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Prenatal tobacco and marijuana co-use: Impact on newborn neurobehavior

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ABSTRACT

Tobacco and marijuana are some of the most common prenatal substance exposures worldwide. The social acceptability and political landscape of marijuana and its potency have changed dramatically in the last two decades leading to increased use by pregnant women. Despite evidence for increasing marijuana use and high rates of co-use of tobacco (TOB) and marijuana (MJ) during pregnancy, the impact of prenatal exposure to each substance is typically studied in isolation. We investigated the influence of co-exposure to TOB and MJ on infant neurobehavioral development over the first postnatal month. Participants were 111 mother-infant pairs from a low-income, diverse sample (Mean age = 25 ± 5; 54% minorities). TOB and MJ use were assessed by Timeline Followback interview with biochemical confirmation. Three groups were identified: (a) prenatal MJ + TOB, (b) prenatal TOB only, (c) controls. Newborn neurobehavior was assessed at seven time points over the first postnatal month using the NICU Network Neurobehavioral Scale. MJ + TOB-exposed infants showed decreased ability to self-soothe (Self-regulation) and attend to stimuli (Attention), and increased need for examiner soothing (Handling) and low motor activity (Lethargy) versus unexposed infants. Despite low levels of MJ use in MJ + TOB co-users, co-exposure was associated with nearly double the impact on infant self-soothing and need for examiner soothing versus TOB-exposure alone. Effects of MJ + TOB co-exposure appeared more pronounced for daughters than for sons. Although results are preliminary, they highlight additional risk from dual exposure to MJ + TOB vs. TOB exposure alone, particularly for daughters. Results also highlight the critical importance of investigating prenatal exposures in concert and the need for intervention efforts to address MJ co-use in pregnant TOB users.

1. Introduction

Maternal tobacco (TOB) use during pregnancy remains an enormous public health problem in the US and worldwide. Despite large-scale public education campaigns, approximately one of every ten infants in the US is born exposed to tobacco (Curtin and Matthews, 2016; Drake et al., 2018; Tong et al., 2013; U.S. Department of Health and Human Services, 2014). Infants born to less educated, poor, and underserved mothers show disproportionately higher rates of TOB exposure (up to ~2 in 10 infants born exposed) (Tong et al., 2013). As documented in the 2014 Surgeon General's Report, prenatal exposure to cigarette smoking is considered causally linked to increased risk for infant morbidity and mortality including low birth weight, preterm birth, and sudden infant death syndrome (U.S. Department of Health and Human Services, 2014). In older children and adolescents, suggestive associations were shown between prenatal TOB exposure and altered neurobehavioral development, including disruptive behaviors/conduct disorder, attention deficits/attention deficit hyperactivity disorder, and smoking/nicotine dependence (Gaysina et al., 2013; Huang et al., 2018; Ruisch et al., 2018; Shenassa et al., 2015; U.S. Department of Health

Abbreviations: TOB, tobacco; MJ, marijuana; THC, Δ^9-tetrahydro-cannabinol; BAM BAM, Behavior and Mood in Babies and Mothers study; NNNS, NICU Network Neurobehavioral Scale; ETS, environmental tobacco smoke; CO, carbon monoxide; SES, socioeconomic status

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and Human Services, 2014).

Maternal marijuana (MJ) use during pregnancy is also one of the most widespread prenatal drug insults in the US and the world (Center for Behavioral Health Statistics and Quality, 2015; World Health Organization, 2016). The social acceptability and political landscape of MJ have changed dramatically in the US in the last decade, accompanied by expanding legalization, decriminalization, and medicalization (Pew Research Center, 2015). Paralleling increased societal acceptance of MJ, rates of MJ use by pregnant women increased by 62% between 2002 and 2014, with current estimates of between 1 and 2 infants in every 20 born exposed, and increased rates in poor, young, and less-educated mothers (Brown et al., 2017; Ko et al., 2015; Substance Abuse and Mental Health Services, 2012; Substance Abuse and Mental Health Services Administration, 2014). Further, potency of Δ^9-tetrahydro-cannabinol (THC), the primary psychoactive ingredient in MJ, has increased 300% since 1995 (ElSohly et al., 2016; Mehmedic et al., 2010). The impact of prenatal MJ exposure on offspring development has received less research attention relative to tobacco. A recent meta-analysis found no effects of prenatal MJ exposure on preterm birth, but demonstrated a 77% increased risk for low birthweight in MJ-exposed infants (Gunn et al., 2016); however, it was not possible to rule out effects on low birthweight due to other substance exposures. Longer-term studies have revealed some evidence for associations between prenatal MJ and impairments in attention and inhibitory control, impulsivity and hyperactivity, and increased risk of MJ use in child, adolescent, and young adult offspring (Day et al., 2006; Day et al., 2011; Day et al., 1994; Fried, 2002; Goldschmidt et al., 2012; Smith et al., 2006; Smith et al., 2016).

Approximately 20 to 30% of pregnant women who use TOB endorse MJ co-use (Chabarria et al., 2016; Coleman-Cowger et al., 2017; Ko et al., 2015). Rates of TOB co-use among pregnant women who use MJ are even higher—approximately two-thirds to three-fourths of pregnant MJ users endorse TOB co-use (Chabarria et al., 2016; Coleman-Cowger et al., 2017; El Marroun et al., 2008; Ko et al., 2015). In non-pregnant populations, MJ + TOB co-use was associated with worse health outcomes, including increased risk of both MJ and TOB use disorders, poorer MJ and TOB cessation outcomes, increased psychiatric conditions, and increased respiratory dysfunction (Agrawal et al., 2012; Peters et al., 2012; Peters et al., 2014; Rabin and George, 2015). In pregnant women, MJ + TOB co-use was associated with increased maternal (e.g., asthma and pre-eclampsia) and neonatal health risks (preterm birth, decreased birthweight and head circumference), increased risk for maternal psychiatric and alcohol use disorders, increases in other drug and poly-tobacco use, and difficulty with TOB cessation (Chabarria et al., 2016; Coleman-Cowger et al., 2017; Emery et al., 2016; Gray et al., 2010).

The impact of MJ + TOB on fetal development may be mediated by THC/cannabinoids and nicotine. Nicotine and THC freely cross the placenta and enter fetal circulation (Little and Vanbeveren, 1996; Luck et al., 1985). In preclinical models, both prenatal nicotine and THC administration result in persistent alterations in neuronal development—nicotine via nicotinic acetylcholine receptors and disruption of brain cell replication and differentiation and THC via cannabinoid receptors and disruption of neuronal wiring (England et al., 2017a; Levin and Slotkin, 1998; Parsons and Hurd, 2015; Richardson et al., 2016). Both prenatal nicotine and THC also result in widespread disruption of neurotransmitter systems, including serotonergic, GABAergic, and dopaminergic systems (England et al., 2017a; Morena et al., 2016). Although to our knowledge, no preclinical models have investigated joint effects of prenatal nicotine and THC exposure, it is plausible that disruption of neuronal development via both nicotinic and endocannabinoid pathways may result in additive or synergistic effects of prenatal MJ + TOB on offspring neurobehavioral development.

Despite plausible neurobiological mechanisms and evidence for increased maternal and neonatal health risks from prenatal MJ + TOB exposure, few studies examined the impact of prenatal co-use on infant neurobehavioral development. Eiden et al. found that MJ + TOB co-exposure was associated with less adaptive autonomic regulation at nine months, which was then associated with diminished emotion regulation at 24 months (Eiden et al., 2018). Schuetze et al. investigated prenatal MJ + TOB co-exposure effects on infant reactivity and regulation in the context of maternal and fetal mediators (maternal stress, anger, fetal growth) (Schuetze et al., 2018). No direct effects were found; however, prenatal MJ + TOB exposure was associated with altered fetal growth, which was then associated with altered regulation and negative affect at 9 months. Finally, El Marroun et al. (2011) found effects of prenatal MJ exposure on offspring inattention and aggressive behavior in 18-month old infants, the majority of whom were also exposed to tobacco (El Marroun et al., 2011).

To our knowledge, no studies have explicitly examined the impact of prenatal MJ + TOB co-exposure on newborn neurobehavioral development over the first postnatal month despite the importance of this period for (1) establishment of parent-infant attachment, (2) documenting the earliest unfolding developmental pathways leading to long-term child behavioral outcomes, and (3) investigating the impact of prenatal exposures prior to long-term exposure to second-hand TOB/MJ smoke. Instead, effects of prenatal exposure to MJ or TOB on newborn neurodevelopment have typically been studied in isolation. Because the goal of many neurodevelopmental studies is to determine fetal neurotoxicity of a specific substance, typical studies include statistical control for co-exposures, but little systematic investigation of the potential additive/synergistic impact of co-exposures on offspring outcomes (Lester and Lagasse, 2010).

Multiple prior studies investigated effects of prenatal TOB alone on newborn neurobehavior. In the early newborn period, TOB-exposed infants have shown increased irritability, excitability, and need for external soothing versus unexposed infants (Godding et al., 2004; Law et al., 2003; Mansi et al., 2007; Stroud et al., 2009a). In the later newborn period and in studies investigating neurobehavior across the first postnatal month, TOB-exposed infants showed decreased ability to self-soothe (self-regulation), increased need for external soothing (need for handling), decreased attention to stimuli (attention/orientation), and alterations in motor activity (including increased lethargy and arousal) (Espy et al., 2011; Stroud et al., 2016; Stroud et al., 2009b; Yolton et al., 2009). A much smaller number of studies examined links between prenatal MJ and newborn neurobehavior. In a middle-class, low risk sample, exposure to prenatal MJ was associated with poorer habituation to visual stimuli, increased arousal, excitability, and irritability, and decreased ability to self-soothe in the early newborn period (Fried, 1980; Fried and Makin, 1987). These effects were corroborated by studies designed to investigate other perinatal risk factors (prenatal cocaine exposure, adolescent pregnancy) (Coles et al., 1992; de Moraes Barros et al., 2006; Lester et al., 2002), but were not replicated in a high risk MJ-exposed sample (Richardson et al., 1989) or in a study of MJ exposure in Jamaican infants (Hayes et al., 1988).

Sex-specific effects of both prenatal TOB and prenatal MJ on offspring neurobehavior have been reported in a small number of studies. In older offspring, there is some evidence that prenatal TOB exposure exerts a more pronounced impact on offspring behavioral dysregulation and disruptive behavior disorders in sons, whereas the impact of prenatal TOB exposure on offspring tobacco and other drug use/disorders (including cannabis, cocaine), was more pronounced in daughters (Brennan et al., 2002; Coles et al., 2012; Fergusson et al., 1998; Kandel et al., 1994; Stroud et al., 2014b; Weissman et al., 1999). Further, prenatal MJ exposure led to increased infant inattention and aggression at 18 months in daughters but not sons (El Marroun et al., 2011). Sex-specific effects of both prenatal THC and prenatal nicotine exposure were also documented in animal models (Bonnin et al., 1996; Cross et al., 2017).