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PRENATAL STRESS PREDICTS OFFSPRING SUBSTANCE USE

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Abstract
This paper examines the association between prenatal stressors and an increased risk of substance use disorders (SUDs) in offspring. Prenatal stress is defined as the exposure of a developing foetus to maternal psychological or physiological stress during pregnancy. SUDs are a group of conditions characterised by recurrent use of alcohol and/or drugs, which can lead to significant impairment. Substance use research is a multifaceted field that seeks to uncover the aetiological factors of SUDs. Investigations into biological, psychological and social factors highlight the complex nature of SUDs and emphasise the need for more holistic approaches to addiction treatment and recovery support. Although prenatal stressors have been linked to adverse health outcomes in offspring, their role in predicting SUDs later in life remains unclear. Given the high plasticity of the foetal brain, emerging research suggests that prenatal stress serves as an early life risk factor that may predispose offspring to the development of SUDs in later life. This paper highlights the importance of addressing these prenatal risk factors to reduce long-term substance use outcomes.

Keywords
Prenatal stress, substance use disorders, foetal programming, epigenetics.

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1. Introduction

This paper aims to enhance our understanding of how prenatal stress can affect substance use outcomes in offspring and how it can influence infant brain development and mental health outcomes (Nolvi *et al*., 2023; Tung *et al*., 2024). However, its effects extend beyond mental health, potentially leading to externalising behaviours, such as SUDs in offspring. Research has demonstrated that children who experience elevated levels of prenatal stress exhibit heightened vulnerability to poor mental and physical health, including substance use and addiction in later life (Horn *et al*., 2018). This vulnerability may stem from alterations in the reward system of the developing brain and stress response mechanisms that are essential for understanding substance use and addiction. Globally, SUDs have significant health and socioeconomic impact. At the community level, substance use affects families, creates financial strain, increases

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domestic violence and reduces workplace productivity, which underscores the need for comprehensive prevention and intervention strategies that address various factors contributing to substance use and addiction.

1.1. Historical context

The idea that the intrauterine environment influences long-term health is not new. The Developmental Origins of Health and Disease (DOHaD) hypothesis, first conceptualised by David Barker, posits that negative experiences in utero can predispose individuals to non-communicable diseases later in life (Davis & Narayan, 2020; Kwon & Kim, 2017). Early studies by Barker et al. focused on physical outcomes such as cardiovascular disease (Arima & Fukuoka, 2020). This is supported by evidence from previous studies linking prenatal maternal health with the future health of offspring. Stephenson et al. (2018) points to the role of preconception healthcare in reducing risks such as neural tube defects during early brain development, which has implications for the long-term outcomes of offspring. Therefore, the application of the biopsychosocial model in prenatal healthcare could enhance both maternal and child health outcomes. However, as the DOHaD has evolved, the framework has expanded to encompass prenatal exposure to stress as a contributory factor in neurobehavioral outcomes in offspring (Monk *et al*., 2019). Understanding how prenatal stressors contribute to SUDs can enhance our knowledge of their impact on offspring development and health (Thomason & Hendrix, 2024).

Likewise, the biopsychosocial model as proposed by Engel (1977), posits that health and illness cannot be attributed solely to biological causes. Instead, they are influenced by a complex interaction of biological, psychological and social factors, all of which play a significant role in health and disease. The biopsychosocial model suggests that these factors contribute to the development of substance use and should be considered in treatment approaches (Becona, 2018; Hinostroza & Mahr, 2025; Skewes & Gonzalez, 2013). Building on this understanding, the following explores how these factors interplay in the context of SUDs.

2. Biological factors

2.1. Epigenetic mechanisms

Having established the foundational role of prenatal stress, it is important to explore how epigenetic mechanisms further complicate the risk of SUDs in offspring. Additional research examining the potential predictors of substance use risk has begun to explore epigenetic mechanisms in pregnancy, such as DNA methylation (DNAm) (Zuccarello *et al*., 2022). Exposure to stress during pregnancy can lead to changes in gene expression through DNAm. These epigenetic markers can affect the genes involved in neurotransmission, stress regulation and reward. Epigenetic changes can also be influenced by various environmental factors such as maternal diet, alcohol consumption and smoking (Alegria-Torres *et al*., 2011; Zuccarello *et al*., 2022). The DOHaD theory suggests that environmental exposure during foetal development can modify gene expression without altering the underlying DNA sequence (Lacagnina, 2019). This can predispose offspring to a range of diseases in adulthood (Kwon & Kim, 2017), including substance use (Horn *et al*., 2018). Having explored the role of epigenetic mechanisms, it is crucial to examine specific maternal behaviours that can directly impact foetal brain development and increase the risk of substance use in offspring.

2.2. Maternal substance use

Maternal substance use has become a significant area of concern and is associated with negative outcomes for offspring (Tsuda-McCaie & Kotera, 2022). According to Dodge et al. (2019), drug and/or alcohol use by expectant mothers can have lasting consequences for the unborn child. Furthermore, substance use can interfere with foetal brain development, particularly in regions associated with reward processing (Müller *et al*., 2013; Pastor *et al*., 2017). These prenatal stressors may increase the likelihood of offspring developing increased sensitivity to the rewarding effects of alcohol and drugs later in life, effectively priming the brain for potential substance use. Longitudinal studies have explored the link between prenatal exposure to substances and increased likelihood of substance use during adolescence. For example, Cornelius et al. (2016) demonstrated that prenatal alcohol exposure directly predicts adolescent drinking levels. Richardson et al. (2013) found that prenatal cocaine exposure predicted alcohol and marijuana use among adolescents. These longitudinal studies offer valuable insights into these long-term effects and raise important questions regarding the specific factors that may contribute to the increased risk of SUDs in offspring.

Furthermore, the placenta plays a critical role in modulating foetal exposure to maternal hormones. Substances, whether licit or illicit, can pass through the placenta, which serves as a physiological link between the mother and developing foetus. For instance, the consumption of alcohol during pregnancy can be transmitted to the foetus via the mother's bloodstream, leading to foetal alcohol spectrum disorders (FASD). This condition has been recognised as significantly increasing the risk of SUDs in offspring (Popova *et al*., 2021). Likewise, Etemadi-Aleagha and Akhgari (2022) investigated the abuse of psychotropic drugs during pregnancy and stated that while the placenta functions as a semi-permeable barrier providing nutrients and oxygen to the developing foetus, certain substances such as cannabidiol (CBD) can increase the permeability of the placenta. This increased permeability can lead to embryotoxic effects, posing risks to foetal development (De Genna *et al*., 2023; Dong *et al*., 2019). Etemadi-Aleagha and Akhgari (2022) concluded that children born to individuals who use drugs were reliable indicators of future neurodevelopmental issues. The authors emphasised the necessity for further research concerning the quantity and timing of substance use.

2.3. Maternal nutrition

Research has also begun to explore the role of maternal nutrition in shaping offspring vulnerability to SUDs. Animal research has identified a link between maternal diet and substance use in offspring. Gawliński et al. (2020) suggested a link between high sugar content and cocaine-seeking behaviour. Similarly, Sarker et al. (2019) identified a link between a maternal high-fat diet and substance addiction. The relationship between maternal nutrition and offspring substance use is a complex yet under-studied area of human research.

Furthermore, Hibbeln et al. (2017b) identified a potential association between reduced meat consumption during pregnancy and offspring substance use; however, the authors also investigated the effect of increased meat consumption but cautioned against increasing meat intake to mitigate this risk (Hibbeln *et al*., 2017a) as sufficient levels of vitamin B12 are already found in fortified foods so could be an alternative source of vitamin B12 (Kumar *et al*., 2023). However, the scarcity of comparable human studies limits our understanding of the full extent and mechanisms of this relationship and

underscores the need for further human studies to fully understand this complex association. Future research could provide more targeted nutritional advice for pregnant women which can help us consider the impact of nutrition on foetal development.

3. Psychological factors

3.1. Prenatal maternal stress

Based on the above findings, prenatal maternal stress is also a significant factor that can disrupt stress systems and increase the likelihood of substance use and addiction in offspring (Horn *et al*., 2018). The link between prenatal stress and substance use risk in offspring has prompted further investigation into the underlying biological and psychological processes. Colamarino et al. (2024) conducted a review indicating that high stress levels during pregnancy may increase the risk of adverse outcomes in offspring, particularly emotional, psychopathological and behavioural development. However, Zijlmans et al. (2015) reported contradictory findings. This systematic review did not find a significant association between maternal prenatal stress and cognitive, emotional regulation or behavioural outcomes in offspring. This suggests that cortisol may not be the primary mechanism linking prenatal stress to offspring outcomes. The review indicates that the heterogeneity in study designs and methods for assessing cortisol makes it too early to draw definitive conclusions. Differences in findings can be attributed to a number of factors such as variability in the sample size, measurement methods, study design, publication bias and timing of exposure to stress, which may influence the results.

Psychological stress during pregnancy is defined by Răchită et al. (2022) as, "the imbalance that a pregnant woman feels when she cannot cope with demands which is expressed both behaviourally and physiologically". Prenatal maternal stress encompasses not only stressors directly associated with pregnancy but also a variety of external factors such as social and environmental influences (Zuccarello *et al*., 2022). Moreover, research indicates that psychological stress during pregnancy is not limited to the mother alone but can affect stress responses, emotion regulation and cause behavioural problems in offspring (Graham *et al*., 2022). These findings underscore the importance of developing well-being interventions during pregnancy that address the needs of both the mother and developing child (Traylor *et al*., 2020).

3.2. Bereavement in pregnancy

Maternal prenatal stress can be further compounded by the experience of bereavement during pregnancy, which may significantly impact both the mother and developing foetus. Loss of a close family member during pregnancy can induce stress and influence the mental health of offspring during childhood and adulthood (Persson & Rossin-Slater, 2018). A population-based cohort study by Liang et al. (2013) provided insights into the association between exposure to spousal bereavement and SUDs. The authors posited the potential intergenerational transmission of grief. However, in contrast to these findings, Black et al. (2016) failed to demonstrate any detrimental effects on adult outcomes following the death of the mother's parent during pregnancy. Although substance use was not the outcome of Black's study, the inconsistency in the results underscores the complexity of intergenerational trauma which necessitates further research to understand the underlying mechanisms involved.

3.3. Prenatal trauma

Prenatal trauma adds another layer of complexity to these risk factors. These experiences can be defined as any traumatic event or prolonged period of stress experienced by a woman during pregnancy that has a direct impact on the well-being of the foetus. Such experiences can include a number of traumatic experiences such as domestic violence and physical, sexual or emotional abuse (Colamarino *et al*., 2024; Wilner, 2020). Black et al. (2016) highlighted the relationship between trauma-related effects transmitted across generations which has implications for the potential development of maladaptive coping mechanisms such as substance use in later life. This is consistent with Beebe et al. (2020), who found that pregnant women exposed to the 9/11 World Trade Centre terrorist attack and developing post-traumatic stress disorder (PTSD) exhibited hypervigilant behaviour with their infants, all of whom were in utero at the time of the attack. The researchers concluded that this behaviour constituted the primary mode of trauma transmission to infants. However, it should be noted that a specific sample of pregnant women from a single traumatic event may limit the generalisability to other pregnant women who have experienced different forms of trauma. Nevertheless, it is essential to provide early interventions to pregnant women who have experienced trauma to mitigate potential negative outcomes for future generations.

Colamarino et al. (2024) provide valuable insights into the long-term consequences of prenatal traumatic exposure on child development. The study's findings suggest that traumatic experiences during pregnancy can affect children's socio-emotional, psychopathological and behavioural outcomes. Trauma not only intensifies the overall stress levels of the mother but also introduces unique challenges for maternal and foetal health. Understanding the diverse nature of prenatal trauma and its potential sources is crucial for developing comprehensive strategies to support pregnant women and mitigate potential negative impacts on maternal and offspring health.

4. Social factors

4.1. Socioeconomic status

Shifting focus to more societal influences. Poor socioeconomic status (SES) is a significant risk factor for negative health outcomes in offspring (Amaro *et al*., 2021; Mirzayeva, 2023). This complex association involves factors, such as limited access to healthcare and financial instability. However, little is known about how low parental SES in early life contributes to the risk of developing SUDs, due to the lack of research on this topic. These factors, in conjunction with maternal prenatal stressors and inadequate nutrition linked to low socioeconomic status (SES), can contribute to adverse prenatal outcomes. Furthermore, the absence of social support during pregnancy may lead to a vicious cycle of socioeconomic disadvantage that impacts all aspects of a pregnant woman's wellbeing (Al-Mutawtah *et al*., 2023). Despite the limited research, evidence has emerged. Salom et al. (2014) found that socioeconomic disadvantage is strongly associated with comorbid alcohol and mental health disorders. Similarly, Zuccarello et al. (2022) stated that parental and environmental risk factors such as SES influence prenatal development via epigenetic modifications, which may contribute to vulnerability to substance use. Recognising the roles of parental and environmental factors has important implications in treatment strategies.

5. Conclusion and future research

Recognising prenatal stress as a modifiable risk factor for SUDs has substantial implications for public health policies and clinical practice. Programmes that screen for and address maternal stressors can play a dual role in improving outcomes for both mothers and their offspring. Understanding these mechanisms may facilitate the development of targeted early interventions in at-risk offspring. The complexities of prenatal stressors and their impact on foetal development are crucial for informing interventions to mitigate the negative effects of long-term outcomes. A holistic approach to substance use treatment, considering prenatal experiences, is essential for understanding of these complex disorders. Future research should identify sensitive periods during pregnancy, explore cross-cultural perspectives, as previous studies have investigated how various cultural norms and practices shape individual experiences and contribute to a deeper understanding of human behaviour (Jackson *et al*., 2024; Kotera *et al*., 2023). Additionally, it should examine the permanence of prenatal stress effects. Additionally, translating findings from animal models to human populations requires careful consideration. Advancements in this field can potentially transform early intervention and substance use prevention.

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