were predicted by weaker social support and higher levels of maternal depressive symptoms (Luecken et al., 2015). According to Stonawski et al. (2018), school-aged children who were exposed to maternal depression symptoms during pregnancy showed altered NR3C1 gene methylation and varied cortisol responses, suggesting that prenatal stress may also have long-lasting effects on neuroendocrine functioning. Moreover, elevated cortisol reactivity in babies between the ages of 11 and 13 months was associated with prenatal exposure to intimate partner abuse (Levendosky et al., 2016). Future studies should look at the combined impact of several prenatal and perinatal stresses on offspring sensitivity to substance abuse, since numerous stressors co-occur.

Summary: Research on animals strongly suggests that exposure to stress during pregnancy increases the risk of substance addiction in the offspring. More research is necessary to gain a fuller understanding of these connections, even though preliminary evidence points to neuroendocrine systems as potential mediators of this relationship. Significant correlations have been shown between prenatal stress and altered cortisol levels and GR gene methylation in offspring, even though there is currently little evidence linking prenatal stress exposure to future substance abuse risk via HPA-axis activity in human studies.

Glucocorticoid Exposure During Pregnancy:

Prenatal corticosteroids, which are frequently given to expectant mothers who are at risk of preterm delivery, may have short-term effects on HPA-axis function by, for example, suppressing cortisol responses to stress. This finding sheds light on the impact of stress hormones on fetal development and the likelihood of substance abuse in the future (De Blasio et al., 2007; Waffarn and Davis, 2012). Van Lieshout et al. (2015) discovered in a prospective research that low birth weight survivors who were exposed to antenatal corticosteroids had the highest risk for mental and drug use disorders, with the risk increasing in direct proportion to the amount of steroid exposure.

Exposure of Prenatal Substances:

One of the most severe types of prenatal stress is drug exposure during pregnancy. According to estimates, between 2.8% and 4.3% of pregnant women in the US use illegal drugs (Lester et al., 2004; Office of Applied Studies, 2005), compared to over 12% who use tobacco (Ebrahim and Gfroerer, 2003). According to Birnbach et al. (2001), these numbers are noticeably higher among women who are poor and those who receive subpar prenatal care. Remarkably, during and after pregnancy, polysubstance use is more common than single-drug use (Birnbach et al., 2001; Ebrahim and Gfroerer, 2003). Fewer research have looked at the combined effects of several prenatal drug exposures, despite the fact that numerous animal studies have established the effects of individual drugs on fetal development. Studies on humans frequently account for the use of other drugs or concentrate on users of a single substance, which may restrict the generalizability of the findings. Though research on the impact of prenatal polysubstance use on offspring outcomes is increasing (e.g., Nygaard et al., 2016), there is still a dearth of information regarding its potential as a predictor of subsequent drug use issues. Furthermore, different chemicals affect neurobiological systems in different ways. According to Ross et al. (2015), there is a notable similarity between the neural systems impacted by substance exposure during pregnancy, such as the dopaminergic and serotonergic pathways, and dopamine is elevated in the brain by all substances. However, comprehending the developmental consequences of polydrug use requires a comprehension of the unique mechanisms of action for each substance (Lester et al., 2004). Because prenatal exposure has varying impacts on fetal development at different stages, timing is also important. Other articles (Forray, 2016; Glantz and Chambers, 2006; Lester et al., 2004) provide comprehensive evaluations that address the varying effects of substance types and time.

Animal Research: Several research on animals have shown that drug exposure during pregnancy is linked to a higher chance of substance abuse in the future. Reviews of animal models show that drug exposure during pregnancy increases the sensitivity and liking for drugs in the offspring, similar to other stress paradigms (Malanga and Kosofsky, 2003). For instance, higher active lever response during drug administration was indicative of increased reinforcing effects of cocaine in rats exposed to the drug during pregnancy (Hecht et al., 1998; Keller et al., 1996; Kippin et al., 2008). Moreover, adult rats' increased self-administration of cocaine and heroin was linked to prenatal morphine exposure (Ramsey et al., 1993).

Clinical Studies: New research suggests that substance exposure during pregnancy may be a predictor of substance use in the offspring (Glantz and Chambers, 2006; Lester and Lagasse, 2010). Remarkable correlations have been shown between

prenatal exposure to alcohol and nicotine and childhood-onset substance use (Lester et al., 2004). The literature on exposure to alcohol, cocaine, nicotine, and cannabis during pregnancy is reviewed in this section. Exposure to both nicotine and cannabis during pregnancy has been associated with an increased risk of developing a nicotine dependence as well as a higher chance of teenage smoking (Kandel et al., 1994; Kandel and Udry, 1999). (De Genna et al., 2017). Moreover, almost 7,000 young people' alcohol and cannabis use disorders were predicted by prenatal nicotine use (Salom et al., 2016). In a large longitudinal research, maternal smoking during pregnancy has also been linked to an increased risk of hospitalization for drug dependence in kids (Brennan et al., 2002). Furthermore, there is a correlation between the use of tobacco and cannabis during pregnancy and the earlier initiation of cannabis and cigarette use in the offspring (Cornelius et al., 2000; Porath and Fried, 2005).

Alcohol Exposure: Even after controlling for prenatal nicotine exposure, familial alcohol problems, and other postnatal variables, longitudinal studies have demonstrated a connection between prenatal alcohol exposure and alcohol-related problems in 21-year-old kids (Baer et al., 2003). According to a different study, prenatal alcohol consumption predicted a higher likelihood of alcohol-related issues and psychiatric illnesses in 25-year-old kids (Streissguth, 2007). Notably, research has shown that prenatal alcohol exposure predicts teenage drinking more accurately than family history of alcohol use (Baer et al., 1998). Cocaine Exposure: Corresponding to this, there is a higher chance of teenage psychoactive substance use when exposed to cocaine during pregnancy (Bennett et al., 2007; Delaney-Black et al., 2011; Frank et al., 2011; Lester et al., 2012; Min et al., 2014; Minnes et al., 2017; Yip et al., 2016). According to one study, teenagers who were exposed to cocaine during pregnancy had a 2.8-fold increased risk of substance use-related problems than their peers who were not exposed (Min et al., 2014).

Clinical Studies on HPA-axis and Prenatal Substance Exposure:

Basal Cortisol: Since prenatal drug exposure has been demonstrated to alter neuroendocrine functioning, changes in the hypothalamic-pituitary-adrenal (HPA) axis provide compelling evidence as a probable causative factor. Generally, depending on the particular substance involved, prenatal substance exposure is associated with higher basal cortisol levels in babies. For example, compared to control infants, newborns exposed to alcohol and smoke during gestation had greater basal cortisol levels (Ramsay et al., 1996). Compared to control children or those with lower prenatal exposure, children aged 6-14 diagnosed with fetal alcohol spectrum disorders and who had substantial prenatal alcohol exposure showed significantly higher levels of cortisol in the afternoon and at bedtime (Keiver et al., 2015). According to Jacobson et al. (1999), 13-month-old infants who consumed large amounts of alcohol during pregnancy had higher baseline cortisol levels; on the other hand, children who used cocaine had lower basal levels.

Chronic stress and the ensuing changes in the HPA axis have been proposed as a neurobiological mechanism that causes the formation and persistence of substance use disorders (SUDs) and addiction, despite the fact that many research did not look into substance use patterns among offspring (Sinha, 2008). This theory is supported by the finding that HPA-axis functioning predicts substance misuse susceptibility in populations exposed to drugs during pregnancy. Research indicates that the discrepancy between baseline cortisol levels at age 11 and the parasympathetic nervous system's ability to support physiological regulation at age 3 may indicate an earlier initiation of alcohol consumption in adolescents exposed to drugs during pregnancy. In females, higher executive dysfunction was linked to discordance between respiratory sinus arrhythmia (RSA) and cortisol (i.e., high RSA with low cortisol or low RSA with high cortisol), which in turn predicted earlier onset of alcohol consumption. On the other hand, only the combination of high cortisol and low RSA in boys showed a similar trend, which resulted in early onset of alcohol consumption and higher executive dysfunction (Conradt et al., 2014). These results highlight the need to investigate how different physiological systems (such the autonomic nervous system and HPA axis) interact with associated behavioral domains (like executive function) in order to accurately predict substance abuse in groups that are at risk.

Cortisol Reactivity: Cortisol reactivity has also been studied in relation to prenatal substance exposure; the results are influenced by various aspects, including the type of substance exposure, age of assessment, and stressor paradigm. In contrast to their counterparts who had not been exposed to prenatal drugs, children in foster care who had been maltreated between the ages of 9 and 12 showed lower levels of HPA reactivity in response to a social stressor in a laboratory setting (Fisher et al., 2012). Adolescents exposed to drugs during pregnancy also showed reduced cortisol responsiveness to task-related stress in comparison to a control group. Crucially, cortisol responsiveness acted as a media-

tor between drug experimentation and prenatal drug exposure; adolescents who exhibited a blunted cortisol response were more likely to experiment with drugs (Buckingham-Howes et al., 2016).

On the other hand, significant alcohol exposure during pregnancy has been associated with elevated cortisol levels in 13-month-old infants after stress (i.e., after a blood draw) (Jacobson et al., 1999). Furthermore, after a "still face" method that evaluates stress control, babies aged 5–7 months who had prenatal alcohol exposure showed increased cortisol reactivity (Haley et al., 2006). Both in 7-month-old infants following an arm-restraint paradigm (Schuetze et al., 2008) and in 1-month-old infants following a neurobehavioral assessment (Stroud et al., 2014), cigarette smoking during pregnancy was connected with increased peak cortisol reactivity. This relationship may be influenced by child sex; a study by Eiden et al. (2015) found a link between prenatal tobacco exposure and decreased cortisol reactivity, but only in male newborns. To fully understand the complex link between prenatal alcohol and tobacco exposure and infant cortisol reactivity, more study is necessary.

Research on cocaine use during pregnancy has yielded mixed results. According to one study, babies exposed to cocaine during pregnancy showed reduced cortisol levels during two stressor scenarios: a "invasive" heel-stick procedure and a "non-invasive" neurobehavioral evaluation (Magnano et al., 1992). On the other hand, opposing data has surfaced, demonstrating that children exposed to cocaine during pregnancy showed increased cortisol reactivity in response to an emotional arousal stress paradigm (Eiden et al., 2009). When children were 11 years old and had been exposed to cocaine during pregnancy, their chances of displaying an increased cortisol reaction to stressors were lower. Moreover, the HPA axis response was most markedly reduced in those who had experienced domestic violence, indicating that neuroendocrine functioning may be profoundly impacted by early trauma in conjunction with prenatal substance exposure (Lester et al., 2010). According to Chaplin et al. (2015), a longitudinal study including low-income adolescents between the ages of 14 and 17 revealed that youth who had been exposed to cocaine during pregnancy showed a lower cortisol response to a social stressor than the control group. Interestingly, at a 6–12 month follow-up, additional biobehavioral markers, such as sorrow in girls and lower sympathetic nervous system reactivity in males, were indicative of substance use, despite cortisol reactivity not being predictive of later substance use (Chaplin et al., 2015).

The contradictory findings reported in the literature could be attributed to factors including the age of the children, the particular stress paradigm applied, and differences in drug exposure. Remarkably, a study conducted on children exposed to drugs during pregnancy discovered a correlation between drug experimentation and reduced HPA-axis response to stressors (Buckingham-Howes et al., 2016). According to some theories, long-term stress first triggers hyperactivity in the HPA axis, which may then lead to the neuroendocrine system being downregulated (Miller et al., 2007). This suppression in response to long-term stress may protect against overexposure to cortisol, but it may also have wide-ranging effects on metabolism and regulation, including significant correlations with substance abuse and psychopathology (Koob and Le Moal, 2001; Miller et al., 2007). Moreover, during the first five years of life, the HPA axis experiences substantial prenatal and postnatal developmental alterations (Glover, O'Connor, & O'Connell, 2010). Thus, different stressor exposure and neuroendocrine adaption times may account for the observed inconsistent results (Roos et al., in press). Overall, research has begun to provide light on how neuroendocrine functioning after prenatal and perinatal stress may increase susceptibility to substance misuse; however, further studies are need to fully understand these pathways.

All things considered, a substantial body of research from both animal and human studies has established a strong correlation between prenatal drug exposure—a major stressor—and changes in the HPA-axis' functionality, as well as ensuing problems with substance dependence. Prenatal drug exposure in animal models is always associated with offspring that are more sensitive to and prefer drugs. Many studies conducted on humans have shown that exposure to drugs and alcohol during pregnancy predicts future drug and alcohol usage in kids. The relationship between prenatal drug exposure and higher basal cortisol levels has been further supported by clinical research. Although the exact path from prenatal drug exposure to substance abuse through elevated basal cortisol levels has not been thoroughly studied, Conradt et al. (2014) showed that among adolescents who were drug exposed during pregnancy, an early onset of alcohol use was predicted by a discrepancy between baseline cortisol levels and parasympathetic nervous system functioning. Numerous investigations have also looked into the potential predictive value of prenatal drug exposure on the cortisol responsiveness of offspring. The results have been conflicting, suggesting that cortisol sensitivity to stressors may be both increased and dulled. In order to fully

comprehend the connections between fetal drug exposure and the risk of substance dependence, more study is required, with a focus on the HPA axis.

Crucially, by simultaneously activating several stress response systems, persistent stress may further increase susceptibility to drug misuse. It has been suggested that by changing the reward circuitry, co-activation of the dopaminergic and HPA axis enhances the rewarding qualities of drugs (Piazza and Le Moal, 1998). An interplay between HPA-axis and dopaminergic functioning is suggested by established associations between neuroendocrine markers (e.g., cortisol) and dopamine release within mesolimbic pathways (Sinha, 2008). It will be necessary to do longitudinal research in the future to examine how neuroendocrine changes and associated stress systems influence the pathways that lead to substance abuse and addiction. The complex, and possibly sex-specific, relationships between prenatal and perinatal experiences in terms of stress systems, neural mechanisms, and behavioral outcomes highlight the need for additional longitudinal studies using a variety of measurement approaches to improve our understanding of the developmental paths of children who are more likely to become addicted in the future (Roos et al., in press).

Postnatal Stress Exposure, HPA Axis, and Substance Abuse Vulnerability:

Animal Studies: Maternal separation paradigms are frequently employed to investigate postnatal stress and its effects on offspring development, particularly concerning neglect during the postpartum period. Given that newborns depend entirely on maternal care for survival, prolonged maternal absence results in behavioral and biological indicators of distress across rodent, primate, and human studies (Lupien et al., 2009). Research in rodents reveals that maternal separation correlates with an increased propensity for ethanol consumption and preference in adult rats, particularly among males (Nylander and Roman, 2013).

A rodent study examining postnatal maternal separation found that affected offspring exhibited heightened vulnerability to ethanol consumption during adolescence, alongside enhanced expression of genes linked to HPA axis functionality (de Almeida Magalhães et al., 2017). Another study indicated that maternally separated offspring displayed a pronounced preference for ethanol and elevated levels of adrenocorticotropic hormone (ACTH) and corticosterone in response to a laboratory stressor, with ethanol consumption correlating to the stress response (Huot et al., 2001). Notably, studies combining prenatal stress and drug exposure have demonstrated their dual impact on development; for instance, one rodent study found that gestational ethanol exposure paired with maternal separation predicted increased anxiety, whereas maternal separation alone heightened ethanol preference (Biggio et al., 2018). Rodents subjected only to prenatal ethanol exposure did not exhibit this increased preference (Biggio et al., 2018). Overall, maternal separation is recognized as a significant risk factor for substance use in animal models, offering theoretical insights into the effects of postnatal stress on the development of alcohol and drug preferences in offspring (as reviewed in Moffett et al., 2007).

Clinical Studies: Human studies have begun to expand on the findings from animal research. Evidence indicates that mothers facing prenatal stress are at an elevated risk for substance abuse during and after pregnancy (Barnet et al., 1995; Kingston et al., 2016; Zambrana et al., 1997). Similar to prenatal stress, research has yielded mixed outcomes regarding the effects of postnatal stress on infant cortisol reactivity. For instance, one study found that infants of postnatally depressed mothers exhibited greater negative emotionality, less mature regulatory behaviors in response to fear, and heightened cortisol reactivity compared to controls (Feldman et al., 2009). Conversely, other studies have reported hyperactivity of infant cortisol in response to stressors, such as a finding linking maternal child abuse to lower baseline cortisol levels during stress (Brand et al., 2010). Further research is necessary to clarify the impact of postnatal stress on neuroendocrine functioning in infants and to investigate associations between postnatal stress, neuroendocrine regulation, and addiction susceptibility. Limited research has specifically explored the connections between postnatal substance use and offspring substance abuse risk. However, this area is crucial, given that many women successfully reduce alcohol and drug use during pregnancy but often relapse postpartum (Forray and Foster, 2015). Postnatal substance use represents a significant form of early life stress, as children of mothers with substance use issues frequently encounter additional stressors, such as poor nutrition. Moreover, mothers may face an increased risk of disrupted caregiving and dysfunctional attachment (as reviewed in Forray and Foster, 2015). One study demonstrated that both prenatal and postnatal cocaine use were uniquely associated with adolescent cocaine use (Delaney-Black et al., 2011).

Summary: Predominantly, animal studies have utilized maternal separation paradigms to examine postnatal stress and its effects on neuroendocrine functioning and offspring susceptibility to sub-

stance misuse. These studies indicate that offspring exhibit stronger preferences and higher rates of ethanol consumption, with preliminary links to altered HPA-axis functioning, including increased ACTH and corticosterone levels associated with ethanol use in maternally separated offspring. Furthermore, animal research has started to explore the interactive effects of prenatal substance exposure and postnatal stress (e.g., Biggio et al., 2018). Given that most children experience multiple stressors, such investigations are critical, warranting further study on the compounded effects of prenatal and postnatal stress and substance exposure. In humans, postnatal stress, including maternal depression, has been associated with both hypo- and hyper-cortisol reactivity. More research is needed to determine whether these alterations in infant neuroendocrine functioning predict future substance abuse.

Early Experiences, the Immune System, and Substance Abuse:

Historically, pregnancy has been viewed as a continuously immune-suppressed state (Mor et al., 2017; Wadhwa et al., 2001). However, emerging evidence suggests that the immune response during pregnancy is multifaceted and dynamic, characterized by periods of suppression and elevation, highlighting a critical interaction between fetal cells and maternal immune responses (Jennewein et al., 2017). During embryo implantation, trophoblast cells invade the uterine lining, initiating the formation of the placenta and triggering an inflammatory cascade (Mor et al., 2017). This inflammatory response is essential for successful implantation, with a pro-inflammatory state predominating in the first trimester (Mor et al., 2017). The subsequent 15 weeks, characterized by rapid fetal growth, can lead to complications such as miscarriage and preterm birth if hyper-inflammation occurs, during which the mother, placenta, and fetus experience immunosuppression (Mor et al., 2017; Romero et al., 2007). Toward the end of pregnancy, the immune response shifts to a pro-inflammatory state during labor and delivery (Mor et al., 2017). Notably, maternal antibodies are transferred to the fetus through the placenta in the first and second trimesters and through breast milk postpartum, contributing to the infant's passive immunity and modulating immune responses (Jennewein et al., 2017).

HPA Axis and the Immune System:

The interplay between the HPA axis and the immune system is significant during pregnancy. Glucocorticoids influence various immune cell functions, including activation, differentiation, growth, and apoptosis (Dhabhar and McEwen, 2001; Oppong and Cato, 2015). An emerging research focus is how prenatal stress may disrupt the placental transfer of maternal antibodies, potentially heightening the risk for dysregulated immune functioning in offspring, with glucocorticoids (GCs) possibly mediating this disruption. Elevated maternal GCs can modify placental function, a key site of immune interaction between mother and fetus (Merlot et al., 2008). In primate studies, chronic social stress has been shown to significantly impact antibody levels in both mothers and neonates, resulting in male offspring with lower immunoglobulin G (IgG) levels and female offspring with elevated IgG levels (Coe and Crispen, 2000). While GCs are posited as mediators in the relationship between prenatal stress and immune functioning, research findings on this topic remain mixed (Merlot et al., 2008). It is likely that GCs, alongside other mediators, play a role in the effects of prenatal stress on immune regulation (Merlot et al., 2008).

Conclusion:

Early life stress, particularly during prenatal and perinatal phases, significantly influences the development of substance use disorders (SUDs) through biological mechanisms involving the neuroendocrine and immune systems. Stressors encountered during these critical periods can alter the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and lead to neurobiological changes that predispose individuals to future substance misuse. The research highlights the importance of understanding how maternal stress, including psychosocial factors and drug exposure, can create intergenerational patterns of vulnerability to addiction. Notably, maternal glucocorticoid levels during pregnancy play a crucial role in fetal programming, affecting gene expression and stress reactivity in offspring, thus linking prenatal adversity with increased likelihood of SUDs. Animal studies corroborate these findings, demonstrating that stress exposure alters sensitivity and preference for addictive substances in later life. The implications for prevention and intervention are profound. By elucidating the pathways through which early stress impacts addiction risk, targeted strategies can be developed to mitigate these effects, particularly in at-risk populations. This translational neuroscience approach not only informs clinical practices but also highlights the need for comprehensive public health initiatives aimed at reducing the incidence of SUDs through early interventions. Further research is warranted to explore the complex interactions among various stressors and their long-term impacts on addiction susceptibility, thereby enhancing our understanding and treatment of substance use disorders.

References

1- AHNERT, L., GUNNAR, M.R., LAMB, M.E. and BARTHEL, M.: Transition to child care: associations with infant–mother attachment, infant negative emotion, and cortisol elevations. Child Dev. 75 (3), 639–650, 2004.

2- BAER, J.S., BARR, H.M., BOOKSTEIN, F.L., SAMPSON, P.D. and STREISSGUTH, A.P.: Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems. J. Stud. Alcohol 59 (5), 533–543, 1998.

3- BAER, J.S., SAMPSON, P.D., BARR, H.M., CONNOR, P.D. and STREISSGUTH, A.P.: A 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. Arch. Gen. Psychiatr. 60 (4), 377–385, 2003.

4- BARNET, B., DUGGAN, A.K., WILSON, M.D. and JOFFE, A.: Association between postpartum substance use and depressive symptoms, stress, and social support in adolescent mothers. Pediatrics 96 (4), 659–666, 1995.

5- BARRETT, E.S., SEFAIR, A.V. and O'CONNOR, T.G.: Prenatal maternal stress in context: maternal stress physiology, immunology, neuroendocrinology, nutrition and infant development. In: Rajendram, R., Preedy, V., Patel, V. (Eds.), Diet, Nutrition, and Fetal Programming. Humana Press, Cham, pp. 3–13, 2017.

6- BENNETT, D., BENDERSKY, M. and LEWIS, M.: Preadolescent health risk behavior as a function of prenatal cocaine exposure and gender. J. Dev. Behav. Pediatr. 28 (6), 467–472, 2007.

7- BIGGIO, F., TALANI, G., LOCCI, V., PISU, M., BOERO, G., CIARLO, B., GRAYSON, D.R. and SERRA, M.: Low doses of prenatal ethanol exposure and maternal separation alter HPA axis function and ethanol consumption in adult male rats. Neuropharmacology 131, 271–281, 2018.

8- BIRNBACH, D.J., BROWNE, I.M., KIM, A., STEIN, D.J. and THYS, D.M.: Identification of polysubstance abuse in the parturient. Br. J. Anaesth. 87 (3), 488–490, 2001.

9- Borçoi, A.R., Patti, C.L., Zanin, K.A., Hollais, A.W., Santos-Baldaia, R., Ceccon, L.M., Berro, L.F., Wuo-Silva, R., Grapiglia, S.B., Ribeiro, L.T. and Lopes-Silva, L.B.: Effects of prenatal immune activation on amphetamine-induced addictive behaviors: contributions from animal models. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 63, 63–69, 2015.

10- BRAND, S.R., BRENNAN, P.A., NEWPORT, D.J., SMITH, A.K., WEISS, T. and STOWE, Z.N.: The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology 35 (5), 686–693, 2010.

11- BRENNAN, P.A., GREKIN, E.R., MORTENSEN, E.L. and MEDNICK, S.A.: Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. Am. J. Psychiatr. 59 (1), 48–54, 2002.

12- BROWN, R., DIAZ, R., ROBSON, A., KOTELEVTSEV, Y., MULLINS, J., KAUFMAN, M. and SECKL, J.: The ontogeny of 11 beta-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology 137 (2), 794–797, 1996.

13- BUCKINGHAM-HOWES, S., MAZZA, D., WANG, Y., GRANGER, D.A. and BLACK, M.M.: Prenatal drug exposure and adolescent cortisol reactivity: association with behavioral concerns. J. Dev. Behav. Pediatr.: JDBP 37 (7), 565–572, 2016.

14- BYRNE, M.L., BADCOCK, P.B., SIMMONS, J.G., WHITTLE, S., PETTITT, A., OLSSON, C.A., MUNDY, L.K., PATTON, G.C. and ALLEN, N.B.: Self-reported parenting style is associated with children's inflammation and immune activation. J. Fam. Psychol. 31 (3), 374–380, 2017a.

15- BYRNE, M.L., HORNE, S., O'BRIEN-SIMPSON, N.M., WALSH, K.A., REYNOLDS, E.C., SCHWARTZ, O.S., WHITTLE, S., SIMMONS, J.G., SHEEBER, L. and ALLEN, N.B.: Associations between observed parenting behavior and adolescent inflammation two and a half years later ina community sample. Health Psychol. 36 (7), 641–651, 2017b.

16- CASH, S.J. and WILKE, D.J.: An ecological model of maternal substance abuse and child neglect: issues, analyses, and recommendations. Am. J. Orthopsychiatry 73 (4), 392–404, 2003.

17- CHAHAL, N., MCLAIN, A.C., GHASSABIAN, A., MICHELS, K.A., BELL, E.M., LAWRENCE, D.A. and YEUNG, E.H.: Maternal smoking and newborn cytokine and immunoglobin levels. Nicotine Tob. Res. 19 (7), 789–796, 2017.

18- CHAPLIN, T.M., VISCONTI, K.J., MOLFESE, P.J., SUSMAN, E.J., KLEIN, L.C., SINHA, R. and MAYES, L.C.: Prenatal cocaine exposure differentially affects stress responses in girls and boys: associations with future substance use. Dev. Psychopathol. 27 (1), 163–180, 2015.

19- COE, C.L. and CRISPEN, H.R.: Social stress in pregnant squirrel monkeys (Saimiri boliviensis peruviensis) differentially affects placental transfer of maternal antibody to male and female infants. Health Psychol. 19 (6), 554–559, 2000.

20- CONRADT, E., LAGASSE, L.L., SHANKARAN, S., BADA, H., BAUER, C.R., WHITAKER, T.M., HAMMOND, J.A. and LESTER, B.M.: Physiological correlates of neurobehavioral disinhibition that relate to drug use and risky sexual behavior in adolescents with prenatal substance exposure. Dev. Neurosci. 36 (3–4), 306–315, 2014.

21- CORNELIUS, M.D., LEECH, S.L., GOLDSCHMIDT, L. and DAY, N.L.: Prenatal tobacco exposure: is it a risk factor for early tobacco experimentation? Nicotine Tob. Res. 2 (1), 45–52, 2000.

22- DAVIS, E.P. and SANDMAN, C.A.: The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. Child Dev. 81 (1), 131–148, 2010.

23- DE ALMEIDA MAGALHÃES, T., CORREIA, D., DE CARVALHO, L.M., DAMASCENO, S. and BRUNIALTI GODARD, A.L.: Maternal separation affects expression of stress response genes and increases vulnerability to ethanol consumption. Brain Behav. 8, e00841, 2017.

24- DE BLASIO, M.J., DODIC, M., JEFFERIES, A.J., MORITZ, K.M., WINTOUR, E.M. and OWENS, J.A.: Maternal exposure to dexamethasone or cortisol in early pregnancy differentially alters insulin secretion and glucose homeostasis in adult male sheep offspring. Am. J. Physiol. Endocrinol. Metabol. 293 (1), E75–E82, 2007.

25- DE GEENA, N.M., GOLDSCHMIDT, L., DAY, N.L. and CORNELIUS, M.D.: Prenatal tobacco exposure, maternal postnatal nicotine dependence and adolescent risk for nicotine dependence: birth Cohort Study. Neurotoxicol. Teratol. 61, 128–132, 2017.

26- DE WEERTH, C., ZIJL, R.H. and BUITELAAR, J.K.: Development of cortisol circadian rhythm in infancy. Early Hum. Dev. 73 (1–2), 39–52, 2003.

27- DELANEY-BLACK, V., CHIODO, L.M., HANNIGAN, J.H., GREENWALD, M.K., JANISSE, J., PATTERSON, G., HUESTIS, M.A., PARTRIDGE, R.T., AGER, J. and SOKOL, R.J.: Prenatal and postnatal cocaine exposure predict teen cocaine use. Neurotoxicol. Teratol. 33 (1), 110–119, 2011.

28- DEMINIÈRE, J.M., PIAZZA, P.V., GUEGAN, G., ABROUS, N., MACCARI, S., LE MOAL, M. and SIMON, H.: Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. Brain Res. 586 (1), 135–139, 1992.

29- DEROCHE, V., PIAZZA, P.V., CASOLINI, P., MACCARI, S., LE MOAL, M. and SIMON, H.: Stressinduced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. Brain Res. 598 (1–2), 343–348, 1992.

30- DEROCHE, V., MARINELLI, M., MACCARI, S., LE MOAL, M., SIMON, H. and PIAZZA, P.V.: Stressinduced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. J. Neurosci. 15 (11), 7181–7188, 1995.

31- DHABHAR, F. and MCEWEN, B.: Bidirectional effects of stress and glucocorticoid hormones on immune function: possible explanations for paradoxical observations. Psychoneuroimmunology 1, 301–338, 2001.

32- DIAZ, R., ÖGREN, S., BLUM, M. and FUXE, K.: Prenatal corticosterone increases spontaneous and d-amphetamine induced locomotor activity and brain dopamine metabolism in prepubertal male and female rats. Neuroscience 66 (2), 467–473, 1995.

33- EBRAHIM, S.H., GFROERER, J.: Pregnancy-related substance use in the United States during 1996-1998. Obstet. Gynecol. 101 (2), 374–379, 2003.

34- EIDEN, R.D., VEIRA, Y. and GRANGER, D.A.: Prenatal cocaine exposure and infant cortisol reactivity. Child Dev. 80 (2), 528–543, 2009.

35- EIDEN, R.D., MOLNAR, D.S., GRANGER, D.A., COLDER, C.R., SCHUETZE, P. and HUESTIS, M.A.: Prenatal tobacco exposure and infant stress reactivity: role of child sex and maternal behavior. Dev. Psychobiol. 57 (2), 212–225, 2015.

36- EIDEN, R.D., LESSARD, J., COLDER, C.R., LIVINGSTON, J., CASEY, M. and LEONARD, K.E.: Developmental cascade model for adolescent substance use from infancy to late adolescence. Dev. Psychol. 52 (10), 1619–1633, 2016.

37- ELKINGTON, K.S., BAUERMEISTER, J.A., BRACKISCOTT, E., DOLEZAL, C. and MELLINS, C.A.: Substance use and sexual risk behaviors in perinatally human immunodeficiency virus-exposed youth: roles of caregivers, peers and HIV status. J. Adolesc. Health 45 (2), 133–141, 2009.

38- ENOCH, M.-A.: The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology 214 (1), 17–31, 2011.

39- ENTRINGER, S., KUMSTA, R., NELSON, E.L., HELLHAMMER, D.H., WADHWA, P.D. and WÜST, S.: Influence of prenatal psychosocial stress on cytokine production in adult women. Dev. Psychobiol. 50 (6), 579–587, 2008.

40- ERATH, S.A., EL-SHEIKH, M. and CUMMINGS, E.M.: Harsh parenting and child externalizing behavior: skin conductance level reactivity as a moderator. Child Dev. 80 (2), 578–592, 2009.

41- ERATH, S.A., EL-SHEIKH, M., HINNANT, J.B. and CUMMINGS, E.M.: Skin conductance level reactivity moderates the association between harsh parenting and growth in child externalizing behavior. Dev. Psychol. 47 (3), 693–706, 2011.

42- FELDMAN, R., GRANAT, A., PARIENTE, C., KANETY, H., KUINT, J. and GILBOA-SCHECHTMAN, E.: Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. J. Am. Acad. Child Adolesc. Psychiatry 48 (9), 919–927, 2009.

43- FISHER, P.A. and BERKMAN, E.T.: Designing interventions informed by scientific knowledge about effects of early adversity: a translational neuroscience agenda for next-generation addictions research. Current Addiction Reports 2 (4), 347–353, 2015.

44- FISHER, P.A., KIM, H.K., BRUCE, J., PEARS, K.C.: Cumulative effects of prenatal substance exposure and early adversity on foster children's HPA-axis reactivity during a psychosocial stressor. IJBD (Int. J. Behav. Dev.) 36 (1), 29–35, 2012.

45- FLANIGAN, C., SHEIKH, A., DUNNGALVIN, A., BREW, B.K., ALMQVIST, C. and NWARU, B.I.: Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. Clin. Exp. Allergy 48 (4), 403–414, 2018.

46- FLEISCHER, L.M., TAMASHUNAS, N. and MILLER, G.M.: Immune dysregulation in drug addiction? Drug Alcohol Depend. 171, e63, 2017.

47- FORRAY, A.: Substance use during pregnancy. F1000 Res. 5, 887. Forray, A., Foster, D., 2015. Substance use in the perinatal period. Curr. Psychiatr. Rep. 17 (11), 91, 2016.

48- FraNK, D.A., ROSE-JACOBS, R., CROOKS, D., CABRAL, H.J., GERTEIS, J., HACKER, K.A., MARTIN, B., WEINSTEIN, Z.B. and HEEREN, T.: Adolescent initiation of licit and illicit substance use: impact of intrauterine

exposures and post-natal exposure to violence. Neurotoxicol. Teratol. 33 (1), 100–109, 2011.

49- GLANTZ, M.D. and CHAMBERS, J.C.: Prenatal drug exposure effects on subsequent vulnerability to drug abuse. Dev. Psychopathol. 18, 893–922, 2006.

50- GLOVER, V., O'CONNOR, T. and O'DONNELL, K.: Prenatal stress and the programming of the HPA axis. Neurosci. Biobehav. Rev. 35 (1), 17–22, 2010.

51- GRANT, J.E., BREWER, J.A. and POTENZA, M.N.: The neurobiology of substance and behavioral addictions. CNS Spectr. 11 (12), 924–930, 2006.

52- GUNNAR, M.R. and DONZELLA, B.: Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology 27 (1), 199–220. S.R. Horn et al. Neurobiology of Stress 9 (2018) 140–150 148, 2002.

53- GUSTAFSSON, H.C., SULLIVAN, E.L., NOUSEN, E.K., SULLIVAN, C.A., HUANG, E., RINCON, M., NIGG, J.T. and LOFTIS, J.M.: Maternal prenatal depression predicts infant negative affect via maternal inflammatory cytokine levels. Brain Behav. Immun. 73, 470–481, 2018.

54- GUTTELING, B.M., DE WEERTH, C., WILLEMSEN-SWINKELS, S.H., HUIZINK, A.C., MULDER, E.J., VISSER, G.H. and BUITELAAR, J.K.: The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. Eur. Child Adolesc. Psychiatr. 14 (1), 41–51, 2005.

55- HALEY, D.W., HANDMAKER, N.S. and LOWE, J.: Infant stress reactivity and prenatal alcohol exposure. Alcohol Clin. Exp. Res. 30 (12), 2055–2064, 2006.

56- HECHT, G.S., SPEAR, N.E. and SPEAR, L.P.: Alterations in the reinforcing efficacy of cocaine in adult rats following prenatal exposure to cocaine. Behav. Neurosci. 112 (2), 410–418, 1998.

57- HELLEMANS, K.G., SLIWOWSKA, J.H., VERMA, P. and WEINBERG, J.: Prenatal alcohol exposure: fetal programming and later life vulnerability to stress, depression and anxiety disorders. Neurosci. Biobehav. Rev. 34 (6), 791–807, 2010.

58- HENRY, C., KABBAJ, M., SIMON, H., MOAL, M. and MACCARI, S.: Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. J. Neuroendocrinol. 6 (3), 341–345, 1994.

59- HENRY, C., GUEGANT, G., CADOR, M., ARNAULD, E., ARSAUT, J., LE MOAL, M. and DEMOTES-MAINARD, J.: Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. Brain Res. 685 (1–2), 179–186, 1995.

60- HOWARD, L.M., ORAM, S., GALLEY, H., TREVILLION, K. and FEDER, G.: Domestic violence and perinatal mental disorders: a systematic review and meta-analysis. PLoS Med. 10 (5), e1001452, 2013.

61- HUOT, R.L., THRIVIKRAMAN, K., MEANEY, M.J. and PLOTSKY, P.M.: Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. Psychopharmacology 158 (4), 366–373, 2001.

62- JACOBSON, S.W., BIHUN, J.T. and CHIODO, L.M.: Effects of prenatal alcohol and cocaine exposure on infant cortisol levels. Dev. Psychopathol. 11 (2), 195–208, 1999.

63- JENNEWEIN, M.F., ABU-RAYA, B., JIANG, Y., ALTER, G. and MARCHANT, A.: Transfer of Maternal Immunity and Programming of the Newborn Immune System. Paper presented at the Seminars in Immunopathology, 2017.

64- KANDEL, D.B. and UDRY, J.R.: Prenatal effects of maternal smoking on daughters' smoking: nicotine or testosterone exposure? Am. J. Publ. Health 89, 1377–1383, 1999.

65- KANDEL, D.B., WU, P. and DAVIES, M.: Maternal smoking during pregnancy and smoking by adolescent daughters. Am. J. Publ. Health 84, 1407–1413, 1994.

66- KAPOOR, A. and MATTHEWS, S.G.: Short periods of prenatal stress affect growth, behaviour and hypothalamo–pituitary–adrenal axis activity in male Guinea pig offspring. J. Physiol. 566 (3), 967–977, 2005.

67- KAPOOR, A., PETROPOULOS, S. and MATTHEWS, S.G.: Fetal programming of hypothalamic–pituitary–adrenal (HPA) axis function and behavior by synthetic glucocorticoids. Brain Res. Rev. 57 (2), 586–595, 2008.

68- KEIVER, K., BERTRAM, C.P., ORR, A.P. and CLARREN, S.: Salivary cortisol levels are elevated in the afternoon and at bedtime in children with prenatal alcohol exposure. Alcohol 49 (1), 79–87, 2015.

69- KELLER JR., R.W., LEFEVRE, R., RAUCCI, J., CARLSON, J.N. and GLICK, S.D.: Enhanced cocaine self-administration in adult rats prenatally exposed to cocaine. Neurosci. Lett. 205 (3), 153–156, 1996.

70- KING, B., NICHOLSON, R. and SMITH, R.: Placental Cortieotrophin-releasing Hormone, local effects and feto-maternal endocrinology. Stress 4 (4), 219–233, 2001.

71- KINGSTON, D., HEAMAN, M., URQUIA, M., O'CAMPO, P., JANSSEN, P., THIESSEN, K. and SMYLIE, J.: Correlates of abuse around the time of pregnancy: results from a national survey of Canadian women. Matern. Child Health J. 20 (4), 778–789, 2016.

72- KIPPIN, T.E., SZUMLINSKI, K.K., KAPASOVA, Z., REZNER, B. and SEE, R.E.: Prenatal stress enhances responsiveness to cocaine. Neuropsychopharmacology 33 (4), 769, 2008.

73- KOOB, G.F. and LE MOAL, M.: Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24 (2), 97–129, 2001.

74- KREEK, M.J., NIELSEN, D.A., BUTELMAN, E.R. and LAFORGE, K.S.: Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat. Neurosci. 8 (11), 1450–1457, 2005.

75- LESTER, B.M. and LAGASSE, L.L.: Children of addicted women. J. Addict. Dis. 29 (2), 259–276, 2010.

76- LESTER, B.M., ANDREOZZI, L. and APPIAH, L.: Substance use during pregnancy: time for policy to catch up with research. Harm Reduct. J. 1 (1), 5, 2004.

77- LESTER, B.M., LIN, H., DEGARMO, D.S., FISHER, P.A., LAGASSE, L.L., LEVINE, T.P., SHANKARAN, S., BADA, H.S., BAUER, C.R., HAMMOND, J.A., WHITAKER, T.M. and HIGGINS, R.D.: Neurobehavioral dis-

inhibition predicts initiation of substance use in children with prenatal cocaine exposure. Drug Alcohol Depend. 126 (1), 80–86, 2012.

78- LEVENDOSKY, A.A., BOGAT, G.A., LONSTEIN, J.S., MARTINEZ-TORTEYA, C., MUZIK, M., GRANGER, D.A. and VON EYE, A.: Infant adrenocortical reactivity and behavioral functioning: relation to early exposure to maternal intimate partner violence. Stress 19 (1), 37–44, 2016.

79- LEWIS-DE LOS ANGELES, C.P., WILLIAMS, P.L., HUO, Y., WANG, S.D., UBAN, K.A., HERTING, M.M., MALEE, K., YOGEV, R., CSERNANSKY, J.G., NICHOLS, S., VAN DYKE, R.B., SOWELL, E.R. and WANG, L.: Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: associations with HIV disease severity, substance use, and cognition. Brain Behav. Immun. 62, 100–109, 2017.

80- LUECKEN, L.J., MACKINNON, D.P., JEWELL, S.L., CRNIC, K.A. and GONZALES, N.A.: Effects of prenatal factors and temperament on infant cortisol regulation in low-income Mexican American families. Dev. Psychobiol. 57 (8), 961–973, 2015.

81- LUPIEN, S.J., MCEWEN, B.S., GUNNAR, M.R. and HEIM, C.: Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10 (6), 434–445, 2009.

82- MAGNANO, C.L., GARDNER, J.M. and KARMEL, B.Z.: Differences in salivary cortisol levels in cocaine-exposed and noncocaine-exposed NICU infants. Dev. Psychobiol. 25 (2), 93–103, 1992.

83- MALANGA, C. and KOSOFSKY, B.E.: Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. Dev. Brain Res. 147 (1–2), 47–57, 2003.

84- MARDINI, V., ROHDE, L.A., CERESÉR, K.M.M., GUBERT, C. D. M., SILVA, E. G. D., XAVIER, F., PARCIANELLO, R., RÖHSIG, L.M., PECHANSKY, F., PIANCA, T.G. and SZOBOT, C.M.: IL-6 and IL-10 levels in the umbilical cord blood of newborns with a history of crack/cocaine exposure in utero: a comparative study. Trends Psychiatr. Psychother. 38 (1), 40–49, 2016.

85- MARKHAM, J.A. and KOENIG, J.I.: Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology 214 (1), 89–106 2011.

86- MARTIN, C.G., KIM, H.K., BRUCE, J. and FISHER, P.A.: Child diurnal cortisol rhythms, parenting quality, and externalizing behaviors in preadolescence. Psychoneuroendocrinology 40, 170–180, 2014.

87- MAYES, L.C. and SUCHMAN, N.E.: Developmental pathways to substance abuse. In: In: Cichetti, D., Cohen, D. (Eds.), Developmental Psychopathology: Risk, Disorder, and Adaptation, vol. 3. Wiley, New York, pp. 599–619, 2006.

88- MCEWEN, B.S.: The brain on stress: toward an integrative approach to brain, body, and behavior. Perspect. Psychol. Sci. 8 (6), 673–675, 2013.

89- MEASELLE, J.R., DAVID, J. and ABLOW, J.C.: Increased levels of inflammation among infants with disorganized histories of attachment. Behav. Brain Res. 325, 260–267, 2017.

90- MELLINS, C.A., ELKINGTON, K.S., BAUERMEISTER, J.A., BRACKIS-COTT, E., DOLEZAL, C., MCKAY, M., WIZNIA, A., BAMJI, M. and ABRAMS, E.J.: Sexual and drug use behavior in perinatally HIV− infected youth: mental health and family influences. J. Am. Acad. Child Adolesc. Psychiatry 48 (8), 810–819, 2009.

91- MELLINS, C.A., TASSIOPOULOS, K., MALEE, K., MOSCICKI, A.B., PATTON, D., SMITH, R., USITALO, A., ALLISON, S.M., VAN DYKE, R. and SEAGE, G.R.: Behavioral health risks in perinatally HIV-exposed youth: co-occurrence of sexual and drug use behavior, mental health problems, and nonadherence to antiretroviral treatment. AIDS Patient Care STDS 25 (7), 413–422, 2011.

92- MERLOT, E., COURET, D. and OTTEN, W.: Prenatal stress, fetal imprinting and immunity. Brain Behav. Immun. 22 (1), 42–51, 2008.

93- MEYER, U., ENGLER, A., WEBER, L., SCHEDLOWSKI, M. and FELDON, J.: Preliminary evidence for a modulation of fetal dopaminergic development by maternal immune activation during pregnancy. Neuroscience 154 (2), 701–709, 2008a.

94- MEYER, U., NYFFELER, M., YEE, B.K., KNUESEL, I. and FELDON, J.: Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. Brain Behav. Immun. 22 (4), 469–486, 2008b.

95- MILLER, G.E., CHEN, E. and ZHOU, E.S.: If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133 (1), 25–45, 2007.

96- MILLER, G.E., CHEN, E. and PARKER, K.J.: Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biologgical mechanisms. Psychol. Bull. 137 (6), 959–997, 2011.

97- MIN, M.O., MINNES, S., LANG, A., WEISHAMPEL, P., SHORT, E.J., YOON, S. and SINGER, L.T.: Externalizing behavior and substance use related problems at 15 years in prenatally cocaine exposed adolescents. J. Adolesc. 37 (3), 269–279, 2014.

98- MINNES, S., MIN, M.O., KIM, J.-Y., FRANCIS, M.W., LANG, A., WU, M. and SINGER, L.T.: The association of prenatal cocaine exposure, externalizing behavior and adolescent substance use. Drug Alcohol Depend. 176, 33–43, 2017.

99- MOFFETT, M., VICENTIC, A., KOZEL, M., PLOTSKY, P., FRANCIS, D. and KUHAR, M.: Maternal separation alters drug intake patterns in adulthood in rats. Biochem. Pharmacol. 73 (3), 321–330, 2007.

100- MOR, G., ALDO, P. and ALVERO, A.B.: The unique immunological and microbial aspects of pregnancy. Nat. Rev. Immunol. 17 (8), 469–482, 2017.

101- MACCHIA, T., LAVIOLA, G.: Prenatal stress affects 3, 4-methylenedioxymethamphetamine pharmacokinetics and drug-induced motor alterations in adolescent female rats. Eur. J. Pharmacol. 489 (1–2), 89–92, 2004.

102- MUTUMBA, M., ELKINGTON, K., BAUERMEISTER, J., BUCEK, A., DOLEZAL, C., LEU, C. and MELLINS, C.: Changes in substance use symptoms across adolescence in youth perinatally infected with HIV. AIDS Behav. 21 (4), 1117–1128, 2017.

103- NAGAHAWATTE, N.T. and GOLDENBERG, R.L.: Poverty, maternal health, and adverse pregnancy outcomes. Ann. N. Y. Acad. Sci. 1136 (1), 80–85, 2008.

104- NEUENSCHWANDER, R., HOOKENSON, K., BRAIN, U., GRUNAU, R.E., DEVLIN, A.M., WEINBERG, J., DIAMOND, A. and OBERLANDER, T.F.: Children's stress regulation mediates the association between prenatal maternal mood and child executive functions for boys, but not girls. Dev. Psychopathol. 30 (3), 953–969, 2018.

105- NYGAARD, E., SLINNING, K., MOE, V. and WALHOVD, K.B.: Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: a longitudinal study. PLoS One 11 (6), e0158054, 2016.

106- NYLANDER, I. and ROMAN, E.: Is the rodent maternal separation model a valid and effective model for studies on the early-life impact on ethanol consumption? Psychopharmacology 229 (4), 555–569, 2013.

107- O'CONNOR, T.G., WINTER, M.A., HUNN, J., CARNAHAN, J., PRESSMAN, E.K., GLOVER, V., ROBERTSON-BLACKMORE, E., MOYNIHAN, J.A., EUNHYUNG LEE, F. and CASERTA, M.T.: Prenatal maternal anxiety predicts reduced adaptive immunity in infants. Brain Behav. Immun. 32, 21–28, 2013.

108- O'DONNELL, K.J., JENSEN, A.B., FREEMAN, L., KHALIFE, N., O'CONNOR, T.G. and GLOVER, V.: Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology 37 (6), 818–826, 2012.

109- OBERLANDER, T.F., WEINBERG, J., PAPSDORF, M., GRUNAU, R., MISRI, S. and DEVLIN, A.M.: Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 3 (2), 97–106, 2008.

110- Office of Applied Studies, 2005. The NSDUH Report: Substance Use during Pregnancy: 2002 and 2003 Update. Substance Abuse and Mental Health Services Administration, S.R. Horn et al. Neurobiology of Stress 9 (2018) 140–150 149 Rockville, MD.

111- OPPONG, E. and CATO, A.C.: Effects of glucocorticoids in the immune system. Adv. Exp. Med. Biol. 872, 217–233, 2015.

112- OTA, M.O., VEKEMANS, J., SCHLEGEL-HAUETER, S.E., FIELDING, K., WHITTLE, H., LAMBERT, P.H., MCADAM, K.P.W.J., SIEGRIST, C.A. and MARCHANT, A.: Hepatitis B immunisation induces higher antibody and memory Th2 responses in new-borns than in adults. Vaccine 22, 511–519, 2004.

113- PASALA, S., BARR, T. and MESSAOUDI, I.: Impact of alcohol abuse on the adaptive immune system. Alcohol Res. Curr. Rev. 37 (2), 185–197, 2015.

114- PASTOR, V., PALLARÉS, M.E. and ANTONELLI, M.C.: Prenatal stress increases adult vulnerability to cocaine reward without affecting pubertal anxiety or novelty response. Behav. Brain Res. 339, 186–194, 2018.

115- PEDERSEN, J.M., MORTENSEN, E.L., CHRISTENSEN, D.S., ROZING, M., BRUNSGAARD, H., MEINCKE, R.H., PETERSEN, G.L. and LUND, R.: Prenatal and early postnatal stress and later life inflammation. Psychoneuroendocrinology 88, 158–166, 2018.

116- PIAZZA, P.V. and LE MOAL, M.: The role of stress in drug self-administration. Trends Pharmacol. Sci. 19 (2), 67–74. Porath, A.J., Fried, P.A., 2005. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicol. Teratol. 27 (2), 267–277, 1998.

117- PRABHUDAS, M., ADKINS, B., GANS, H., KING, C., LEVY, O., RAMILO, O. and SIEGRIST, C.A.: Challenges in infant immunity: implications for responses to infection and vaccines. Nat. Immunol. 12 (3), 189–194, 2011.

118- PROVENÇAL, N. and BINDER, E.B.: The effects of early life stress on the epigenome: from the womb to adulthood and even before. Exp. Neurol. 268, 10–20, 2015.

119- QUINLIVAN, J.A. and EVANS, S.: Impact of domestic violence and drug abuse in pregnancy on maternal attachment and infant temperament in teenage mothers in the setting of best clinical practice. Arch. Wom. Ment. Health 8 (3), 191–199, 2005.

120- RAMSAY, D.S., BENDERSKY, M.I. and LEWIS, M.: Effect of prenatal alcohol and cigarette exposure on two-and six-month-old infants' adrenocortical reactivity to stress. J. Pediatr. Psychol. 21 (6), 833–840, 1996.

121- RAMSEY, N.F., NIESINK, R.J. and VAN REE, J.M.: Prenatal exposure to morphine enhances cocaine and heroin self-administration in drug-naive rats. Drug Alcohol Depend. 33 (1), 41–51, 1993.

122- RODRIGUES, A.J., LEÃO, P., PÊGO, J.M., CARDONA, D., CARVALHO, M., OLIVEIRA, M., COSTA, B.M., CARVALHO, A.F., MORGADO, P., ARAÚJO, D., PALHA, J.A., ALMEDIA, O.F.X. and SOUSA, N.: Mechanisms of initiation and reversal of drug-seeking behavior induced by prenatal exposure to glucocorticoids. Mol. Psychiatr. 17 (12), 1295–1305, 2012.

123- RODRIGUEZ, E.M., MOFENSON, L.M., CHANG, B.-H., RICH, K.C., FOWLER, M.G., SMERIGLIO, V., LANDESMAN, S., FOX, H.E., DIAZ, C., GREEN, K. and HANSON, I.C.: Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. AIDS 10 (3), 273–282, 1996.

124- ROMERO, R., ESPINOZA, J., GONÇALVES, L.F., KUSANOVIC, J.P., FRIEL, L. and HASSAN, S.: The role of inflammation and infection in preterm birth. Semin. Reprod. Med. 25, 21–39, 2007.

125- ROOS, L.E., BEAUCHAMP, K.G., FLANNERY, J.E., HORN, S.R. and FISHER, P.A.: Interventions, stress during development, and psychosocial adjustment. In: International Handbook of Social Endocrinology, in press, 2018.

126- ROSS, E.J., GRAHAM, D.L., MONEY, K.M. and STANWOOD, G.D.: Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. Neuropsychopharmacology 40 (1), 61–87, 2015.

127- SALOM, C.L., BETTS, K.S., WILLIAMS, G.M., NAJMAN, J.M. and ALATI, R.: Predictors of comorbid polysubstance use and mental health disorders in young adults–a latent class analysis. Addiction 111 (1), 156–164, 2016.

128- SARIDJAN, N.S., HUIZINK, A.C., KOETSIER, J.A., JADDOE, V.W., MACKENBACH, J.P., HOFMAN, A., KIRSCHBAUM, C., VERHULST, F.C. and TIEMEIER, H.: Do social disadvantage and early family adversity affect the diurnal cortisol rhythm in infants? The Generation R Study. Horm. Behav. 57 (2), 247–254, 2010.

129- SCHINDLER, A., THOMASIUS, R., SACK, P.-M., GEMEINHARDT, B., KÜSTNER, U. and ECKERT, J.: Attachment and substance use disorders: a review of the literature and a study in drug dependent adolescents. Am. J. Bioeth. 7 (3), 207–228, 2005.

130- SCHUCKIT, M.A.: Comorbidity between substance use disorders and psychiatric conditions. Addiction 101 (s1), 76–88, 2006.

131- SCHUETZE, P., LOPEZ, F.A., GRANGER, D.A. and EIDEN, R.D.: The association between prenatal exposure to cigarettes and cortisol reactivity and regulation in 7 month old infants. Dev. Psychobiol. 50 (8), 819–834, 2008.

132- SECKL, J.R.: Glucocorticoids, developmental 'programming'and the risk of affective dysfunction. Prog. Brain Res. 167, 17–34, 2007.

133- SECKL, J.R. and HOLMES, M.C.: Mechanisms of disease: glucocorticoids, their placental metabolism and fetal'programming'of adult pathophysiology. Nat. Rev. Endocrinol. 3 (6), 479–488, 2007.

134- SINHA, R.: Chronic stress, drug use, and vulnerability to addiction. Ann. N. Y. Acad. Sci. 1141 (1), 105–130, 2008.

135- SINHA, R.: New findings on biological factors predicting addiction relapse vulnerability. Curr. Psychiatr. Rep. 13 (5), 398–405, 2011.

136- SOBRIAN, S.K., BURTON, L.E., ROBINSON, N.L., ASHE, W.K., JAMES, H., STOKES, D.L. and TURNER, L.M.: Neurobehavioral and immunological effects of prenatal cocaine exposure in rat. Pharmacol. Biochem. Behav. 35 (3), 617–629, 1990.

137- SOSNOWSKI, D.W., BOOTH, C., YORK, T.P., AMSTADTER, A.B. and KLIEWER, W.: Maternal prenatal stress and infant DNA methylation: a systematic review. Dev. Psychobiol. 60 (2), 127–139, 2018.

138- STONAWSKI, V., FREY, S., GOLUB, Y., ROHLEDER, N., KRIEBEL, J., GOECKE, T.W., FASCHING, P.A., BECKMANN, M.W., KORNHUBER, J., KRATZ, O., MOLL, G.H., HEINRICH, H. and EICHLER, A.: Associations of prenatal depressive symptoms with DNA methylation of HPA axisrelated genes and diurnal cortisol profiles in primary school-aged children. Dev. Psychopathol. 1–13, 2018.

139- STONE, A.L., BECKER, L.G., HUBER, A.M. and CATALANO, R.F.: Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict. Behav. 37 (7), 747–775, 2012.

140- STREISSGUTH, A.: Offspring effects of prenatal alcohol exposure from birth to 25 years: the Seattle Prospective Longitudinal Study. J. Clin. Psychol. Med. Settings 14 (2), 81–101, 2007.

141- STROUD, L.R., PAPANDONATOS, G.D., RODRIGUEZ, D., MCCALLUM, M., SALISBURY, A.L., PHIPPS, M.G., LESTER, B., HUESTIS, M.A., NIAURA, R., PADBURY, J.F. and MARSIT, C.J.: Maternal smoking during pregnancy and infant stress response: test of a prenatal programming hypothesis. Psychoneuroendocrinology 48, 29–40, 2014.

142- SUCHMAN, N.E., PAJULO, M., DECOSTE and C., MAYES, L.: Parenting Interventions for drug dependent mothers and their young children: the case for an attachment-based approach. Fam. Relat. 55 (2), 211–226, 2006.

143- SULLIVAN, K.A., MESSER, L.C. and QUINLIVAN, E.B.: Substance abuse, violence, and HIV/ AIDS (SAVA) syndemic effects on viral suppression among HIV positive women of color. AIDS Patient Care STDS 29 (S1), S42–S48, 2015.

144- SWENDSEN, J.D. and MERIKANGAS, K.R.: The comorbidity of depression and substance use disorders. Clin. Psychol. Rev. 20 (2), 173–189, 2000.

145- SWOFFORD, C.D., KASCKOW, J.W., SCHELLER-GILKEY, G. and INDERBITZIN, L.B.: Substance use: a powerful predictor of relapse in schizophrenia. Schizophr. Res. 20 (1–2), 145–151, 1996. US Department of Health and Human Services, Office of the Surgeon General, November 2016. Facing Addiction in America: the Surgeon General's Report on Alcohol, Drugs, and Health. US Department of Health and Human Services, Washington, DC Accessed January 2, 2018. https://addiction.surgeongeneral.gov/surgeon-generals-report.pdf.

146- SAIGAL, S., MORRISON, K. and SCHMIDT, L.A.: Mental health of extremely low birth weight survivors in their 30s. Pediatr., peds 2014–3143. Vuillermot, S., Weber, L., Feldon, J., Meyer, U., 2010. A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia. J. Neurosci. 30 (4), 1270–1287, 2015.

147- WADHWA, P.D.: Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology 30 (8), 724–743, 2005.

148- WADHWA, P.D., CULHANE, J.F., RAUH, V. and BARVE, S.S.: Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. Matern. Child Health J. 5 (2), 119–125, 2001.

149- WAFFARN, F. and DAVIS, E.P.: Effects of antenatal corticosteroids on the hypothalamicpituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations. Am. J. Obstet. Gynecol. 207 (6), 446–454, 2012.

150- WAGNER, N.J., MILLS-KOONCE, W.R., WILOUGHBY, M.T., COX, M.J., FAMILY LIFE PROJECT KEY INVESTIGATORS,VERNON-FEAGANS, L., BLAIR, C., BURCHINAL, M.R., CRNIC, K., CROUTER, A. and GARRETT-PETERS, P.: Parenting and Cortisol in Infancy Interactively Predict Conduct Problems and Callous-unemotional Behaviors in Childhood. Child Development, pp. 1–19, 2017.

151- YIP, S.W., LACADIE, C.M., SINHA, R., MAYES, L.C. and POTENZA, M.N.: Prenatal cocaine exposure, illicit-substance use and stress and craving processes during adolescence. Drug Alcohol Depend. 158, 76–85, 2016.

152- ZAMBRANA, R.E., SCRIMSHAW, S., COLLINS, N., DUNKEL-SCHETTER, C.: Prenatal health behaviors and psychosocial risk factors in pregnant women of Mexican origin: the role of acculturation. Am. J. Publ. Health 87 (6), 1022–1026, 1997.

153- ZUCKERMAN, L., REHAVI, M., NACHMAN, R. and WEINER, I.: Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology 28 (10), 1778–1789, 2003.