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Additive drug-specific and sex-specific risks associated with co-use of marijuana and tobacco during pregnancy: Evidence from 3 recent developmental cohorts (2003–2015)

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ABSTRACT

Background: Methodologic challenges related to the concomitant use (co-use) of substances and changes in policy and potency of marijuana contribute to ongoing uncertainty about risks to fetal neurodevelopment associated with prenatal marijuana use. In this study, we examined two biomarkers of fetal neurodevelopmental risk—birth weight and length of gestation—associated with prenatal marijuana use, independent of tobacco (TOB), alcohol (ALC), other drug use (OTH), and socioeconomic risk (SES), in a pooled sample ($N = 1191$) derived from 3 recent developmental cohorts (2003–2015) with state-of-the-art substance use measures. We examined differential associations by infant sex, and multiplicative effects associated with co-use of MJ and TOB.
Methods: Participants were mother-infant dyads with complete data on all study variables derived from Growing Up Healthy ($n = 251$), Behavior and Mood in Babies and Mothers (Cohorts 1 and 2; $n = 315$), and the Early Growth and Development Study ($N = 625$). We estimated direct effects on birth weight and length of gestation associated with MJ, TOB, and co-use (MJ x TOB), using linear regression analysis in the full sample, and in male ($n = 654$) and female ($n = 537$) infants, separately.
Results: Mean birth weight and length of gestation were 3277 g ($SD = 543$) and 37.8 weeks (SD = 2.0), respectively. Rates of prenatal use were as follows: *any* use, $n = 748$ (62.8%); MJ use, $n = 273$ (22.9%); TOB use, $n = 608$ (51.0%); co-use of MJ and TOB, $n = 230$ (19.3%); ALC use, $n = 464$ (39.0%); and OTH use $n = 115$ (9.7%.) For all infants, unique effects on birth weight were observed for any MJ use [$B(SE) = -84.367(38.271)$, 95% C.I. −159.453 to −9.281, $p = .028$], any TOB use [$B(SE) = -0.99.416(34.418)$, 95% C.I. −166.942 to −31.889, $p = .004$], and each cigarette/day in mean TOB use [$B(SE) = -12.233(3.427)$, 95% C.I. −18.995 to −5.510, $p < .001$]. Additional effects of co-use on birth weight, beyond these drug-specific effects, were not supported. In analyses stratified by sex, while TOB use was associated with lower birth weight in both sexes, MJ use during pregnancy was associated with lower birth weight of *male* infants [$B(SE) = -153.1$ (54.20); 95% C.I.

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−259.5 to −46.7, $p = .005$], but not female infants [$B(SE) = 8.3(53.1)$, 95% C.I. −96.024 to 112.551, $p = .876$]. TOB, MJ, and their co-use were not associated with length of gestation.
Conclusions: In this sample, intrauterine co-exposure to MJ and TOB was associated with an estimated 18% reduction in birth weight not attributable to earlier delivery, exposure to ALC or OTH drugs, nor to maternal SES. We found evidence for greater susceptibility of male fetuses to any prenatal MJ exposure. Examination of dose-dependence in relationships found in this study, using continuous measures of exposure, is an important next step. Finally, we underscore the need to consider (a) the potential moderating influence of fetal sex on exposure-related neurodevelopmental risks; and (b) the importance of quantifying expressions of risk through subtle alterations, rather than dichotomous outcomes.

1. Introduction

Marijuana is the most commonly-reported illicit drug used by pregnant women in the United States (Berg et al., 2015; SAMHSA, 2013). Based on epidemiologic surveys, between 5% and 28% of the approximately 4 million infants born annually in the United States are born prenatally-exposed to marijuana (Ko et al., 2018). As intrauterine exposure to marijuana is not apparent at birth via a recognizable morphologic or physiologic syndrome, as is the case with alcohol (Clarren and Smith, 1978), and late term opioid exposure (Jansson and Velez, 2012), respectively, the nature and magnitude of impact on fetal development is an area of intense inquiry (Volkow et al., 2017).

Marijuana could adversely influence fetal development via several biological mechanisms (Grant et al., 2017; Richardson et al., 2016). A full third of THC consumed during pregnancy reaches the fetal circulation through the placenta (Hurd et al., 2005; Little and VanBeveren, 1996) and is met by cannabinoid receptors present in placental and fetal tissue, including the fetal brain, from early stages of embryonic development (Galve-Roperh et al., 2009; Park et al., 2003). Preclinical studies document alterations in normal patterns of fetal brain development (Jutras-Aswad et al., 2009), intrauterine growth, and early social and cognitive function of offspring prenatally exposed to marijuana, with early evidence for increased vulnerability in males (Bara et al., 2018; Benevenuto et al., 2017). Results from clinical studies are inconclusive, with confounding by concomitant use (or co-use) with tobacco and drugs as a major methodologic limitation of research to date (Huizink, 2014).

Separate from methodologic challenges, are recent changes in public perception, state policy, and apparent potency of marijuana in the United States (ElSohly et al., 2016; Warner et al., 2014). Critically, these changes occurred since the largest and most comprehensive teratologic investigations developed for this purpose were conducted (Day and Richardson, 1991; Jaddoe et al., 2012). While ramifications of these changes are yet to be fully appreciated, concern about greater prevalence and magnitude of prenatal exposures is warranted. Marijuana is perceived by many pregnant women as 'natural,' and relatively safe, and even preferable to prescription and over-the-counter remedies for nausea and hyperemesis (Oh et al., 2017). In the context of the resulting urgency to provide contemporary estimates of risk associated marijuana use during pregnancy, we conducted a secondary analysis using existing data from several recent well-described birth cohorts to overcome several critical methodologic barriers to knowledge.

1.1. Co-use of marijuana with tobacco, alcohol, and other drugs

Among the most challenging methodologic dilemmas in etiologic research on substance use disorders is the common practice of co-use. In the examination of any particular substance of abuse, failure to detect co-use by women who are categorized as *users* could inflate estimates of risk, while failure to detect substances used by women categorized as *non-users* could dilute between-group differences (Conner et al., 2016). Indeed, conflicting findings to date regarding the risk for preterm delivery of low birth weight infants following marijuana during pregnancy derived from the Ottawa Prenatal Prospective Study (Fried et al., 1998), the Maternal Health Practices and Child Development Study (MHPCD) (Day and Richardson, 1991), and the Generation R study (El Marroun et al., 2009) has been attributed to confounding by tobacco and other drugs (Huizink, 2014). Two comprehensive reviews and meta-analyses of these and other studies were similarly limited in their ability to adjust for co-use (Conner et al., 2016; English et al., 1997; Huizink, 2014).

The most recent and well-controlled meta-analysis to our knowledge which included 31 studies of prenatal marijuana exposure published through August of 2015 also concluded a lack of risk for preterm delivery and low birth weight infants associated with prenatal marijuana use once tobacco and maternal socioeconomic factors were controlled (Conner et al., 2016). However, most cohorts included in this meta-analysis were recruited prior to aforementioned policy and potency changes. Moreover, only four of reviewed studies assessed drugs other than tobacco, rendering between-sample harmonization of alcohol or other drug use during pregnancy impossible. Finally, only 5.9% of infants in the meta-analytic sample were prenatally exposed to marijuana; Conner et al. (2016) cautioned that analyses was severely underpowered to detect a statistically-significant effect, were it present. To provide risk estimates that capture recent changes in policy, perception, and potency of marijuana in the U.S., and are adequately powered to detect effects on birth outcome, we examined prenatal cohorts recruited domestically between 2003 and 2015 that were directly or indirectly oversampled for tobacco and other drug exposures.

1.2. Measurement quality

We addressed two additional limitations of research to date that have received less attention, the first of which concerns measurement quality. Measurement can have a robust influence on estimates—of prevalence, extent, and putative effects of—prenatal tobacco exposure (Estabrook et al., 2016; Gunn et al., 2016; Shisler et al., 2017) yet is highly variable. Measurement quality is typically highest in mechanism-focused cohort studies that are usually underpowered to stratify outcomes by substances, and very limited in survey-based reports of use in large epidemiologic cohorts. This dilemma could contribute to mixed findings and inaccurate estimates of effects. To illustrate, in an earlier study of over 1200 women, Zuckerman and colleagues found that prenatal marijuana use was independently associated with fetal growth restriction, but only when urine screens for THC were used, and *not* when exposure was measured by self-reports alone (Zuckerman et al., 1989).

Indeed, even with widespread legalization and increased social acceptance of marijuana (Berg et al., 2015), when studying pregnant women, non-disclosure of marijuana use (Chang et al., 2017), and also tobacco use (Pickett et al., 2005; Shisler et al., 2017), still constitute potential sources of error. Data used in the current study contained fine-grained interview-based multi-substance prenatal exposure measures collected in the context of multiple post-2000 mechanistic studies. These cohorts contained a substantially higher prevalence of exposure (s), (two were specifically oversampled for tobacco exposure) which enhanced our power to quantify substance-specific effects.