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Co-use of tobacco and marijuana during pregnancy: Impact on nervous system development

Co-use of tobacco and marijuana during pregnancy is three times more common than prenatal marijuana use in the absence of cigarette use (Coleman-Cowger et al., 2017; Ko et al., 2018). Although overall rates of tobacco smoking during pregnancy have decreased (Ebrahim et al., 2000; Hansen et al., 2018), they have remained the same among some groups of women, including those with less than a high school education, Black women, and women over 26 years of age (Agrawal et al., 2019). In addition, marijuana use has become increasingly more acceptable in North America (Jarlenski et al., 2017), with a corresponding surge in prenatal marijuana use (Brown et al., 2017; Agrawal et al., 2019) and in prenatal co-use of marijuana with cigarettes (Coleman-Cowger et al., 2017). In fact, most pregnant cigarette smokers also use marijuana (Ko et al., 2015). In this Special Issue, we define co-use as the use of both marijuana and tobacco in the form of cigarettes during pregnancy, also known as concurrent or dual use, resulting in fetal co-exposure. Women who co-use are more likely to be dependent on marijuana than women who only use marijuana (Montgomery, 2015; Peters et al., 2012). Thus, pregnant co-users may have more difficulties reducing or quitting during pregnancy. Despite the increasing rates of co-use among pregnant women, very little is known about the short- and long-term effects of prenatal co-exposure to tobacco and marijuana on offspring.

The goal of this Special Issue of *Neurotoxicology and Teratology* was to capture the status of the field and gather evidence for the effects, if any, of co-exposure on human development. We were particularly interested in studies with prospective measurement of multiple substances at more than one time point during pregnancy. This collection includes papers highlighting the current prevalence of co-use among pregnant women, related birth outcomes, and associations of prenatal co-exposure with behavioral problems from infancy to adulthood. Sex differences were examined in all studies with offspring outcomes, given the importance of considering sex as a biological variable in research funded by the National Institutes of Health. By describing what is known in the literature about co-exposure to tobacco and marijuana, we can identify important gaps in the literature and promising areas for future research. Although most papers in this issue reported effects of single exposures in addition to co-exposure, here we highlight results related to co-exposure.

Ashford et al. (2019) investigated markers of immune and psychosocial function in first trimester pregnant women in a preliminary midpoint analysis of 138 primarily White, lower socioeconomic status (SES) women recruited from private and public prenatal clinics in Kentucky from 2016 to 2017. Maternal urine samples were used to identify co-users and tobacco-only users. Maternal serum cytokines (IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, CRP, and MMP 8) in pregnant co-users were compared to those in tobacco-only users. Co-use of marijuana and tobacco in the first trimester was associated with lower TNF-α, indicating a depressed proinflammatory immune response. However, the groups did not differ on the other markers, or in levels of depressive symptoms or self-reports of stress. Although a preliminary analysis, this is the first study to examine markers of immune function in pregnant women who used marijuana and tobacco, adding to a very small body of literature on the effects of prenatal substance use on maternal immune response (e.g., Ashford et al., 2013; Simhan et al., 2005). Future work should examine maternal and fetal immune response across pregnancy in pregnant women who only use marijuana, only tobacco, both, or neither substance.

Coleman-Cowger et al. (2018) examined the prevalence of prenatal co-use and associated birth outcomes in a racial/ethnically diverse, low SES sample of 500 women recruited from two urban University obstetric clinics in Maryland in 2017. More pregnant women reported marijuana-only use (12%) than co-use with tobacco (9%) or tobacco use alone (8%). Urine and hair samples were used to validate maternal self-reported substance use. The babies of women who used both cigarettes and marijuana during pregnancy had much higher odds of small head circumference and birth defects, compared to the babies of women who only used tobacco or marijuana. There were no effects of co-exposure on birth weight or length of gestation. The effects of co-exposure on head circumference and birth defects were not moderated by sex. The results of this study suggest that there may be additional risk for some adverse birth outcomes associated with prenatal co-exposure to tobacco and marijuana.

Massey et al. (2018) pooled data from three prenatal cohorts to investigate the effects of marijuana and co-exposure on length of gestation and birth weight in over 1100 births. Data were collected from women across the United States between 2003 and 2015. The pooled sample included two studies that oversampled for prenatal tobacco use, so it is not surprising that tobacco use was most common (51%), followed by marijuana use (23%) and co-use of tobacco and marijuana (19%). Co-exposure to tobacco and marijuana did not predict shorter gestation or lower birth weight, after controlling for the effects of individual exposures. Analyses stratified by infant sex revealed that prenatal tobacco and prenatal marijuana exposure were separately associated with reduced birth weight in male infants. There was no significant interaction by sex for co-exposure. Although these findings, together with null results in Coleman-Cowger et al. (2018), do not support an effect of prenatal co-exposure to tobacco and marijuana on duration of gestation or infant birth weight, more research is needed using population-based samples that are better powered to detect interaction. Measurement of maternal substance use and length of co-exposure may also be important because co-exposure assessed via self-report in combination with meconium assay (positive for cotinine and THC) did predict restricted fetal growth in a recent study (e.g., Schuetze et al., 2018).

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Stroud et al. (2018) examined the impact of prenatal co-use on newborn neurobehavior in a subsample of 111 dyads from a prospective longitudinal study. This study oversampled for prenatal tobacco use and recruited pregnant women from clinics and community sites feeding a large obstetric hospital in New England from 2006 to 2010. Maternal tobacco and marijuana use were measured by intensive maternal interview (Timeline Follow-Back), supplemented by biochemical verification. Among pregnant women with complete substance use data, 22% were co-users, 41% used tobacco only, and 38% were biochemically-verified controls. Infant neurobehavior was assessed up to seven times across the first postnatal month using a standardized examination, the NICU Network Neurobehavioral Scale (NNNS). Maternal co-use of tobacco and marijuana predicted decreased ability to self-soothe, decreased attention to stimuli, lower motor activity, and greater need for external soothing compared to unexposed infants. Moreover, co-exposure was associated with nearly double the impact on infant self-soothing and need for external soothing versus exposure to tobacco alone. There were also sex differences, with stronger effects of co-exposure on infant neurobehavior among girls compared to boys. These findings provide evidence of compromised neurodevelopment among co-exposed infants, and intriguing sex differences that warrant further research.

Eiden et al. (2018) examined the effects of co-exposure on infant autonomic regulation and toddler emotion regulation in a racial/ethnically diverse, lower SES sample of 247 pregnant women recruited from an urban university-affiliated hospital in New York from 2006 to 2009. Biological samples were used for verification of maternal substance use, observational data were used to supplement self-reported data, and the authors were able to examine postnatal exposure to maternal substance use. Infant autonomic regulation was measured by respiratory sinus arrhythmia in response to stress (an arm restraint task). Prenatal co-exposure predicted poorer infant autonomic regulation at 9 months, which was associated with poorer emotion regulation at 24 months of age. Prenatal co-use also predicted lower levels of postpartum maternal sensitivity, another pathway to toddler emotion regulation. There were no sex differences in the effects of co-exposure on pathways to offspring dysregulation. Together with Stroud et al. (2018), these findings provide converging evidence for an indirect role of prenatal co-exposure to marijuana and tobacco on behavior problems in offspring via deficits in infant autonomic regulation. Given these results, future research on this pathway is warranted.

Godleski et al. (2018) investigated pathways from prenatal substance use to toddler behavior problems in the same study sample ($N = 247$) from New York as Eiden et al. Similarly, biological samples were used to validate maternal self-report of prenatal smoking and marijuana use. Strengths of this study included an observational data component and the consideration of postpartum substance use. Prenatal co-use of tobacco and marijuana was more common (39%) than the use of tobacco in isolation (33%). Co-use was not directly related to toddler externalizing behavior problems. However, prenatal co-use predicted maternal affective dysregulation during infancy, which was associated with externalizing behavior problems at 24 months. Prenatal co-exposure also predicted higher levels of maternal marijuana use 2 to 24 months postpartum, which was directly related to toddler behavior problems. Although male offspring had higher levels of externalizing behavior by 36 months, there was a co-exposure by sex interaction, such that exposed girls had more behavior problems at 36 months than non-exposed girls and similar levels of problems as exposed boys. These results suggest that there may be an indirect link between prenatal co-exposure to tobacco and marijuana and toddler behavior problems via maternal postpartum behavior, and that co-exposed girls may be at higher risk of child behavior problems.

De Genna et al. (2018) studied long-term trajectories of maternal co-use of tobacco and marijuana, and the associations between maternal trajectories of co-use and substance use in 603 22-year-old offspring from a prospective, prenatal cohort recruited at a teaching hospital in Pennsylvania from 1983 to 1985. The sample was roughly half White and half Black, lower SES, and was oversampled for prenatal marijuana and alcohol use. This study included pregnant women who used only marijuana, only tobacco, both, or neither of these substances. Self-report data on maternal substance use during and after pregnancy from eight time points were used to calculate growth trajectories from the first trimester of pregnancy to 16 years postpartum. The results indicated significant variation in patterns of maternal co-use of marijuana and tobacco, including a substantial minority (17%) gradually decreasing co-use over time and a small group (7%) engaging in chronic co-use at every time point. The decreasing maternal pattern of co-use was linked to co-use in the young adult offspring, whereas the offspring of chronic co-users were more likely to have a substance use disorder by age 22. Stratifying by sex revealed that there may be a stronger effect of maternal co-use trajectories on the intergenerational risk of co-use among male offspring. Although the data are older, these findings provide evidence that maternal co-use of tobacco and marijuana may persist long into the postpartum period, and different patterns of co-use may have implications for co-exposed offspring.

Taken together, these papers provide a much-needed contribution to the field of prenatal co-exposure to tobacco and marijuana and highlight the need for future studies. The prevalence of co-exposure in these community samples ranged from 9 to 39%, with the caveat that most studies oversampled pregnant women who smoked cigarettes. Nationally representative data indicate that 3% of all pregnant women have used both substances in the past month (Coleman-Cowger et al., 2017). Compared to non-pregnant women who use marijuana and tobacco, pregnant women who use both substances are more likely to be lower SES, Black, and tobacco- and marijuana-dependent (Coleman-Cowger et al., 2017). The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice has recommended that health care providers screen for tobacco and marijuana use in women who are pregnant or contemplating pregnancy and encourage these women to discontinue marijuana use (ACOG, 2017). Clinicians may be unaware that co-use is more common than prenatal marijuana use in isolation, and may not realize that marijuana use may inhibit tobacco cessation efforts during pregnancy. Education efforts for obstetric providers, pediatricians, and pregnant smokers are needed regarding the screening for co-use and the potential risks of co-use/co-exposure. Innovative intervention efforts are also needed to address co-use in pregnancy and in reproductive age women.

The results of the studies in this Special Issue highlight the potential risks of co-exposure on selected birth outcomes and infant development, with implications for long-term externalizing behavior problems among co-exposed offspring. More work is needed on the effects of co-exposure compared to exposure to only marijuana use and only tobacco use. Future work should examine the impact of smoking cessation across pregnancy and investigate possible trimester-specific effects. Most of the studies were underpowered to detect sex differences, potentially contributing to the mixed results in the effects of co-exposure on boys vs. girls. There were no sex differences in the effects of co-exposure on birth outcomes (Coleman-Cowger et al., 2018; Massey et al., 2018) and toddler emotion regulation (Eiden et al., 2018; Godleski et al., 2018). There was evidence that co-exposed girls may be at greater risk of poor neonatal self-regulation (Stroud et al., 2018), but co-exposed boys may be at greater risk of co-use themselves (De Genna et al., 2018). Future work should consider sex differences in both single and co-exposure effects on developmental outcomes, given the paucity of research on sex differences and the mixed results thus far (Coles et al., 2012; Willford et al., 2012).

This collection of papers includes recent findings from several intensive prospective cohort studies that include self-report data and biochemical verification of exposure to marijuana and tobacco. The samples were racially diverse and primarily urban and lower SES. The studies cover a range of decades and include rigorous observational measures of offspring outcomes across development. Most of the studies

included a wealth of potential confounders using multivariate analysis, which is important because prenatal tobacco and marijuana use are associated with many other risk factors for development. There were also limitations to the articles in this Special Issue that should be addressed in future research. Most parent studies in the Special Issue were designed to investigate effects of prenatal tobacco, and thus did not include a comparison group of marijuana-only users. Although most included very intensive data collection efforts, these studies were primarily based on regional samples and all but one recruited from urban settings. Several papers (Eiden et al., 2018; Godleski et al., 2018; Massey et al., 2018; Stroud et al., 2018) included analyses of data drawn from the same cohorts. Future research is needed to determine the prevalence of prenatal co-exposure across all three trimesters of pregnancy in a nationally representative sample that includes biomarkers of pregnancy use, and to replicate the effects described here in samples designed specifically to address co-exposures.

The papers in this Special Issue suggest etiological pathways to child outcomes that include teratogenic effects, as well as contextual effects from postnatal experiences. However, this complexity also creates challenges in disentangling multiple co-occurring risks. These clinical studies are also limited in the extent to which they can examine potential mechanisms explaining teratogenic effects. Animal models are invaluable in elucidating mechanisms of action while controlling for the numerous comorbid risks associated with maternal substance use in clinical studies. Studies using animal models have highlighted the role of nicotine as a teratogen (England et al., 2017; Slotkin, 2008), sex differences in the effect of prenatal nicotine exposure on nicotine self-administration (Pogun and Yararbas, 2009), and a complex pattern of sex differences in the effect of prenatal cannabis exposure on developmental outcomes (Bara et al., 2018; Willford et al., 2012). However, to our knowledge, there have been no animal studies of co-exposure effects. The papers in this Special Issue emphasize the importance of considering animal models that contrast exposure to both tobacco and marijuana with exposure to each substance alone. Future translational studies might include both human and animal components with parallel content to the extent possible, so that each may inform and enrich the other.

Unique findings from this Special Issue highlight the importance of explicitly investigating perinatal use of multiple substances in concert. Co-use of multiple substances in pregnancy (and in non-pregnant adults) is common; however, most studies focus on use or exposure to a single substance while controlling for other substances statistically or utilizing highly restricted samples that may not be generalizable. While single exposure studies are critical to determine the specific effects of any given substance, co-exposure studies like those described in this Special Issue offer the potential to (a) better generalize to understanding “real-world” patterns of substance use, (b) determine interactive effects of multiple exposures on offspring outcomes, (c) allow greater insight into mechanisms underlying effects of prenatal exposures on mothers and offspring, and (d) lead to improved and targeted education, prevention, and intervention efforts for pregnant women and their providers.

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