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Tobacco Exposure and Maternal Psychopathology: Impact on Toddler Problem Behavior

Stephanie A. Godleski,

Rochester Institute of Technology

Rina D. Eiden,

Research Institute of Addictions

Pamela Schuetze,

Buffalo State College

Craig Colder, and

University at Buffalo, The State University of New York

Marilyn Huestis

National Institute of Health

Abstract

Prenatal exposure to tobacco has consistently predicted later problem behavior for children. However, little is known about developmental mechanisms underlying this association. We examined a conceptual model for the association between prenatal tobacco exposure and child problem behavior in toddlerhood via indirect paths through fetal growth, maternal depression, and maternal aggressive disposition in early infancy and via maternal warmth and sensitivity and infant negative affect in later infancy. The sample consisted of 258 mother-child dyads recruited during pregnancy and assessed periodically at 2, 9, and 16 months of child age. Pathways via maternal depression and infant negative affect to toddler problem behavior were significant. Further, combined tobacco and marijuana exposure during pregnancy and reduced fetal growth also demonstrated important associations with infant negative affect and subsequent problem behavior. These results highlight the importance of considering the role of maternal negative affect and poor fetal growth as risk factors in the context of prenatal exposure.

Keywords

Prenatal tobacco exposure; prenatal marijuana/cannabis exposure; problem behavior; maternal psychopathology

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Cigarettes are the most commonly used substance during pregnancy (CDC, 2014; NSDUH, 2005), despite efforts directed at disseminating information regarding the negative impact of persistent smoking for the exposed child. Prenatal exposure to tobacco (PTE) poses risk for later developmental sequelae including inattention, oppositional behavior, emotional instability, and physical aggression in both early and later development (e.g., Ashford, Lier, Timmermans, Cuijpers, & Koot, 2008; Coles, Kable, & Lynch, 2012; Cornelius & Day, 2000; Day, Richardson, Goldschmidt, & Cornelius, 2000; Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002). There is robust evidence of this association between prenatal exposure to cigarette smoking and arousal dysregulation and problem behavior in children (for review see USDHHS, 2014). Despite consistent findings regarding the direct association between PTE and problem behavior, little is known about the mechanisms of this relationship. However, understanding this association could inform intervention and prevention efforts that reduce the negative impact of persistent behavioral problems. The pathway between PTE and later behavioral problems is likely influenced by both parental and child influences.

PTE and Behavior Problems

One pathway to risk for child problem behavior may be due specifically to PTE's teratological impact on the developing fetus (e.g., Estabrook et al., 2016). Prenatal exposure to maternal smoking restricts uterine blood flow to the fetus producing nutrient and oxygen deprivation (Coles et al., 2012; Suzuki, Minei, & Johnson, 1980), which can negatively impact the developing fetus both in regards to gestational growth as well as neural development (DiFranza, Aligne, & Weitzman, 2004). When examining the teratological impact of PTE, it is also important to consider the influence of marijuana exposure given the strong association between heavy tobacco and marijuana use (e.g., Gray et al., 2010), the increasing use of marijuana in recent years (SAMHSA, 2013), and considering the comorbidity of tobacco and marijuana use is relatively understudied with the exception of prospective research (e.g., Porath & Fried, 2005; Richardson, Day, & Goldschmidt, 1995). Together, tobacco and marijuana use during pregnancy have been found to be negatively associated with length, weight, and head circumference at birth (Day, Cornelius, Goldschmidt, Richardson, Robles, & Taylor, 1992; DiFranza et al., 2004; Knopik, Marceau, Palmer, Smith, & Heath, 2016). Reduced fetal growth parameters have also each been found to be associated with the later development of behavioral problems for children (Yang, Fombonne, & Kramer, 2011). Thus, one indirect mechanism explaining the association between PTE and behavior problems may be poor fetal growth.

In animal research, nicotine is a neuroteratogen irreversibly impacting the fetal nervous system development leading to neuronal damage, reducing cell number, and impairing synaptic activity and function (Slotkin, 1998). Given the impact of nicotine on neurons that control arousal and attention such as neurons in the pedunculopontine nucleus (Mamiya, Buchanan, Wallace, Skinner, & Garcia-Rill, 2005), these teratogenic effects are then directly

implicated in the atypical development of attention and arousal systems which are associated with many externalizing behavior problems. For example, PTE is associated with neurotoxic effects as early as the newborn period, such as being more highly aroused, reactive, and hypertonic (Law et al., 2003). Higher levels of infant negative affect, often conceptualized as both negative arousal (e.g., fear, sadness) as well as disruptions in arousal modulation (Garstein & Rothbart, 2003), is associated with higher behavioral problems among children (Shields & Cicchetti, 1998). Indeed, intense negative emotional reactivity and low behavioral regulation (e.g., distraction, self-soothing) are consistently theoretically and empirically implicated as specific predictors of problem behavior (Eisenberg & Fabes, 1992; Eisenberg, Fabes, Guthrie, & Reiser, 2000; Loeber & Hay, 1997), particularly for boys (Coles et al., 2012). Therefore, it is important to consider not only the direct PTE teratological influence, but also the indirect pathways that this influence may have via fetal growth and child affect and arousal.

Maternal Smoking, Psychopathology, and Parenting

In addition to this potential teratogenic effect, associated familial and contextual factors may also play a role in the development of problem behavior (Ellingson, Goodnight, Van Hulle, Waldman, & D'Onofrio, 2014; Knopik, 2009; Massey & Compton, 2013; Palmer, Bidwell, Heath, Brick, Madden, & Knopik, 2016). For instance, mothers who smoke during pregnancy are often younger, single parents (Ellingson, Rickert, Lichtenstein, Langstrom, & D'Onofrio, 2012) who are of lower income with less education (Cornelius, Leech, & Goldschmidt, 2004). Mothers who smoke during pregnancy also express higher levels of psychopathology, including higher anger, hostility, and aggression, compared to non-smoking mothers (Eiden et al., 2011). Cigarette smoking during pregnancy is associated with other aspects of socio-emotional maladjustment, including depression and stress (Knopik, 2009; Ludman et al., 2000). Maternal depression has been demonstrated to be a robust predictor of child behavior problems in past research (Beck, 1999; for review see Goodman, Rouse, Connell, Broth, Hall, & Heyward, 2011), as depressed mothers may be less effective at parenting (e.g., provide little positive reinforcement), model negative affect, and have lower quality or disengaged relationships with their children (Gelfand & Teti, 1990; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). The relation between maternal depression and child behavior problems is especially strong in the context of lower socio-economic status (Goodman et al., 2011), which is often the case for mothers who smoke during pregnancy (Cornelius et al., 2004). Mothers who smoked cigarettes during pregnancy and their children may be an especially at-risk population for the development of child problem behavior given associated familial factors (e.g., D'Onofrio et al., 2012) as these mothers may be modeling less effective behavioral and coping strategies (Pickett, Wilkinson, & Wakschlag, 2009).

Further, mothers may be influencing their child through their parenting practices. Taken together, both maternal psychopathology and maternal smoking are associated with lower maternal warmth and sensitivity in the parent-child relationship. More specifically, maternal smoking during pregnancy is associated with negative parenting practices (Wakschlag et al., 2002), such as conflictual parent-child relationships (Brook, Brook, & Whiteman, 2000) and harsh discipline (Tandon et al., 2013). Mothers who smoke have been found to be less

nurturing (Fergusson, Woodward, & Horwood, 1998), and had higher levels of insensitivity and lower levels of warmth (Schuetze, Eiden, & Dombkowski, 2006). Importantly, harsh parenting practices and negative parent-child interactions are well-established in the literature as predictive of poor behavioral outcomes for children, such as self-regulation (Eiden, Schuetze, & Coles, 2011) as well as aggression (e.g., Dodge, Coie, & Lynam, 2006; Loeber & Hay, 1997). High affective attunement and warmth/sensitivity may be protective and predict lower levels of dysregulation and aggression (Wakschlag & Hans, 2002). Therefore, for children already at risk due to PTE, modeling, poor parenting, and negative parent-child interactions may create a context that increases the risk for problem behavior.

Sex Differences

In studies of PTE and the development of behavior problems that include the investigation of child sex, the relation is often more robust for males (for review see Coles et al., 2012). However, sex difference results are not consistent and vary depending on the specific outcome, study design, and sample assessed. Therefore, the current study sought to examine potential sex differences in the prediction of problem behavior during toddlerhood.

Present Study

We examined a conceptual model for development of early problem behavior among tobacco-exposed and demographically similar non-exposed children that included the role of both maternal and infant influences. In addition to examining potential direct effects of PTE on problem behavior at 16 months, we examined indirect or mediational pathways linking maternal tobacco and marijuana use to children's problem behavior, including indirect paths through maternal depression and aggressive disposition in early infancy and via maternal warmth and sensitivity and infant negative affect in later infancy. The role of fetal growth as a significant mediator of problem behavior risk also was considered. Finally, we examined if the association between PTE and problem behavior was stronger for boys compared to girls.

Methods

Participants

Sample Selection.—Pregnant women who presented for prenatal care at a large city hospital were asked to complete a self-report screening form at their first prenatal appointment. Women who met initial eligibility criteria were invited to participate in an ongoing prospective study of maternal health and child development. Eligibility criteria included maternal age over 18 years, that women were between 12 and 20 weeks gestation, and to rule out the effects of other substances: no illicit drug use other than cannabis and no heavy alcohol or cannabis consumption (i.e., no chronic or binge use so less than 1 drink or 1 joint per day or less than 4 drinks or 4 joints on a single occasion after pregnancy recognition). At the end of each month, the closest matching non-smoking women to the group of smokers enrolled that month were recruited into the study based on maternal age and education. Smokers were oversampled so that a full range of light to heavy smokers were included in order to be able to examine potential dose response relationships.

Participants.—The sample consisted of 258 mother-infant dyads with 181 (99 boys and 82 girls) exposed to tobacco and 77 non-exposed (35 boys and 42 girls) recruited prenatally. Mothers ranged in age from 18 to 39 ($M = 24.01$, $SD = 4.96$) at the first appointment. The women in the sample were 52% African-American, 30% Caucasian, 18% Hispanic (i.e., of the 18%, 8% Hispanic White, 11% Hispanic Black, and 81% only identifying race/ethnicity as Hispanic), and 8% other or mixed race, with several identifying as more than one race. Forty-five percent of the expectant mothers were married or living with their partner, 33% were in a relationship, but not living with their partner, 21% were single, and 1% were divorced. Twenty-nine percent of women had less than a high school education, 29% completed high school, 29% completed some college, 9% had a vocational/technical or associates degree, and 4% had a bachelor's degree. The sample may overall be characterized as primarily low-income, minority women with high school or below education, with 1 to 2 children.

Measures

Prenatal Exposure.—Maternal cigarette and marijuana use during pregnancy was assessed using a combination of maternal self-report, maternal saliva samples collected at each trimester of pregnancy, and infant meconium. Mothers were assigned to the smoking group if they acknowledged smoking during pregnancy, if saliva samples were positive for cotinine at or above 10ng/mL, or if infant meconium was positive for cotinine, nicotine, or *trans-3'* hydroxycotinine (OHCOT). Saliva samples were assayed for cotinine using liquid chromatography - tandem mass spectrometry (LC-MSMS) for majority of cases (with the exception of the first 32 women recruited into the study who had trimester 1 saliva samples assayed using ELISA at 10 ng/mL). Meconium samples were assayed with a validated LC-MSMS method (Gray et al., 2010) at 2.5 ng/g nicotine, 1 ng/g cotinine, and 5 ng/g OHCOT. Group differences across substance exposure assessment methodologies were examined. For the purposes of this study, analyses were based on meconium testing positive for tobacco and/or marijuana following results from preliminary analyses (see results).

Maternal Aggressive Disposition.—Maternal aggressive disposition was assessed using the Buss-Perry Aggression Questionnaire (Buss & Perry, 1992) during the third trimester of pregnancy and at 2 months of infant age. The AGQ is a 29 item self-report measure of adult aggression, anger, and hostility where participating parents ranked statements, such as “I can't help getting into arguments when people disagree with me,” on a scale from 1 = extremely uncharacteristic of me to 2 = extremely characteristic of me. The subscales (Verbal Aggression, Physical Aggression, Hostility, and Anger) were summed into a composite measure of general aggressive disposition. One item was missing at both time points, resulting in a measure with 28 items instead of 29 items. This composite scale was internally consistent in the present sample (Cronbach's $\alpha = .92$ in 3rd Trimester and at 2 months of child age).

Maternal Depression.—Maternal depression was assessed with the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996). Mothers rated 21 statements (e.g., loss of pleasure) on the extent to which they had been experiencing that symptom for the last two weeks (0 = I get as much pleasure as I ever did from the things I enjoy, 1 = I don't enjoy

things as much as I used to, 2 = I get very little pleasure from the things I used to enjoy, 3 = I can't get any pleasure from the things I used to enjoy). Maternal depression was measured during the third trimester of pregnancy and at 2 months of child age. This composite scale demonstrated acceptable internal consistency (Cronbach's $\alpha = .86$ in 3rd Trimester and $\alpha = .88$ at 2 months of child age).

Fetal Growth.—Head circumference, birth weight, birth length, and gestational age were used as measured indicators of the latent construct reflecting fetal growth. The obstetrical nurses in the delivery room recorded the three growth measures: birth weight (g), birth length (cm), and head circumference (cm). The Obstetrical Complications Scale (OCS; Littman & Parmelee, 1978), a scale designed to assess perinatal risk factors experienced by the infant, was completed by medical chart review after delivery. Higher numbers on this scale indicate lower obstetrical risk. Gestational age was calculated by dates and extracted from medical records.

Maternal Warmth and Sensitivity.—Maternal warmth and sensitivity towards their infant was assessed during free play observations at 9 months of child age. Mothers were asked to interact with their infants as they normally would at home for 10 minutes in a room filled with toys. These interactions were videotaped and coded using a collection of global 5-point rating scales called the *Parent-Child Early Relational Assessment* (Clark, 1999). A composite maternal warmth/sensitivity scale was created based on observed maternal warmth and sensitivity, such as a parent's enjoyment and pleasure in interacting with their infant, positive affect, and sensitivity to their child's state (Clark, 1999). The internal consistency for the maternal warmth/sensitivity scale was Cronbach's $\alpha = .95$. Two coders rated the play interactions. Both coders were trained by the second author until inter-rater reliability criterion was reached (exact agreement or within 1 scale point for each item on the composite). Subsequently inter-rater reliability was established on 13% of tapes. Inter-rater reliability for maternal warmth/sensitivity was high, intraclass correlation = .90.

Infant Negative Affect.—Infant negative affect at child age of 9 months was measured using mother-report on the Revised Infant Behavior Questionnaire (R-IBQ; Gartstein & Rothbart, 2003). Infant negative affectivity was comprised of the mean of the Activity Level (i.e., gross motor activity), Sadness (i.e., lower mood), Falling Reactivity (i.e., rate of recovery from arousal), Distress to Limits (i.e., distress when confined or unable to perform desired activity), and Fear scales (i.e., startle or distress to stimulation or novelty). Items, such as "When in the presence of several unfamiliar adults, how often did the baby cry?," were rated on a 7 point scale from Never (1) to Always on infant behavior (7). This composite scale demonstrated acceptable internal consistency (Cronbach's $\alpha = .72$).

Toddler Problem Behavior.—Toddler problem behavior was assessed at 16 months of child age using mother report on the Brief Infant Toddler Social Emotional Assessment (BITSEA; Briggs-Gowan & Carter, 2008). The BITSEA is a 42 item measure that assesses social-emotional and behavioral problems and/or delays and social-emotional competence on a scale from 0 = Not True/Rarely to 2 = Very True/Often. The 31 item problem behavior

scale (e.g., “Hits, shoves, kicks, or bites children” and “Has trouble falling asleep or staying asleep”) showed adequate internal consistency (Cronbach’s $\alpha = .83$).

Procedure

Informed written consent was obtained from interested, eligible women at their first laboratory visit in the first trimester of pregnancy. Prenatal assessments were conducted once in each trimester of pregnancy, and at 2, 9, and 16 months of child ages at age corrected for prematurity. Data from prenatal interviews during the third trimester, from maternal interviews conducted at the 2, 9, and 16 month visits, and the free play observation conducted at the 9-month visit were included in these analyses.

The study protocol was approved by the Children and Youth Institutional Review Board at the State University of New York. Participants were informed that data confidentiality was protected by a Federal Certificate of Confidentiality issued by the National Institute on Drug Abuse. Participants received compensation for their time at all visits.

Analytic Strategy

We first examined associations between the different prenatal substance exposure variables and the mediator and outcome variables in the model using Pearson correlations or ANOVAs as appropriate. These included the smoking group status variable that was a combination of all PTE indices, the marijuana group status variable that was a combination of all indices of marijuana exposure, the fetal exposure variables of meconium positive for tobacco and marijuana, the dose response variables of the average number of cigarettes and marijuana per day and the continuous nano moles per gram of total nicotine markers in meconium, and the timing of exposure variables of the average number of cigarettes and marijuana joints per day in each trimester of pregnancy. Analyses of potential confounds were conducted next using correlations or ANOVAs as appropriate. Examination of the direct relation between prenatal variables and child problem behavior was then conducted, as well as investigation of potential sex differences in this direct relation using correlations, ANOVA, and structural equations modeling (SEM) as appropriate. SEM was also used to test the hypothesized model with fetal growth, maternal aggressive disposition, and maternal depression in early infancy as well as maternal warmth and sensitivity and infant negative affect in late infancy as intervening variables between prenatal variables and toddler problem behavior at 16 months. A composite variable for fetal growth was used instead of latent variable to simplify the model given concerns about model complexity. SEM analyses were conducted using Amos (Arbuckle, 2006) and Mplus, Version 7 software (Muthen & Muthen, 1998–2012) using full-information maximum likelihood estimation procedures (Arbuckle, 1996) with standard errors and chi-square statistic that are robust to non-normality and can be estimated with missing data (MLR). Indirect effects were tested using the bias-corrected bootstrap method. This method has been found to provide a more accurate balance between Type 1 and Type 2 errors compared with other methods used to test indirect effects (MacKinnon, Lockwood, & Williams, 2004). Five thousand bootstrap samples and the 95% bias-corrected confidence intervals (CIs) were used to test significance of indirect effects.

Results

Consideration of Exposure Assessment, Covariates, and Descriptive Data

The first goal was to examine potential dose response, timing, and fetal exposure associations with the hypothesized mediators and infant outcomes using correlations or ANOVAs (with tobacco/marijuana group status based on all indices and meconium positive vs. negative for tobacco or marijuana). There were no direct associations between any of the tobacco or marijuana variables and toddler problem behavior ($p > .05$). However, higher reported maternal tobacco and marijuana use (average across pregnancy and per trimester) were associated with higher prenatal and postnatal aggressive disposition, with correlations ranging from $r = .14$ to $r = .23$, $p < .05$. Higher average number of cigarettes per day during pregnancy and in each trimester was also associated with higher maternal depression both prenatally ($r = .14$, $p < .05$) and postnatally ($r = .14$, $p < .05$). All fetal growth variables were negatively correlated with positive meconium for marijuana and nicotine (r s ranging from $-.15$ to $-.35$, $p < .05$). In examination of differences based on smoking and marijuana groups using a composite of all exposure indices (maternal saliva, self-reports, meconium) using ANOVAs, there were significant differences on head circumference and birth weight ($p < .05$) such that exposed groups had reduced head circumference and birth weight.

Given the importance of nicotine and marijuana metabolites in meconium as reflecting fetal exposure to maternal substance use, ANOVAs based on meconium group status (i.e., negative for both marijuana and tobacco, positive for tobacco only, and positive for both marijuana and tobacco) indicated significant differences in all fetal growth variables such that children positive for both marijuana and tobacco had lower head circumference, gestational age, birth weight, and birth length than infants that were negative for both substances (see Table 1). Infants exposed to tobacco only were also lower on head circumference than those infants not exposed to either tobacco or marijuana prenatally. Mothers in the positive for tobacco and marijuana group reported higher levels of prenatal aggressive disposition and mothers in the tobacco only group reported higher levels of depression during their child's early infancy visit (see Table 2). Exposure to tobacco and marijuana for subsequent analyses was based on infant meconium group status as associations were consistent between exposure and potential mediators. Further, meconium may provide a more accurate indication of the infant's level of exposure. Given that the exposure groups did not differ on any basic demographic information (e.g., maternal age, education), these variables were not included in model testing.

Correlations among mediator and outcome variables included in model testing are presented in Table 3. Of note, reported toddler problem behavior at 16 months was significantly positively associated with maternal prenatal and postnatal depression, maternal aggressive disposition postnatally, and infant negative affect in late infancy.

PTE Direct Effect on Problem Behavior

As noted in Table 2 and 3, there were no direct associations between PTE with or without marijuana exposure and child problem behavior, and exploration of group differences on prenatal exposure also yielded no significant differences. Gender differences were examined

next. In the overall sample, there was a marginal gender difference on problem behavior at 16 months ($F(1)=3.27, p=.07$), such that boys had slightly higher levels of problem behavior (Males $M=13.28, SD=7.33$; Females $M=11.55, SD=6.15$). Given this marginal difference, child gender was not included as a covariate in the overall model.

Model Testing

Structural Equations Modeling (SEM) was used to test the mediational model (see Figure 1). Goodness of fit indices indicated that this hypothesized model fit the data well, $\chi^2(51) = 70.62, p = .04, CFI = .98, RMSEA = .04, 95\% CI [.01, .06]$. Results indicated that many of the prenatal variables were associated with each other and that the combination of prenatal tobacco and marijuana exposure (dummy coded from the 3 level meconium variable) was associated with decreased fetal growth, as measured by head circumference, gestational age, birth weight, and birth length. PTE only (dummy coded from the 3 level meconium variable) tended to be associated with decreased fetal growth and was significantly associated with maternal aggressive disposition in early infancy. There were no direct associations between prenatal exposure and infant negative affect or child problem behavior. PTE was prospectively predictive of change in maternal aggressive disposition from pregnancy to the postnatal period in early infancy; and postnatal maternal aggressive disposition at early infancy was predictive of lower maternal warmth and sensitivity in later infancy. Maternal depression during early infancy was directly associated with toddler problem behavior and was associated with infant negative affect during late infancy. Infant negative affect during late infancy was then significantly associated with toddler problem behavior. Lower fetal growth was significantly predictive of greater infant negative affect and higher levels of fetal growth tended to be predictive of higher levels of maternal warmth and sensitivity. Together, prenatal exposure, maternal aggressive disposition and depression, fetal growth, maternal warmth sensitivity, and child negative affect accounted for 20% of the variance for child problem behavior in toddlerhood.

The initial model included a directional pathway from maternal depression in early infancy to maternal warmth and sensitivity in later infancy. However, there was no association between these variables at the bivariate level and inclusion of this path in the model resulted in a significant positive association indicating a suppressor effect. Thus, this path was not included in the final model. Interestingly, higher maternal aggressive disposition in early infancy was associated with lower maternal warmth and sensitivity during mother-infant interactions in later infancy. However, observed maternal warmth and sensitivity during play interactions in infancy was not associated with maternal reports of problem behavior.

Indirect effects and the pattern of path coefficients provided support for potential indirect pathways from prenatal exposure and toddler problem behavior via fetal growth, maternal psychopathology, maternal warmth and sensitivity, and infant negative affect. The indirect association between maternal depression during pregnancy and toddler problem behavior via maternal depression in early infancy and infant negative affect was significant, $\beta = .03, 95\% CI [.01, .05]$. The indirect association between combined marijuana and tobacco exposure and problem behavior via fetal growth and infant negative affect was not significant, $\beta = .01, 95\% CI [-.002, .03]$.

Moderation by Sex.

Multiple group models examining if the direct association between prenatal variables and problem behavior was different for boys and girls were explored. For females, only prenatal maternal depression was predictive of problem behavior ($\beta = .23, p = .03$). For males, both the direct paths from PTE ($\beta = .22, p = .04$) and prenatal maternal depression ($\beta = .30, p = .01$) were significantly predictive of problem behavior. Despite potential evidence of gender differences in the impact of prenatal risk on problem behavior, gender was not included as a moderator in the subsequent models given the inconsistency of these findings and insufficient power to investigate moderated mediation.

Discussion

The purpose of the present study was to examine if there were direct or indirect associations between PTE and toddler problem behavior at 16 months. Our results indicated no significant direct associations between tobacco exposure or combined tobacco and marijuana exposure and problem behavior in toddlerhood for the full sample. This finding is contrary to past research that has demonstrated direct relations between PTE and the later development of child problem behavior (e.g., Ashford et al., 2008; Coles et al., 2012; Cornelius & Day, 2000; Day et al., 2000; Hutchinson, Pickett, Green, & Wakschlag, 2009; Wakschlag et al., 2002). However, the majority of this research was conducted with children preschool aged and above, whereas the present study assessed problem behavior during an earlier developmental period that may account for the lack of direct relationship. Several studies have found the direct link between PTE and problem behavior as early as three years old (Dolan et al., 2016; Hutchinson et al., 2009). The association between PTE and problem behavior may manifest when the key developmental tasks required of children may increase their interactions with peers, such as in early childhood, or make their attentional and regulation deficits more apparent, such as during middle childhood.

Past research has demonstrated a greater risk for boys prenatally exposed to tobacco to develop later problem behavior (e.g., Hutchinson et al., 2009; for review see Coles et al., 2012). Consistent with this work, there was some evidence for a potential direct effect from PTE to toddler problem behavior for boys. Although significant in models exploring the direct effect between prenatal variables and toddler problem behavior for boys, this effect was marginal in exploring group mean differences between boys and girls. Future research should continue to explore possible differences in risk for boys and girls within this context.

Indirect Pathways to Problem Behavior from Early Risk

Several potential indirect pathways between PTE and problem behavior were examined. To begin, poor fetal growth was hypothesized as a potential indirect path as tobacco and marijuana use during pregnancy are associated with lower fetal growth (Day et al., 1992; DiFranza et al., 2004) and poor fetal growth has subsequently been associated with behavior problems (Yang et al., 2011). In the present study and consistent with hypotheses, reduced fetal growth was significantly associated with the combination of marijuana and tobacco exposure. This may be because there are synergistic effects when prenatal tobacco and marijuana exposure are combined and that those who used both were more likely to be

heavier smokers in this sample. Poor fetal growth was then predictive of higher levels of infant negative affect that was subsequently associated with toddler problem behavior. However, the indirect pathway was not significant. The current findings still suggest the importance of considering poor fetal growth as a risk factor in the context of tobacco and marijuana exposure for disrupted infant affect and arousal and potentially for the development of later social-emotional difficulties.

The influence of maternal psychopathology and parenting as a possible indirect pathway between early risk and problem behavior was also examined. Past research has demonstrated that mothers who smoke during pregnancy use less effective parenting strategies (Wakschlag et al., 2002), are less warm and sensitive towards their children (Schuetze et al., 2006), and have higher levels of social-emotional maladjustment (Ludman et al., 2000); each of which have been demonstrated in past research to be associated with the development of problem behavior for children. In the present study and consistent with past research on PTE, combined exposure to marijuana and tobacco was associated concurrently with higher levels of maternal aggressive disposition and tobacco exposure was associated with increased levels of post-natal maternal aggressive disposition (Eiden et al., 2011). Interestingly, maternal depression during pregnancy was predictive of increased depressive symptomatology during the post-natal period in early infancy. Post-natal depression was also significantly associated with both higher levels infant negative affect and toddler problem behavior. Further, the indirect pathway between maternal depression during pregnancy and toddler problem behavior via maternal depression in early infancy and infant negative affect in later infancy was significant. This is consistent with past research on the association between maternal depression and child behavior problems (Beck, 1999). Importantly, mothers with children exposed to higher levels of tobacco reported significantly higher levels of depression during their child's early infancy. Further, the mothers who smoke during their pregnancies are on average of lower income status and have less education (Cornelius, Leech, & Goldschmidt, 2004). As such, mothers who persistently smoke during their pregnancies may be in a context of high risk, increasing the possibility for higher levels of depression and subsequent negative affective and behavioral consequences for their children. These results highlight the importance of considering the role of maternal negative affect or psychopathology in studies of PTE. These aspects of maternal behavior may also be important targets of intervention, resulting in lower risks for infants by potentially lowering smoking during pregnancy as well as by promoting higher maternal warmth/sensitivity and lowering post-partum negative affect.

Limitations and Future Research

This study presents many strengths, such as a diverse and at risk sample, investigating PTE while considering comorbid marijuana use during pregnancy, as well as considering important indirect pathways to risk and resilience via maternal and child influences. However, the study is not without its limitations. To begin, accurate substance use data can be difficult to obtain as mothers may be reticent to provide such information; however, in order to address this potential concern the present study employed a variety of methods in order to determine exposure during the prenatal period. In order to take into account the fluctuations in a woman's smoking throughout pregnancy (e.g., Pickett, Wakschlag, Dai, &

Leventhal, 2003) and address the potential limitation of categorizing women as smokers vs. non-smokers, future research should assess these smoking patterns and the impact that subsequent dose and timing differences may have on child outcomes (e.g., Estabrook et al., 2016; Hutchinson et al., 2009). Incorporating additional familial and maternal characteristics in models investigating the connection between PTE and problem behavior (e.g., genetic risk, maternal personality traits, and maternal fetal attachment; Knopik, 2009; Massey et al., 2015; 2016) is another important area for future work. As discussed, the toddler period may also be early to investigate the full impact of PTE on problem behavior. Therefore, future research could examine later developmental periods, such as early and middle childhood when problem behavior may be more likely to manifest or be noticeable as developmentally atypical. In addition, the present study was insufficiently powered to investigate the role of gender moderation. Future research should consider the influence of child gender on the development of problem behavior in this population given that past research has demonstrated greater risk for boys exposed prenatally to tobacco to develop problem behavior (see Coles et al., 2012). Future research should also investigate additional informants or observations of infant negative affect to reduce concerns about shared method variance and given that a mother's depression may affect her perception of her infant (e.g., Gartstein, Bridgett, Dishion, & Kaufman, 2009). Finally, the present study added important information regarding concurrent marijuana and tobacco use during pregnancy and indicated heightened risk in the context of using both substances for both mothers and children that warrants replication. Further, given increasing levels of marijuana use nationally (SAMSHA, 2013) and greater legalization of the use of marijuana, continued research of comorbid use will be critical.

Implications and Conclusions

In conclusion, the results of the present study highlighted the important roles of maternal psychological symptoms, poor fetal growth, and infant negative temperament as potential mechanisms linking early risk to problem behavior in the toddler years. In addition to prevention of substance use during pregnancy, intervention and prevention efforts targeted at reducing maternal depression and fostering more positive infant affect during infancy may be particularly important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Structural Equations Model for PTE and Toddler Problem Behavior

Note: Non-significant paths and residuals are not depicted in the model for ease of presentation. The numbers are standardized path coefficients. Solid lines indicate paths that are $p < .05$ and dotted lines indicate paths that are $p < .10$.

Table 1.

Sample Demographics

Exposure Group	Non-Smoking		Tobacco Only		Marijuana & Tobacco		F value	Partial η^2
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>		
Demographics:								
BM age	24.32	5.13	24.56	5.29	25.73	5.47	0.96	.01
BM parity	2.14	1.49	2.35	1.65	2.57	2.13	0.90	.01
Years education	12.59	1.85	11.92	1.79	12.16	1.92	2.48	.03
Occupational status	2.16	1.76	1.98	1.49	1.86	1.42	0.50	.01
Average cigarettes per day during pregnancy	0.57	1.15	5.75	4.95	6.35	5.50	46.18***	.33
Average joints per day during pregnancy	0.01	0.05	0.13	0.36	0.82	0.88	44.54***	.33
Fetal Growth:								
Gestational age (weeks)	39.08	1.37	38.74	1.48	38.58	1.89	4.26*	.07
Birth weight (gms)	3376.47	435.28	3183.09	534.14	2939.63	417.69	7.71**	.11
Birth length (cm)	50.61	1.78	50.02	2.42	49.31	2.49	3.26*	.05
Head circumference (cm)	34.44	1.63	33.45	1.81	32.99	1.32	8.32***	.12
OCS	88.25	12.94	84.24	14.16	83.54	13.71	2.36	.03

Note. BM: biological mother; OCS: Obstetrical complications scale score, high scores are more optimal. Occupational status was coded using Hollingshead (1957, 1975) scoring system.

*
 $p < .05$

**
 $p < .01$

***
 $p < .001$

Table 2.

Group Differences in Maternal and Child Variables

Exposure Group	Non-Smoking		Tobacco Only		Marijuana & Tobacco		F value	Partial η^2
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>		
Maternal Variables:								
Depression 3 rd tri	14.10	6.50	16.30	9.27	15.79	7.42	1.11	.02
Agg Disposition 3 rd tri	2.58	0.74	2.75	0.69	3.10	0.69	4.45 *	.07
Depression 2 mos	9.25	7.88	13.23	7.86	8.92	5.44	4.23 *	.06
Agg Disposition 2 mos	2.36	0.65	2.59	0.75	2.75	0.78	2.87	.05
Warmth/Sensitivity 9 mos	4.08	0.66	4.17	0.48	3.84	0.70	2.25	.04
Child Variables:								
Negative affect 9 mos	3.96	0.50	3.98	0.67	3.84	0.70	0.11	.00
Problem Behavior	11.51	5.36	13.91	7.75	9.42	5.78	4.10	.06

* Note. $p < .05$

Tri = Trimester; Agg = Aggressive; Mos = months.

Table 3.

Correlations among mediator and outcome variables

	1	2	3	4	5	6	7	8	9	10	11
1. Mat. Depression 3 rd tri	X										
2. Mat. Agg Disposition 3 rd tri	.44**	X									
3. Head circumference (cm)	-.02	-.04	X								
4. Gestational age (wks)	.00	-.03	.47**	X							
5. Birthweight (g)	-.13	-.17**	.63**	.56**	X						
6. Birth length (cm)	-.02	-.05	.64**	.44**	.67**	X					
7. Mat. Depression 2 mos	.54**	.31**	-.03	-.03	-.08	-.01	X				
8. Mat. Agg Disposition 2 mos	.36**	.65**	-.06	-.04	-.10	-.04	.36**	X			
9. Mat. Warmth/Sensitivity 9 mos	-.09	-.20**	.17*	.07	.10	.13	.03	-.22**	X		
10. Infant Negative affect 9 mos	.20**	.05	-.12	-.04	-.08	-.17*	.17*	.02	-.11	X	
11. Problem Behavior 16 mos	.29***	.16*	.06	-.01	-.01	-.09	.26***	.21**	-.13	.29***	X

* Note . . $p < .05$

** $p < .01$

*** $p < .001$

Tri = Trimester; Mat = Maternal; Agg = Aggressive; Mos = months; 2 months of child age = Early Infancy; 9 months of child age = Late Infancy; 16 months of child age = Toddlerhood.