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REVIEW ARTICLE

A review of the literature: How does prenatal opioid exposure impact placental health and fetal brain development?

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Abstract

In recent years, there has been a sixfold increase in the number of pregnant people with opioid use disorder (OUD). Rates of neonatal opioid withdrawal syndrome (NOWS), previously known as neonatal abstinence syndrome (NAS), have significantly increased in virtually every state and demographic group (Healthcare Cost Utilization Project, HCUP, 2010). NOWS is a condition resulting from chronic exposure to either therapeutic opioid use (e.g., medication for OUD, chronic pain conditions) or nonprescribed opioid use. To date, there is no known prenatal treatment to help decrease the risk of infants developing NOWS and subsequent neurodevelopmental outcomes. Given the increasing support for how placental signaling, or placental programming, may play a role in downstream pathology, prospective research investigating how the placenta is affected by chronic opioid exposure morphologically, histologically, and at the cellular level may open up potential treatment opportunities in this field. In this review, we discuss literature exploring the physiological roles of nitric oxide and dopamine not only in the vascular development of the placenta, but also in fetal cerebral blood flow, neurogenesis, neuronal differentiation, and neuronal activity. We also discuss histological preclinical studies that suggest chronic opioid exposure to induce some combination of placental dysfunction and hypoxia in a manner similar to other well-known placental pathologies, as denoted by the compensatory neovascularization and increased utilization of the placenta's supply of trophoblast cells, which play an essential role in placental angiogenesis. Overall, we found that the current literature, while limited, suggests chronic opioid exposure negatively impacts placental function and fetal brain development on a cellular and histopathological level. We conclude that it is worthwhile to consider the placenta as a therapeutic target with the ultimate goal of decreasing the incidence of NOWS and the long-term impacts of prenatal opioid exposure.

KEYWORDS

neonatal abstinence syndrome, neonatal opioid withdrawal syndrome, neurodevelopment, opioid use disorder, placenta, placental programming hypothesis, placental signaling

1 | THE US OPIOID EPIDEMIC AND PRENATAL OPIOID EXPOSURE

In the United States from 1999 to 2014, there has been greater than a fourfold increase in the number of pregnant people with opioid use disorder (OUD) (Haight, 2018). In 2014, the incidence of neonatal opioid withdrawal syndrome (NOWS), previously known as neonatal abstinence syndrome (NAS), was so high that there was a new diagnosis every 15 min (Winkelman et al., 2018). NAS/NOWS is a postnatal withdrawal syndrome characterized by hyperactivity of the central and autonomic nervous systems and the gastrointestinal tract (Ordean & Chisamore, 2014; Sanlorenzo et al., 2018). According to national data collected from the Healthcare Cost and Utilization Project National Inpatient Sample in 2017, the median hospital stay for neonates with NAS/NOWS was 9.2 days longer than other hospitalized neonates (Hirai et al., 2021). This condition may be acquired from nonprescribed opioid use, as well as for opioids prescribed for chronic pain conditions and OUD (i.e., medication for OUD [MOUD]) during pregnancy. With the incidence of NAS/NOWS skyrocketing, the long-term neurodevelopmental and neurobehavioral impacts have become an increasing public health concern (McQueen & Murphy-Oikonen, 2016; Nygaard et al., 2017; Zwicker et al., 2016).

Prenatal opioid exposure is associated with relative microcephaly, abnormal electroencephalograms (van Baar et al., 1989), and deficits in several neurodevelopmental domains including motor, language, and cognition in infants (Conradt et al., 2019; de Castro et al., 2011; Doberczak et al., 1987; Hunt et al., 2008; Kocherlakota, 2014; Larson et al., 2019; Logan et al., 2013; Merhar et al., 2020; Nygaard et al., 2015; Sirnes et al., 2017; Visconti et al., 2013; Walhovd et al., 2007; Yeoh et al., 2019). There is also evidence of neurodevelopmental delays and decreased educational attainment in children and teenagers with a history of prenatal opioid exposure (Baldacchino et al., 2014; Oei et al., 2017). While the individual findings of these studies can be appreciated, it is key to acknowledge that this observational work has focused on nonprescribed opioids (Nygaard et al., 2015; Walhovd et al., 2007), prescribed opioids as in the case for MOUD (de Castro et al., 2011; Doberczak et al., 1987; Hunt et al., 2008), or a combination of both (Conradt et al., 2019; Kocherlakota, 2014; Larson et al., 2019; Logan et al., 2013; Merhar et al., 2020; Sirnes et al., 2017; van Baar et al., 1989; Visconti et al., 2013; Yeoh et al., 2019). Although in both of these situations the dyad is exposed to opioids during gestation, there are many differences in the underlying contexts of the dyads that may also contribute to outcomes (e.g., social support, access to care, systemic racism, stigma, etc.). It is not the intention of this review to address these additional influences, but rather to present evidence, solely in the context of prenatal opioid exposure regardless of whether the exposure was related to treatment, that chronic opioid exposure in utero negatively impacts the placenta and fetus during a critical developmental period where unyielding foundational processes for brain growth are initiated, ultimately impacting long-term brain development and providing a target to improve outcomes related to exposure.

2 | THE PLACENTA AND OPIOID EXPOSURE

Given that the placenta is the most important fetal-derived organ for prenatal development, there has been an increasing research interest in how placental signaling, or placental programming, may play a role in downstream adult pathology (Barker & Thornburg, 2013a, 2013b). The fetal programming hypothesis, often referred to as the developmental origins of health and disease or DOHaD hypothesis, postulates there to be a fetal origin to various chronic adult diseases. First described by physician and epidemiologist David J. P. Barker over 30 years ago, the theory proposes that various fetal organ systems undergo programming, potentially permanent epigenetic modifications that develop permanent homeostatic set points for metabolic and physiologic processes that persist into adulthood. The role of the placenta in the programming hypothesis is supported by evidence that the placenta plays a more active, signaling role in fetal organ system development in addition to its well-known, seemingly passive role of facilitating nutrient and oxygen transfer, detoxifying drugs and other metabolites, and mediating the maternal–fetal blood and immune system barrier. Recent human and animal studies suggest that the placenta secretes enzymes and hormones that modulate chromatin activity in response to nutritional changes, thereby controlling which proteins may be expressed by various fetal cells to help facilitate fetal neurodevelopment (Bale, 2015; Bowers & Yehuda, 2016; Brown et al., 1996; Shallie & Naicker, 2019; Wyrwoll et al., 2009). These prior studies suggest the placenta is a key signaling organ involved in fetal brain development. Thus, it is possible that aberrant, pathological changes in placental structure and function in response to prenatal opioid exposure play a role in the observed neurobehavioral delays observed in infants, children, and adolescents.

While it is unclear how chronic opioid exposure may induce placental dysfunction at the cellular level, it has been suggested that chronic opioid exposure may desensitize or downregulate the placenta's natural opioid receptors (Ahmed et al., 2009; Rosenfeld, 2022), which are thought to play a physiological role in regulating the immune, vascular, and endocrine functions of the placenta (Mantione et al., 2010). The body's endogenous opiates, such as endorphins, may play a role in fetal brain development. Interestingly, Mantione et al. demonstrated that mu opioid receptor stimulation in human placentas ex vivo resulted in nitric oxide (NO) release. NO has been thought to participate in not only vascular development in the placenta (Krause et al., 2011), but preclinical evidence also suggests that NO contributes to the maturation of cerebral blood flow regulation as well as the development of neuronal activity (Northington et al., 1997). Furthermore, there is evidence that L-DOPA decarboxylase, the enzyme that catalyzes the formation of dopamine from its precursor L-DOPA, is present in human placenta cells (Siaterli et al., 2003). Not only is dopamine thought to have a critical impact on early brain development through modulating neurogenesis, neuronal migration, and neuronal differentiation (Araki et al., 2007; Bhide, 2009; McCarthy et al., 2007; Turner et al., 2006; Yarlagadda et al., 2019), but Stratakis et al. (1996) found evidence

TABLE 1 Current proposed mechanisms for placenta hypoxia and poor vascular integrity following chronic opioid exposure

Reduced area of trophoblast giant cells → Trophoblastic proliferation and budding
Reduced maternal blood vessel area → Neovascularization
Chronic hypoxia → Increased fibrin (clotting protein) deposition (Yan et al., 1999)

in preclinical rat studies that dopamine may play a role in regulating opioid release from placenta tissue. Although more concrete conclusions cannot be made given the translational limitations of ex vivo and preclinical studies, taken together this evidence suggests that chronic opioid use in pregnancy may induce desensitization and subsequent dysfunction of the placental opioid receptors, which normally function to regulate and facilitate key processes in fetal brain and vascular development.

3 | CLUES FROM PLACENTAL PATHOLOGY

There is evidence that prenatal opioid exposure (confirmed via self-reported maternal opioid use and/or confirmed diagnosis of NOWS) significantly increases the risk for fetal growth restriction and preterm labor (Azuine et al., 2019). Although fetal growth restriction and preterm labor are conditions believed to be primarily due to placental insufficiency (Malhotra et al., 2019; Morgan, 2014), there are few studies that have explored how chronic opioid exposure impacts the gross morphological and histological structure of the placenta (Table 1). Vavrinková et al. (2001) and Köpp and Vogel (1982) found there to be an increase in fibrin (clotting) protein depositions, evidence of significant neovascularization, and trophoblastic proliferation and budding in human placentas associated with prenatal opioid exposure, all findings suggestive of chronic hypoxia and poor vascular integrity. Vavrinková et al. (2001) additionally reported evidence of infection and necrotizing processes in these placental samples. More recently, a preclinical study found that oxycodone exposure in pregnant mice led to a reduced area of trophoblast giant cells and a general decrease in the maternal blood vessel area within the labyrinth region of the placenta (Green et al., 2020). Corresponding with the general theme of these studies, Malek et al. (2009) demonstrated that ex vivo human placental samples exposed to methadone had a significant reduction in placental permeability. Together, these results suggest that chronic opioid exposure may induce some combination of placental dysfunction and hypoxia, as denoted by the compensatory neovascularization and increased utilization of the placenta's supply of trophoblast cells, which play an essential role in placental angiogenesis. While these findings can be appreciated, it is difficult to come to concrete conclusions due to differences in the type of opioid (i.e., heroin, oxycodone, or methadone), and the setting of administration (i.e., non-prescribed, prescribed for OUD, and/or prescribed for chronic pain conditions).

4 | IMPACTS ON FETAL BRAIN DEVELOPMENT

While these studies open the possibility of a direct link between the placenta and fetal brain development, it is also possible that dysfunctional placental and fetal vascular development induced by chronic opioid exposure may subsequently impact fetal brain development. After observing an increase in human placental weight to be significantly associated with a decreased length to head circumference ratio in infants, Barker et al. (1990) postulated that during chronic periods of intrauterine hypoxia and compensatory vasodilation and neovascularization, the placental weight increases in efforts to maximize nutrient and oxygen transfer. They further hypothesized that the fetus's autoregulatory system responds appropriately to chronic hypoxia by diverting peripheral vasculature blood flow away from the trunk in efforts to maximize blood flow to the brain. It has been suggested that such compensatory mechanisms made in response to harmful maternal or intrauterine environmental states may be due to potentially permanent epigenetic modifications intended to maximize the survival of the fetus. While these fetal or placental programming mechanisms may temporarily benefit the health of the fetus, it is thought to be done at the expense of long-term health in adulthood (Barker & Thornburg, 2013a, 2013b; Kwon & Kim, 2017).

5 | POTENTIAL TREATMENT TARGETS

To the best of our knowledge, there are currently no completed studies investigating how placental pathology in birthing parents with OUD correlates with perinatal and postnatal infant brain and neurobehavioral development. Prospective research focusing initially on histopathology is a reasonable first step based on feasibility and current investigational placental therapies already being studied. If preliminary studies find significant vascular pathology and/or villous inflammation associated with chronic opioid use, it may be beneficial to consider current investigational placental therapies (Sibley, 2017) indicated for other placental pathology such as preeclampsia (vasodilatory/antioxidant) and chorioamnionitis (anti-inflammatory) as potential therapies for NOWS/NAS prevention in pregnant parents with OUD. Prenatal treatments intended to prevent or reduce the potential risks of opioid exposure secondary to prescribed opioids (e.g., MOUD) may also have the benefit of reducing the guilt felt by these parents as they navigate treatment.

Another potentially fruitful research direction is to investigate changes in placental signaling in response to chronic opioid use. Measuring various serum levels of placenta-derived metabolites (e.g., NO, dopamine, serotonin, endorphins, bone morphogenetic proteins, and microRNAs) that have a potential application in fetal brain development (Bond et al., 2012; Bonnin et al., 2011; Chang et al., 2018; Gámez et al., 2013; Zhao et al., 2018) could reveal novel therapeutic targets that are specific for decreasing an infant's risk of neurodevelopmental delays secondary to chronic opioid exposure in utero. While there are currently no approved placental therapies targeting placental-derived metabolites, there has been increasing interest in the

field. Utilizing animal models, Phillips et al. (2017) demonstrated that it may be possible to prevent the harmful long-term neurodevelopmental consequences of gestational hypoxia with a mitochondria-targeted antioxidant called MitoQ, short for mitoquinone mesylate (synthetic analogue of coenzyme Q10). They were not only able to identify altered microRNAs being secreted by the placenta in response to intervals of oxidative stress or gestational hypoxia, but they also found evidence that the gene targets of these microRNAs have previously been associated with gene expression changes in the fetal brain (Phillips et al., 2017).

Translating the preclinical studies focused on placental therapies into clinical trials has historically been challenging both ethically and logistically (Chappell & David, 2016; Fisk & Atun, 2008). Not only is the face validity of using preclinical animal models in investigational placental treatments unclear due to widely differing placental anatomy among mammalian species including humans, pigs, mice, and sheep (Dilworth & Sibley, 2013; Erlandsson et al., 2016; McCarthy et al., 2011; Swanson & David, 2015), but investigational placental treatments also carry an increased risk of side effects by involving two people in vulnerable patient populations, the pregnant parent and fetus. Together, these barriers are often the predominant reasons as to why maternal and fetal medicine has been disproportionately behind in therapeutic advancements in comparison to other fields. While these barriers are no less prominent and are bound to yield limitations in future research, the increasing need for placental/fetal therapies in the United States warrants prospective preclinical and clinical research in this field of study. Not only will the growing rates of NOWS/NAS secondary to the opioid epidemic contribute to this need, but the increasing prevalence of preeclampsia, which is thought to be related to the increasing rates of cardiovascular disease and obesity in the United States, has facilitated growth in research in fetal medicine. Furthermore, additional preclinical methods can be utilized in addition to current animal models to help facilitate translation to clinical research. Colin P. Sibley discusses in vitro systems that when used in combination with animal models may provide sufficient proof of concept and the safety screening necessary to transition into phase 1 clinical trials (Sibley, 2017).

In summary, there is mounting evidence for involvement of placental dysfunction in the long-term outcomes of in utero opioid exposure, whether through nonprescribed opioids or prescribed opioids for OUD or chronic pain conditions. Given that the rates of OUD continue to rise in our country's opioid epidemic, it is critical that research begins to focus on understanding the role of the placenta with regard to neurodevelopmental and neurobehavioral risks secondary to in utero exposure so that efficacious, preventive therapies can be developed. Providing pregnant parents with OUD or other conditions requiring opioid medications as many opportunities as possible to support their fetus' development while navigating treatment should be of the highest priority for all those involved in both research and clinical care.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

There are no shared data associated with this work.

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