Early Human Development 148 (2020) 105119

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Self-regulation and emotional reactivity in infants with prenatal exposure to opioids and alcohol

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A B S T R A C T

Background: Infants with prenatal substance exposure are at increased risk for developmental problems, with self-regulatory challenges being some of the most pronounced. The current study aimed to investigate the extent to which prenatal substance exposure (alcohol, opioids) impacts infant self-regulation during a relational stressor and the association between self-regulation and infant affect.

Methods: Participants were 100 mother-child dyads recruited prenatally (Mean = 23.8 gestational weeks) and completed the Still Face Paradigm (SFP) when infants were 5 to 8 months of age (Mean = 6.9 months) as part of an ENRICH prospective birth cohort study. Based on prospective repeated assessment of maternal substance use in pregnancy, infants were grouped into: 1) Unexposed controls; 2) Alcohol-exposed; 3) Opioid-exposed due to maternal use of medications for opioid use disorder (MOUD) with or without other opioids; 4) MOUD and alcohol. Infant stress reactivity (negative affect) and self-regulation were assessed during the validated 5-episode SFP. Mixed effects linear models were used to analyze differences in the percent of self-regulation and percent of negative affect among the study groups across SFP episodes, as well as the group-by-self-regulation interaction with respect to infant negative affect.

Results: The MOUD + Alcohol group demonstrated significantly lower self-regulation at baseline compared to controls ($p < 0.05$). There was a significant group-by-self-regulation interaction ($p = 0.028$). Higher self-regulation was associated with lower negative affect across SFP episodes in the MOUD + Alcohol group ($p = 0.025$) but not other groups.

Conclusion: Self-regulation skills are particularly important for emotional modulation in infants with prenatal polysubstance exposure, highlighting the development of these skills as a promising intervention target.

1. Introduction

Substance use during pregnancy remains an ongoing public health concern. Despite the well-documented teratogenic effects of prenatal alcohol exposure (PAE), approximately 10–15% of women in the U.S. report alcohol use during pregnancy [1–3]. Given the unfolding opioid crisis in the U.S, opioid use during pregnancy has substantially increased with estimates of more than 30% of pregnant women reporting some use of opioid pain medications within the last year, and approximately 1–5% of pregnant women reporting opioid pain medication misuse (i.e., without a prescription, at higher dose or longer interval than prescribed) during pregnancy [4,5]. Likewise, opioid use disorder (OUD) during pregnancy has also greatly increased 127% from 1998 to 2011 [6]. Furthermore, neonatal opioid withdrawal syndrome (NOWS) now affects 5.8 per 1000 hospital deliveries [7].

Infants with prenatal substance exposure are at increased risk for deficits in important developmental domains related to cognitive and emotional functioning. For example, children with fetal alcohol spectrum disorders (FASD) demonstrate a range of neurocognitive, motor, social, and regulatory deficits [8,9]. Deficits in emotion regulation in individuals with FASD have been shown to be associated with increased risk for severe mental health problems in adulthood [10]. The developmental impacts of opioid exposure are unclear in part due to the confounding effects of pre- and postnatal environment; yet, existing evidence suggests that deficits are most pronounced in the domains of behavior and language, while the effects on neurocognitive functioning have been documented infrequently [11]. In a relatively small sample, researchers demonstrated increases in parent report of sensation-seeking behaviors and decreases in observed self-regulation in 6-month-old infants exposed to opioids compared to healthy controls [12], while

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https://doi.org/10.1016/j.earlhumdev.2020.105119
Received 19 February 2020; Received in revised form 20 May 2020; Accepted 29 June 2020

a multi-site study found that children exposed prenatally to opioids had average developmental trajectories in cognitive, language, and motor domains across the first 3 years of life [13]. Of note, this larger multi-site study did find differences on a parent-report measure of infant behavior between infants treated for NOWS and those not treated for NOWS, with infants treated for NOWS scoring higher on a measure of distress [13]. The identification of early indicators of developmental challenges associated with prenatal substance exposure is an under-explored area of research with important implications for early intervention recommendations.

Self-regulation, or the ability to regulate one's behavior and emotions, is a key foundational skill that underlies the development of executive functioning and predicts important outcomes across behavioral domains [14]. In infancy, early forms of self-regulation, such as self-soothing techniques, can be observed in structured paradigms like the Still Face Paradigm (SFP) [15]. Previous work demonstrated that maternal contingent responding is associated with positive affect in infants with prenatal alcohol and opioid exposure during the SFP [16]. Additionally, infants with prenatal opioid exposure have lower levels of self-regulation during the SFP [12], suggesting that self-regulation measured during this paradigm is sensitive to prenatal exposure. The extent to which infant' self-regulation behaviors influence their affect during a stressor and how this may be impacted by prenatal exposure(s) have not been studied to our knowledge.

The objectives of this study were to examine 1) the differences in infant self-regulation across episodes of the SFP (both baseline and stress-induced) among different prenatal exposure groups; 2) the association between infant self-regulation and negative infant affect; and 3) the interaction between self-regulation and study group with respect to negative infant affect. We focused specifically on prenatal exposure to alcohol, opioids, and a combination of both exposures given that they are known to affect fetal programming of the hypothalamic pituitary adrenal (HPA) axis [17], a key physiological mediator of self-regulation. The updated clinical guidelines for diagnosing FASD list self-regulation, which includes impaired stress reactivity and deficits in pain regulation, as one of the key behavioral deficits; however, results in young children are mixed. In newborns and 2-month old infants, the HPA response to an acute stressor was blunted [18,19], while at 5–7 months of age heightened stress reactivity was observed [20]. While preclinical data demonstrate the effect of exogenous opioid exposure in utero on HPA axis signaling in offspring [17,21–23], effects on human infant stress regulation/reactivity beyond those seen during the neonatal opioid withdrawal syndrome (NOWS) are largely unknown. Some evidence exists for altered regulation with opioids and co-exposures; one-month old infants with opioid and cocaine co-exposures showed reduced respiratory sinus arrhythmia, a measure of parasympathetic nervous system functioning and an indicator of overall physiological regulation, in response to a sustained visual attention task compared to infants with single exposure to cocaine, opioids, or other substances (e.g. alcohol, marijuana, and tobacco [24]). We are not aware of prior studies examining the combined effect of opioids and alcohol – two common co-exposures in pregnancy. We hypothesized that infants in the healthy control group would demonstrate higher levels of self-regulation compared to the infants in the exposed groups. Additionally, we hypothesized that higher levels of self-regulation would be associated with lower negative affect, and the strength of that association would vary by study group (i.e., there will be a significant group-by-self-regulation interaction with respect to infant affect).

2. Method

2.1. Study design, participants, and study group determination

Data for the current study were obtained from a prospective cohort study, called ENRICH, conducted at the University of New Mexico (UNM), which recruited participants between 2013 and 2018 and is described in detail elsewhere [25,26]. Briefly, all participants were recruited from prenatal care clinics affiliated with [*blinded for review*]. Participants on medications for opioid use disorder (MOUD), with or without concurrent use of other opioids, were recruited from a comprehensive prenatal clinic at UNM that specifically serves pregnant and early postpartum women with substance use disorders. The research goals of the study focused on alcohol and opioids as primary exposures of interest, while other substances were treated as co-exposures. For purposes of this analysis, sample was limited to participants who completed the first three study visits: 1) a prenatal visit during one of the first prenatal care clinic appointments, 2) an early postpartum visit during the hospital stay after delivery, and 3) SFP and neurodevelopmental assessments when the child was approximately 6 months of age. Inclusion criteria for all study groups were as follows: 1) at least 18 years old; 2) singleton pregnancy; 3) currently residing and planning to stay in the Albuquerque metropolitan area to complete all study visits; 4) ability to give informed consent in English. The following exclusion criteria were applied: 1) fetal diagnosis of a major structural anomaly; 2) more than occasional (>1 urine drug test or more than monthly frequency per self-report) use of cocaine, methamphetamines, or MDMA during the first trimester and any use of these substances in the second or third trimesters.

Each participant was recruited into one of four mutually exclusive study groups: participants 1) without any prenatal substance use (Control); 2) receiving MOUD who did not use alcohol during pregnancy; 3) with alcohol use during pregnancy (Alcohol); and 4) with concurrent use of MOUD and Alcohol. Participants in the Control group were lifetime abstainers of illicit drugs and tobacco, abstinent from alcohol during pregnancy, and reported no more than minimal alcohol use in the periconceptional period (≤ 2 standard drinks/week on average, no binge drinking episodes). Eligibility criteria for the alcohol-exposed groups (Alcohol, MOUD + Alcohol) included: 1) at least moderate alcohol use during the periconceptional period (≥ 3 drinks per week or ≥ 2 binge drinking episodes [binge defined as ≥ 4 drinks per occasion] during the month around the last menstrual period (LMP)); and 2) alcohol use after periconceptional period as confirmed by prospective repeated Timeline Follow Back (TLFB) interviews and/or positive ethanol biomarkers (described in detail below). To be eligible for the opioid-exposed groups (MOUD, MOUD + Alcohol), participants were required to be currently on MOUD with or without additional opioid use. The final sample size for the current study consisted of 100 infants of study participants who completed the six-month follow-up visit. The majority of these infants (98%) were accompanied by their biological mother to this study visit (one infant was accompanied by the grandmother and another by the aunt). All study activities were reviewed and approved by the UNM Human Research Protections Program; all participants provided written informed consent.

2.2. Alcohol, substance use, and covariate measures

Both prospective self-report measures (by TLFB interviews administered at enrollment and during the hospital stay) and biomarkers were used to capture alcohol and substance use. Street names of substances were provided to facilitate recall. Quantity and frequency of alcohol use were converted into the ounces of absolute alcohol per day (AA/day; [27]). Maternal blood and urine specimens were collected at enrollment and admission for delivery and analyzed at the U.S. Drug Testing Laboratory (Des Plaines, IL). Urine biomarkers included ethyl-glucuronide (uEtG), ethylsulfate (uEtS), urine drug screen (UDS)-7 (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, PCP, cannabinoids/THC), and nicotine metabolites. Maternal biomarkers included phosphatidylethanol (PEth), gamma-glutamyltranspeptidase (GGT), and carbohydrate-deficient transferrin (%dCDT). Additionally, alcohol exposure was confirmed by PEth in dried blood spots (PEth-DBS) collected from the newborn. Finally, UDS test results collected for clinical purposes were abstracted from medical records.

2.3. The Still Face Paradigm

The Still Face Paradigm (SFP; [28]) was administered as part of the third study visit, which also included a neurodevelopmental evaluation and questionnaires administered with the child's caregiver. The SFP involves a series of interaction episodes between an infant and a caregiver in which the caregiver shifts from interacting with to ignoring the infant, which is experienced by the infant as a stressor. Infants often engage in self-regulation strategies (i.e., mouthing, rubbing hands or feet together) during the still face episodes in order to manage negative affect associated with the caregiver's withdrawal of attention. Infants were between 5 and 8 months of age at the time of the study visit. For infants born prematurely (< 37 weeks gestation), adjusted age was used to schedule the study visit. At the beginning of the study visit, a developmental specialist and a research assistant (blinded to the exposure status) explained the SFP study procedures and administered the SFP while the infant was awake. The SFP assessment typically lasted 15 min in total, including instructions. A modified version of the original SFP was used that included a total of five episodes, each 120 s in length: Episode 1) a baseline play episode to determine typical maternal-child interaction patterns for the dyad, Episode 2) the 'still-face' episode in which the mother maintains a neutral expression while refraining from responding or making eye contact with the infant, Episode 3) a play or reunion episode during which the mother returns to a typical style of interaction, Episode 4) a second 'still-face' episode, and Episode 5) a second reunion or play episode. This modified version of the SFP was employed given previous evidence of augmented effects following a second 'still face' episode [20].

All SFP videos were coded second-by-second offline by reliable coders who were trained by a developmental specialist with extensive experience with the SFP. Consistent with previous work [16], infant affect was coded as: −3 (rhythmic crying for ≥3s), −2 (shorter cry in duration, a protest or yell), −1 (mild fuss/frown), 0 (baby is neutral), +1 (corners of the mouth straight, soft coo), +2 (corners of the mouth go up, cheeks raised, chuckle or small giggle), +3 (laugh ≥2 s). Crying was coded using a duration of ≥3 s to systematically differentiate crying from fussing. The SFP was discontinued if an infant cried for more than 30 consecutive seconds. For this study, we focused on infant negative affect, which was operationalized as the percentage of time the infant displayed negative affect (i.e., a score < 0) over the course of each episode. Self-regulation was coded as the presence or absence of self-regulatory techniques by the infant (e.g., rubbing feet together, mouthing a toy). Self-regulation was operationalized as the percentage of time the infant engaged in self-regulation over the course of each episode. Baseline self-regulation was operationalized as the percentage of time self-regulation behaviors were used during episode 1, and stress-induced self-regulation was operationalizaed as the percentage of time self-regulation behaviors were used during episodes 2 and 4.

Inter-rater reliability was assessed by coding of every 7th tape by a second rater and subsequent calculation of inter-class correlations between the two raters for these select tapes. For infant affect, the inter-rater reliability ranged from 0.76 to 0.91 across episodes. For self-regulation, the inter-rater reliability ranged from 0.92 to 0.99 across episodes.

2.4. Data analysis

We used one-way analysis of variance (ANOVA) and Fisher's exact tests to characterize differences across demographic and medical variables between the four study groups. For the main analyses, linear mixed effects models were used to examine the association between the study group and a) infant self-regulation and b) infant negative affect. Linear mixed effects modeling is particularly well suited for repeated measures data and allows for examination of the outcomes of interest across multiple episodes of the SFP while adjusting for the variance-covariance structure. "Type 3 Tests of Fixed Effects" from SAS *proc mixed* procedure were reported. Compound symmetry variance-covariance structure was used for all models based on improved model fit (i.e., lower Akaike information criterion [AIC] and Bayesian information criterion [BIC] values) as compared to other structures. For the self-regulation model, all episodes were modelled, with group, episode, and group-by-episode interaction included as predictors of self-regulation; analyses were performed both with and without adjusting for self-regulation at episode 1 (baseline). For the negative affect model, only SF episodes [2 and 4] were examined given the heightened levels of negative affect typically seen during these episodes (as opposed to the 'play' episodes). Group, episode, self-regulation during the current episode, self-regulation during the previous episode, current self-regulation-by-group interaction, and baseline self-regulation were used as predictors of negative affect during the SF episodes [2 and 4]. Non-significant model terms were removed using a backwards elimination procedure to increase parsimony in final models. Possible covariates, i.e., maternal age, marital status (single-mother vs. two-parent household), maternal education, family income, were added to final models one-by-one to test for possible influences on directionality and significance of effects. For significant main effects, significant differences in the least means squares with associated Tukey-Kramer adjusted p-values were presented. For significant interactions, contrast estimates within SAS *proc mixed* were used to further interrogate interactions. All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The demographic characteristics of the study sample by group are presented in Table 1. Study groups did not differ significantly by gestational age at delivery, infant age at SFP assessment, infant sex, maternal ethnicity, or maternal race (all $p > 0.05$). There were significant differences in maternal age, gestational age at enrollment, marital status, maternal education, and family income among the study groups ($p < 0.05$). These demographic variables were added to the final statistical models as covariates to investigate potential effects on associations of interest.

Patterns of maternal substance use are presented in Table 2. Consistent with our eligibility criteria, controls reported no more than minimal alcohol use during the periconceptual period and no use during pregnancy and did not have any positive ethanol biomarkers during pregnancy. One control participant reported brief use of pain relievers during early pregnancy; otherwise, control participants had no substance exposures. At the time of admission for delivery, the average dose of methadone was 122.9 mg and the average dose of buprenorphine was 22.0 mg in the MOUD group. In the MODU + Alcohol group, the average dose of methadone was 110.6 mg and the average does of buprenorphine was 21.1 mg. Alcohol use did not differ significantly between the MOUD + Alcohol group and the Alcohol group. The MOUD + Alcohol group reported alcohol use of a median of 0.41 AA/day (equivalent to approximately 6 standard drinks per week) during the periconceptual period and 0.14 AA/day (equivalent to approximately 2 standard drinks per week) during pregnancy. The Alcohol group reported alcohol use of a median of 0.84 AA/day (equivalent to approximately 12 standard drinks per week) during the periconceptual period and 0.3 AA/day (equivalent to approximately 4 standard drinks per week) during pregnancy. The exposure groups also reported tobacco use (MOUD: 77.3%, MOUD + Alcohol: 85%, Alcohol: 28.6%) and marijuana use (MOUD: 31.8%, MOUD + Alcohol: 20%, Alcohol: 57.1%). In the Alcohol group, a small percentage (9.5%) reported use of pain relievers during early pregnancy. In the MOUD and MOUD + Alcohol groups, 45.5% and 50%, respectively, reported use of other opioids besides MOUD, including pain relievers and/or heroin during pregnancy.

Fig. 1 shows mean percent self-regulation by study group. Study groups differed significantly on baseline self-regulation ($F(3,96) = 3.14$, $p = 0.029$). The MOUD + Alcohol group had the lowest

Table 1
Comparisons of demographic variables across study groups.

	Control (n = 37)	MOUD (n = 22)	MOUD + Alcohol (n = 20)	Alcohol (n = 21)	p[1]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Maternal age (years)	26.9 (5.6)	29.4 (5.2)	26.7 (4.6)	30.7 (6.2)	0.036
Gestational age at enrollment (weeks)	25.3 (7.7)	20.0 (6.2)	24.5 (7.2)	25.5 (7.8)	0.037
Gestational age at delivery (weeks)	39.2 (1.3)	38.7 (1.6)	39.0 (2.0)	38.3 (3.0)	0.436
Birth weight (grams)	3326.9 (518.2)	2983.9 (568.8)	2977.2 (558.6)	3010 (677.2)	0.051
Birth length (cm)	50.7 (2.3)	48.4 (2.7)	48.2 (2.9)	48.7 (4.1)	0.004
Birth head circumference (cm)	34.2 (1.5)	33.9 (1.7)	33.1 (1.9)	33.6 (2.2)	0.165
Infant age at SFP assessment (months)	7.0 (1.0)	6.5 (1.1)	7.2 (1.3)	6.8 (1.2)	0.225
	n (%)	n (%)	n (%)	n (%)	
Infant gender:					0.641
Female	17 (46%)	10 (45%)	11 (55%)	13 (62%)	
Male	20 (54%)	12(55%)	9 (45%)	8 (38%)	
Maternal ethnicity:					0.246
Hispanic/Latina	23 (62%)	16 (73%)	13 (65%)	9 (43%)	
Non-Hispanic/Latina	14 (38%)	6 (27%)	7 (35%)	12 (57%)	
Maternal race:					0.053
White	36 (97%)	19 (86%)	17 (85%)	16 (76%)	
African American	1 (3%)	0	1 (5%)	0	
American Indian	0	2 (9%)	1 (5%)	4 (19%)	
Other	0	1 (5%)	1 (5%)	1 (5%)	
Marital status:					0.001
Single/separated/divorced	10 (27%)	13 (59%)	14 (70%)	4 (19%)	
Married/cohabitating	27 (73%)	9 (41%)	6 (30%)	17 (81%)	
Maternal education:					0.002
Less than high school	5 (14%)	11 (50%)	6 (30%)	3 (14%)	
High school/some college	23 (62%)	11 (50%)	13 (65%)	10 (48%)	
College/professional degree	9 (24%)	0	1 (5%)	8 (38%)	
Income:					< 0.001
< $20,000	8 (22%)	14 (67%)	13 (65%)	3 (14%)	
$20,000–$39,999	8 (22%)	6 (29%)	5 (25%)	6 (29%)	
≥$40,000	21 (57%)	1 (5%)	2 (10%)	12 (57%)	

Note: percentages may not add up to 100% due to pairwise deletion of missing values.
[1] p-values correspond to one-way ANOVA F-tests for continuous variables and Fisher exact tests for categorical variable.

percent self-regulation across all episodes (Episode 1: 20.8%; Episode 2: 32.8%; Episode 3: 31%; Episode 4: 51.4%; Episode 5: 36.8%). The control group had the highest (or nearly so) across all episodes (Episode 1: 46.6%; Episode 2: 64%; Episode 3: 49.8%; Episode 4: 70.7%; Episode 5: 46.8%), and other groups were intermediate. As noted above, there was a significant baseline difference in percent self-regulation ($p = 0.029$); however, after using a Tukey adjustment for multiple comparisons significant differences were observed only between MOUD + Alcohol and Control groups ($p < 0.05$) at baseline. Of note, 90% of infants at least partially completed the second still face episode (episode

Table 2
Substance use pattern by study group.

Exposure	Controls (n = 37)	MOUD (n = 22)	MOUD + Alcohol (n = 20)	Alcohol (n = 21)	p
	n (%)	n (%)	n (%)	n (%)	
MOUD before delivery	0 (0.0)			0 (0.0)	
Methadone	–	9 (40.9)	8 (40.0)	–	1.00[3]
Buprenorphine	–	13 (59.1)	12 (60.0)[7]	–	1.00[3]
Other opioids[1]	1[2](2.7)	10 (45.5)	10 (50.0)	2[2] (9.5)	1.00[3]
Marijuana	0 (0.0)	7 (31.8)	4 (20.0)	12 (57.1)	0.045[4]
Tobacco	0 (0.0)	17 (77.3)	17 (85.0)	6 (28.6)	< 0.001[4]
Positive for ≥1 ethanol biomarker	0 (0.0)	0 (0.0)	9 (45.0)	11 (52.4)	0.758[5]

Exposure	Median [Q1,Q3]	Median [Q1,Q3]	Median [Q1,Q3]	Median [Q1,Q3]	p
AA/day in periconceptional period	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.41 [0.11,1.08]	0.84 [0.50,1.93]	0.106[6]
AA/day during pregnancy	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.14 [0.04,0.36]	0.30 [0.18,0.81]	0.070[6]

AA, absolute alcohol (oz).
Note: percentages may not add up to 100% due to pairwise deletion of missing values.
[1] Heroin and/or opioid analgesics used during pregnancy.
[2] Short-term use of opioid analgesics during early pregnancy.
[3] Fisher exact test comparing MOUD and MOUD + Alcohol groups only.
[4] Fisher exact test comparing MOUD, MOUD + Alcohol, and alcohol groups only.
[5] Fisher exact test comparing MOUD + Alcohol and alcohol groups only.
[6] Mann-Whitney-Wilcoxon exact test comparing MOUD + Alcohol and Alcohol groups only.

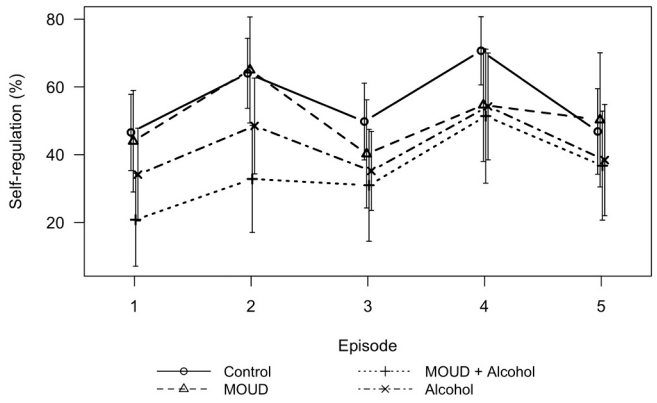

Fig. 1. Percentage of Self-regulation by group across episodes. Vertical lines are 95% one-sample *t*-test confidence intervals.

4), and 87% of infants completed all 5 episodes of the SFP. There were no differences observed between patients who completed all episodes and those for whom the procedure was stopped early (data not shown).

Unadjusted for the baseline difference, a linear mixed model (Model 1) demonstrated no significant group-by-episode interaction ($p = 0.227$), which agreed with the consistent ordering of groups seen across episodes in Fig. 1; the main effects of group ($p = 0.025$) and episode ($p < 0.0001$) were significant. For that model, tests for differences in the least squares means of groups (effectively averages across episodes) were calculated with Tukey adjustments of p-values to correct for multiple comparisons. Compared to Control, differences in the self-regulation were −4.8 (MOUD, $p = 0.921$), −22.7 (MOUD + Alcohol, $p = 0.023$), and −14.0 (Alcohol, $p = 0.265$). No other significant group differences in the least squares means were seen so that the pattern observed at baseline followed through the remaining episodes. A sensitivity analysis, adjusting for baseline (episode 1) differences in self-regulation and fitting only episodes 2–5, found no group effect ($p = 0.601$) but a significant effect of baseline self-regulation and episode (both $p < 0.0001$). Thus, group differences across the SFP appear to be attributable to baseline differences. With both analyses, demographic characteristics from Table 1 were introduced (individually) to assess possible confounding effects, and none were significant nor changed any pattern or significance and thus were not retained.

To examine the association between infant self-regulation and negative affect at episodes 2 and 4, a linear mixed effects model (Model 2) was constructed with the following predictors: study group, SFP episode, self-regulation during the current episode, and current self-regulation-by-group interaction. Other variables (baseline self-regulation, baseline negative affect, self-regulation in the previous episode, episode-by-group interaction) also were fit initially but dropped since they all had large p-values (> 0.50) or did not show a significant group difference at baseline (negative affect). Similar to our previous model for self-regulation, we added demographic variables one by one as covariates to examine the impact on the overall model and found that none of these variables changed the pattern or significance of the results.

In the final Model 2, SFP episode ($p < 0.0001$) and the self-regulation-by-group interaction ($p = 0.028$) emerged as significant predictors of infant negative affect. Neither of the main effects (self-regulation and group) was significant. An interaction plot (Fig. 2) demonstrates the significant interaction. For the Control, MOUD, and Alcohol groups, there was no significant association between percent current self-regulation and percent negative affect. However, for the MOUD + Alcohol group, there emerged a strong negative association ($p = 0.025$), such that the MOUD + Alcohol infants with high self-regulation were the ones who demonstrated lower negative affect, a phenomenon not observed with other groups.

4. Discussion

Results of this study indicate baseline differences in self-regulation across the prenatal substance exposure groups, with the polysubstance MOUD + Alcohol group showing the lowest levels of self-regulation. Problems with self-regulation, inhibition, and attention are well documented in infants with prenatal alcohol exposure [[29,30]]. Previous work has demonstrated lower levels of self-regulation during the SFP in opioid-exposed infants [12], and a recent meta-analysis identified lower scores on measures of attention in preschool and school aged opioid-exposed children compared to healthy controls with effects in the moderate effect size range [31]. Our finding that the polysubstance exposure group demonstrated the lowest levels of self-regulation at baseline and across the SFP is both consistent and complementary to prior research, which focused largely on infant affect [32] and single-substance exposure [20]. Understanding polysubstance exposure effects is of particular importance given the high prevalence of polysubstance use in the current context of the opioid crisis [33]. Lester and colleagues (2009) found that in a group of polysubstance exposed infants, both indirect and direct effects resulted in neurobehavioral problems in childhood [34]. Infants with polysubstance exposure had increased reactivity and stress at one month of age that were associated with difficult temperament scores at 4 years, and increased behavioral problems at 3 and 7 years [34]. It has been hypothesized that multiple exposures to both illicit drugs and environmental factors, such as stress and poverty, could have additive effects that result in greater difficulty with self-regulation for polysubstance exposed groups [35]. To our knowledge, the current study is the first to date focusing on self-regulation and its relation to affect regulation during a social stressor in infants exposed to opioids and opioids + alcohol.

We also found that baseline self-regulation was a significant predictor of self-regulation during subsequent 'still face' and play episodes of the SFP. This finding suggests that self-regulation was a relatively stable individual characteristic in this sample of varying prenatal exposures and that the baseline levels of self-regulation determined the level of stress-induced self-regulation. Infants prenatally exposed to both MOUD and alcohol had the lowest levels of self-regulation at baseline, pointing to potentially synergistic effects of these exposures on baseline regulatory capacity. Furthermore, given that baseline self-regulation predicted self-regulation strategies during the still face episodes, these results also suggest that alcohol and opioid co-exposure impacts behavioral reactivity to the stressor; indeed, this group demonstrated the lowest levels of self-regulation across the SFP (though differences did not reach statistical significance in subsequent episodes). This finding is broadly consistent with preclinical studies that demonstrate the impact of prenatal opioid exposure on both baseline functioning and reactivity of the HPA axis [23].

Increased maternal psychosocial stress and mental health conditions (e.g., depression), which often co-occur with polysubstance use, have been associated with negative affect [36], poor attentional regulation [37], and lower soothability [38] during infancy. Prenatal polysubstance use was also associated with poorer infant self-regulation, higher excitability, and lower arousal at one month of age [39]. Another possibility is that self-regulation is influenced by environmental factors (i.e., intimate partner violence, early life adversity) and genetic factors involved in HPA axis signaling [40,41]. These findings have important implications for how to support infants with prenatal exposure in the context of environmental and life stressors. Given that these infants often experience a high degree of environmental and psychosocial stress (e.g., poverty, housing instability, changes in caregivers, maternal psychopathology, violence) in addition to prenatal exposures [opioids: [42]; alcohol: [43]], early intervention strategies to support these infants in their management of psychosocial stress are particularly relevant. Increasing baseline levels of self-regulation may thus be a viable stress coping strategy for infants with prenatal exposure.

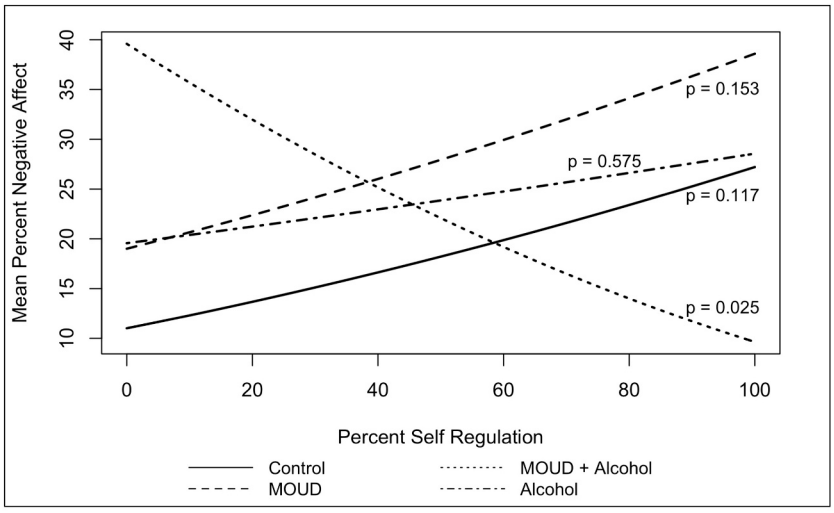

Fig. 2. Interaction of self-regulation and negative affect. The MOUD + Alcohol group demonstrated a negative association between percent negative affect and percent regulation during SFP episodes (analyses for Episode 2 depicted here; similar results were found for Episode 4). Lines shown are predicted values of negative affect from the linear mixed effects model fitting study group, current self-regulation, episode, and the group-by-self-regulation interaction.

Interestingly, a negative association between self-regulation and infant affect was observed only in the MOUD + Alcohol group; as self-regulation increased negative affect decreased. Given the limited and heterogeneous prior results [44] for the association between self-regulation and negative affect, we provide multiple possible interpretations for this finding. One possible interpretation is that this association was present in the MOUD + Alcohol group and not others because the MOUD + Alcohol group had the lowest baseline self-regulation levels and the largest increase in self-regulation behavior across the SFP, thus allowing sufficient variability for the association with negative affect to emerge. Another possible interpretation is that the MOUD + Alcohol group was likely to have experienced higher levels of psychosocial stress in addition to polysubstance exposure, which could impact both self-regulation and emotional reactivity in this group, resulting in a cascade of effects, including dysregulation, difficult temperament, and behavior problems [45]. Polysubstance exposure has been linked with more depression and mood related issues in the mother [46], which could in turn impact the infant's self-regulatory behaviors and emotional reactivity. Future studies should investigate the contributions of maternal mood and psychopathology to infant emotional reactivity during the SFP. Finally, it is possible that differences in the physiological systems that influence self-regulation and the stress response may account for this negative association in the MOUD + Alcohol group due to polysubstance prenatal exposure. Evidence shows that functioning of the endogenous opioid system, particularly kappa opioid receptors, plays a key role in regulating mood following stress [47]; thus, disruption of this system by prenatal opioid exposure may impact the extent to which self-regulation behaviors are needed to regulate negative affect related to stressors in particular. Prenatal exposure to alcohol, opioids, and psychosocial stressors impacts infant emotion regulation in response to stress via fetal programming of the HPA axis and autonomic nervous system, with the potential for additive or interactive effects of co-exposures [35,42,48–50]. Such additive or interactive effects on the underlying physiology of self-regulation and emotional reactivity could explain our finding that the MOUD + Alcohol group displayed the strongest association between the two [51]; future work is needed to measure physiological responses (e.g., heart rate variability) during the SFP to further investigate this possibility. It is important to note that we considered the impact of socioeconomic status (operationalized here as maternal education, single/two-parent household, and household income), and that these factors did not change model estimates, suggesting that the combined opioid and alcohol exposure was a more salient factor for self-regulation than these markers of socioeconomic status. This finding also points to the utility of identifying strategies that parents can use to encourage self-regulation (i.e., infant sucking on their hand or infant holding onto a blanket or their hands) [52], particularly in infants with polysubstance exposure.

Notably, the level of prenatal alcohol use across groups in this sample would be considered relatively low (2–4 drinks/week) in comparison to other studies which typically focus on heavy drinking (> 13 drinks/week) or repeated binge episodes [e.g. [53–55]]; however, the combination of opioids and even low-moderate alcohol use still had a significant effect on infant self-regulation. This finding points to the importance of characterizing polysubstance use particularly in high-risk samples, such as women misusing prescription opioids during pregnancy or those in treatment for opioid use disorder (OUD). In addition, all substance exposure groups also reported use of marijuana and tobacco, as well as additional opioid use (heroin and/or opioid analgesics) in the opioid-exposed groups. This profile of polysubstance exposure is common in pregnant women with OUD [33,56] and those who use alcohol [57,58], increasing the external validity of our findings and further underscoring the unique contribution of the combined effect of opioids and alcohol on infant self-regulation.

The current study was limited by the relatively small sample size across the four study groups as well as potentially confounded by sociodemographic characteristics not captured in the study, such as number of children in the home or violence in the home. We do note that we expected that important sociodemographic variables, such as maternal education and ethnicity, may have impacted the results; however, when added to the reported models, the effect of these variables was non-significant. These limitations were additionally balanced by the considerable strengths inherent in the prospective cohort design, the extensive assessment of substance use during pregnancy, including the state-of-the-art ethanol biomarker battery, rigorous administration and coding of the SFP, and the use of three substance exposure groups, allowing for comparisons across primary exposures of interest (opioids, alcohol) and polysubstance exposures.

In conclusion, our results highlight the impact of prenatal substance exposure on infants' capacity to effectively use self-regulation strategies to manage negative affect during a relational stressor. A critical future direction is to explore the association between self-regulation during the first year of life and future developmental outcomes known to be affected by prenatal substance exposure, including executive functioning, impulsivity, and learning problems. While traditionally mechanistic studies focused on the primary exposure of interest or a 'stressor', it is important for future studies to consider the cumulative effect of polysubstance exposures and maternal psychosocial stress on fetal programming of stress reactivity and regulation. Given the prominent role of emotional reactivity and self-regulation in neurobehavioral outcomes in high risk infants, improving infant self-regulation

with targeted caregiver support around scaffolding these skills should be examined as an early intervention approach to minimize long-term adverse outcomes. Future work should examine different profiles of emotional reactivity in infants and interventions to appropriately provide caregivers with strategies to help these infants more effectively manage higher levels of emotional dysregulation.

Funding

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA; research grant number R01 AA021771) and the National Institute on Drug Abuse (NIDA; research grant number R34 DA050237) of the National Institutes of Health.

References

[1] C.H. Denny, C.S. Acero, T.S. Naimi, S.Y. Kim, Consumption of alcohol beverages and binge drinking among pregnant women aged 18–44 years — United States, 2015–2017, Morb. Mortal. Wkly Rep. 68 (16) (2019) 365–368. Apr 26.
[2] S. Popova, S. Lange, C. Probst, N. Parunashvili, J. Rehm, Prevalence of alcohol consumption during pregnancy and fetal alcohol Spectrum disorders among the general and aboriginal populations in Canada and the United States, Eur J Med Genet 60 (1) (2017) 32–48 Jan 1.
[3] D. Shmulewitz, D.S. Hasin, Risk factors for alcohol use among pregnant women, ages 15–44, in the United States, 2002 to 2017, Prev. Med. 124 (2019) 75–83 Jul 1.
[4] B. St. Marie, L. Coleman, J.A. Vignato, S. Arndt, L.S. Segre, Use and misuse of opioid pain medications by pregnant and nonpregnant women, Pain Manag Nurs 21 (1) (2020) 90–93 Feb 1.
[5] K.B. Kozhimannil, A.J. Graves, R. Levy, S.W. Patrick, Nonmedical use of prescription opioids among pregnant U.S. women, Womens Health Issues 27 (3) (2017) 308–315 May 1.
[6] Maeda A, Creanga AA. Opioid abuse and dependence during pregnancy. Perioper Med. :8.
[7] S.W. Patrick, M.M. Davis, C.U. Lehmann, W.O. Cooper, Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012, J. Perinatol. 35 (8) (2015) 650–655. Aug.
[8] A. Schoeps, E.R. Peterson, Y. Mia, K.E. Waldie, L. Underwood, S. D'Souza, et al., Prenatal alcohol consumption and infant and child behavior: evidence from the growing up in New Zealand cohort, Early Hum. Dev. 123 (2018) 22–29. Aug 1.
[9] P.W. Kodituwakku, Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review, Neurosci. Biobehav. Rev. 31 (2) (2007) 192–201 Jan 1.
[10] V.K. Temple, J.L. Cook, K. Unsworth, H. Rajani, M. Mela, Mental health and affect regulation impairment in fetal alcohol spectrum disorder (FASD): results from the Canadian national FASD database, Alcohol Alcohol. 54 (5) (2019) 545–550 Jan 9.
[11] E. Conradt, T. Flannery, J.L. Aschner, R.D. Annett, L.A. Croen, C.S. Duarte, et al., Prenatal opioid exposure: neurodevelopmental consequences and future research priorities, Pediatrics 144 (3) (2019) Sep. e20190128.
[12] L.N. Bakhireva, B.D. Holbrook, S. Shrestha, Y. Leyva, M. Ashley, S. Cano, et al., Association between prenatal opioid exposure, neonatal opioid withdrawal syndrome, and neurodevelopmental and behavioral outcomes at 5–8 months of age, Early Hum. Dev. 128 (2019) 69–76 Jan 1.
[13] K. Kaltenbach, K.E. O'Grady, S.H. Heil, A.L. Salisbury, M.G. Coyle, G. Fischer, et al., Prenatal exposure to methadone or buprenorphine: early childhood developmental outcomes, Drug Alcohol Depend. 185 (2018) 40–49. Apr 1.
[14] T.E. Moffitt, L. Arseneault, D. Belsky, N. Dickson, R.J. Hancox, H. Harrington, et al., A gradient of childhood self-control predicts health, wealth, and public safety, Proc. Natl. Acad. Sci. 108 (7) (2011) 2693–2698 Feb 15.
[15] P.C. MacLean, K.N. Rynes, C. Aragón, A. Caprihan, J.P. Phillips, J.R. Lowe, Mother–infant mutual eye gaze supports emotion regulation in infancy during the still-face paradigm, Infant Behav Dev 37 (4) (2014) 512–522 Nov.
[16] J. Lowe, F. Qeadan, L. Leeman, S. Shrestha, J.M. Stephen, L.N. Bakhireva, The effect of prenatal substance use and maternal contingent responsiveness on infant affect, Early Hum. Dev. 115 (2017) 51–59 Dec.
[17] A.L. Franks, K.J. Berry, D.B. DeFranco, Prenatal drug exposure and neurodevelopmental programming of glucocorticoid signalling, J. Neuroendocrinol. 32 (1) (2020) e12786.
[18] D.S. Ramsay, M.I. Bendersky, M. Lewis, Effect of prenatal alcohol and cigarette exposure on two- and six-month-old infants' adrenocortical reactivity to stress, J. Pediatr. Psychol. 21 (6) (1996) 833–840 Dec 1.
[19] T.F. Oberlander, S.W. Jacobson, J. Weinberg, R.E. Grunau, C.D. Molteno, J.L. Jacobson, Prenatal alcohol exposure alters biobehavioral reactivity to pain in newborns, Alcohol. Clin. Exp. Res. 34 (4) (2010) 681–692.
[20] D.W. Haley, N.S. Handmaker, J. Lowe, Infant stress reactivity and prenatal alcohol exposure, Alcohol. Clin. Exp. Res. 30 (12) (2006) 2055–2064.
[21] A. Fodor, J. Tímár, D. Zelena, Behavioral effects of perinatal opioid exposure, Life Sci. 104 (1) (2014) 1–8 May 28.
[22] C. Castellano, M. Ammassari-Teule, Prenatal exposure to morphine in mice: enhanced responsiveness to morphine and stress, Pharmacol. Biochem. Behav. 21 (1) (1984) 103–108 Jul 1.
[23] E.M. Byrnes, F.M. Vassoler, Modeling prenatal opioid exposure in animals: current findings and future directions, Front. Neuroendocrinol. 51 (2018) 1–13 Oct 1.
[24] E. Conradt, S.J. Sheinkopf, B.M. Lester, E. Tronick, L.L. LaGasse, S. Shankaran, et al., Prenatal substance exposure: neurobiologic organization at 1 month, J. Pediatr. 163 (4) (2013) 989–994.e1 Oct.
[25] Blinded for review.
[26] Blinded for review.
[27] S.W. Jacobson, L.M. Chiodo, R.J. Sokol, J.L. Jacobson, Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome, PEDIATRICS 109 (5) (2002) 815–825 May 1.
[28] J. Mesman, M.H. van IJzendoorn, M.J. Bakermans-Kranenburg, The many faces of the still-face paradigm: a review and meta-analysis, Dev. Rev. 29 (2) (2009) 120–162 Jun.
[29] L. Garrison, S. Morley, C.D. Chambers, L.N. Bakhireva, Forty years of assessing neurodevelopmental and behavioral effects of prenatal alcohol exposure in infants: what have we learned? Alcohol. Clin. Exp. Res. 43 (8) (2019) 1632–1642.
[30] S.N. Mattson, G.A. Bernes, L.R. Doyle, Fetal alcohol spectrum disorders: a review of the neurobehavioral deficits associated with prenatal alcohol exposure, Alcohol. Clin. Exp. Res. 43 (6) (2019) 1046–1062.
[31] S.J. Lee, S. Bora, N.C. Austin, A. Westerman, J.M.T. Henderson, Neurodevelopmental outcomes of children born to opioid-dependent mothers: a systematic review and meta-analysis, Acad. Pediatr. 20 (3) (2020) 308–318. Apr.
[32] J. Lowe, N. Handmaker, C. Aragón, Impact of mother interactive style on infant affect among babies exposed to alcohol in utero, Infant Ment. Health J. 27 (4) (2006) 371–382.
[33] T.J. Cicero, M.S. Ellis, Z.A. Kasper, Polysubstance use: a broader understanding of substance use during the opioid crisis, Am. J. Public Health 110 (2) (2020) 244–250 Feb.
[34] B.M. Lester, J.F. Padbury, Third pathophysiology of prenatal cocaine exposure, Dev. Neurosci. 31 (1–2) (2009) 23–35.
[35] C. Monk, C. Lugo-Candelas, C. Trumpff, Prenatal developmental origins of future psychopathology: mechanisms and pathways, Annu. Rev. Clin. Psychol. 15 (1) (2019) 317–344.
[36] B. Lin, K.A. Crnic, L.J. Luecken, N.A. Gonzales, Maternal prenatal stress and infant regulatory capacity in Mexican Americans, Infant Behav Dev 37 (4) (2014) 571–582 Nov.
[37] S.-C. Chong, B.F. Broekman, A. Qiu, I.M. Aris, Y.H. Chan, A. Rifkin-Graboi, et al., Anxiety and depression during pregnancy and temperament in early infancy: findings from a multi-ethnic, Asian, prospective birth cohort study, Infant Ment. Health J. 37 (5) (2016) 584–598.
[38] Y. Nomura, J. Finik, J. Salzbank, J. Ly, N. Huynh, T. Davey, et al., The effects of preeclampsia on perinatal risks and infant temperaments among mothers with antenatal depression, Psychol Res Lib Ill 4 (6) (2014) 451–461 Jun.
[39] B.M. Lester, E.Z. Tronick, L. LaGasse, R. Seifer, C.R. Bauer, S. Shankaran, et al., The maternal lifestyle study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants, PEDIATRICS 110 (6) (2002) 1182–1192 Dec 1.
[40] T. Halldorsdottir, D. Kurtoic, B. Müller-Myhsok, E.B. Binder, C. Blair, Neurobiology of self-regulation: longitudinal influence of FKBP5 and intimate partner violence on emotional and cognitive development in childhood, Am. J. Psychiatry 176 (8) (2019) 626–634. Apr 5.
[41] W.R. Lovallo, M.-A. Enoch, A. Acheson, A.J. Cohoon, K.H. Sorocco, C.A. Hodgkinson, et al., Early-life adversity interacts with FKBP5 genotypes: altered working memory and cardiac stress reactivity in the Oklahoma family health patterns project, Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 41 (7) (2016) 1724–1732.
[42] E. Conradt, S.E. Crowell, B.M. Lester, Early life stress and environmental influences on the neurodevelopment of children with prenatal opioid exposure, Neurobiol Stress 9 (2018) 48–54 Nov.
[43] C. Kambeitz, M.G. Klug, J. Greenmyer, S. Popova, L. Burd, Association of adverse childhood experiences and neurodevelopmental disorders in people with fetal alcohol spectrum disorders (FASD) and non-FASD controls, BMC Pediatr. 19 (1) (2019) 498 Dec.
[44] P.C. Maclean, S.J. Erickson, J.R. Lowe, Comparing emotional reactivity and regulation in infants born ELGA and VLGA, Infant Behav Dev 32 (3) (2009) 336–339 Jun 1.
[45] B.M. Lester, D.M. Bagner, J. Liu, L.L. LaGasse, R. Seifer, C.R. Bauer, et al., Infant neurobehavioral dysregulation: behavior problems in children with prenatal substance exposure, PEDIATRICS 124 (5) (2009) 1355–1362 Nov 1.
[46] M. Romanowicz, J.L. Vande Voort, J. Shekunov, T.S. Oesterle, N.J. Thusius, T.A. Rummans, et al., The effects of parental opioid use on the parent–child relationship and children's developmental and behavioral outcomes: a systematic review of published reports, Child Adolesc. Psychiatry Ment. Health 13 (1) (2019) 5 Jan 12.
[47] P.-E. Lutz, B.L. Kieffer, Opioid receptors: distinct roles in mood disorders, Trends Neurosci. 36 (3) (2013) 195–206 Mar 1.
[48] K.G.C. Hellemans, J.H. Sliwowska, P. Verma, J. Weinberg, Prenatal alcohol exposure: fetal programming and later life vulnerability to stress, depression and anxiety disorders, Neurosci. Biobehav. Rev. 34 (6) (2010) 791–807 May.
[49] K. Keiver, C.P. Bertram, A.P. Orr, S. Clarren, Salivary cortisol levels are elevated in the afternoon and at bedtime in children with prenatal alcohol exposure, Alcohol 49 (1) (2015) 79–87 Feb.
[50] K. McLachlan, C. Rasmussen, T.F. Oberlander, C. Loock, J. Pei, G. Andrew, et al., Dysregulation of the cortisol diurnal rhythm following prenatal alcohol exposure and early life adversity, Alcohol 53 (2016) 9–18 Jun.
[51] I. Ettekal, R.D. Eiden, A.B. Nickerson, D.S. Molnar, P. Schuetze, Developmental cascades to children's conduct problems: the role of prenatal substance use,

socioeconomic adversity, maternal depression and sensitivity, and children's conscience, Dev. Psychopathol. 32 (1) (2020) 85–103 Feb.
[52] L. Giusti, L. Provenzi, R. Montirosso, The face-to-face still-face (FFSF) paradigm in clinical settings: socio-emotional regulation assessment and parental support with infants with neurodevelopmental disabilities, Front. Psychol. 9 (2018) 789 May 22.
[53] G. Bandoli, C.D. Coles, J.A. Kable, W. Wertelecki, L. Yevtushok, N. Zymak-Zakutnya, et al., Patterns of prenatal alcohol use that predict infant growth and development, Pediatrics 143 (2) (2019) Feb. e20182399.
[54] S.W. Jacobson, R.C. Carter, C.D. Molteno, M.E. Stanton, J.S. Herbert, N.M. Lindinger, et al., Efficacy of maternal choline supplementation during pregnancy in mitigating adverse effects of prenatal alcohol exposure on growth and cognitive function: a randomized, double-blind, placebo-controlled clinical trial, Alcohol. Clin. Exp. Res. 42 (7) (2018) 1327–1341.
[55] T.J. Hendrickson, B.A. Mueller, E.R. Sowell, S.N. Mattson, C.D. Coles, J.A. Kable, et al., Two-year cortical trajectories are abnormal in children and adolescents with prenatal alcohol exposure, Dev Cogn Neurosci 30 (2018) 123–133.
[56] M.V. Smith, D. Costello, K.A. Yonkers, Clinical correlates of prescription opioid analgesic use in pregnancy, Matern. Child Health J. 19 (3) (2015) 548–556 Mar.
[57] C. McQuire, R. Daniel, L. Hurt, A. Kemp, S. Paranjothy, The causal web of foetal alcohol spectrum disorders: a review and causal diagram, Eur Child Adolesc Psychiatry 16 (2019) 1–20 Jan.
[58] M.J. Cannon, Y. Dominique, L.A. O'Leary, J.E. Sniezek, R.L. Floyd, Characteristics and behaviors of mothers who have a child with fetal alcohol syndrome, Neurotoxicol. Teratol. 34 (1) (2012) 90–95 Jan 1.