Assessing the Independent and Joint Effects of Unmedicated Prenatal Depressive Symptoms and Alcohol Consumption in Pregnancy and Infant Neurodevelopmental Outcomes

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Background: Prenatal alcohol exposure (PAE) is an established risk factor for neurodevelopmental deficits in the offspring. Prenatal depression has been associated with neurodevelopmental deficits in the offspring, although investigations into unmedicated prenatal depression have been inconsistent. We hypothesized that unmedicated prenatal depressive symptoms would independently and jointly with PAE predict neurodevelopmental outcomes in infant offspring.

Methods: We studied 344 participants from a randomized clinical trial of multivitamin supplements in pregnant women in Ukraine. Women were recruited based upon periconceptional alcohol use and followed up to 12 months postpartum. Prenatal depressive symptoms were assessed at approximately 32 weeks of gestation using the Beck Depression Inventory score. Neurodevelopment was assessed with the Bayley Scales of Infant Development II Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 6 and 12 months postpartum. Generalized linear regression models were constructed to assess the independent and joint effects of prenatal depressive symptoms and PAE in models adjusted for sociodemographic and pregnancy characteristics.

Results: PAE was independently associated with deficits in neurodevelopmental outcomes at 6 and 12 months, however, level of prenatal depressive symptoms was not. We found marginal evidence of synergism of depressive symptoms and PAE, with larger deficits in those with both exposures observed for the PDI-6 months ($p = 0.05$) and MDI-12 months ($p = 0.09$). Additionally, there was a suggestion of sexual dimorphism; females had stronger deficits from joint exposures than males (depressive symptom [MDI-6 months] female: −8.28, 95% CI −13.06, −3.49; male: 0.68, 95% CI −4.58, 5.94; p for interaction 0.04). While not statistically significant for the MDI or PDI at 12 months, the trend persisted.

Conclusions: Infants exposed to PAE and prenatal depression may be at an increased risk of neurodevelopmental deficits. Healthcare providers should be aware of this possible synergism in their efforts to mitigate the neurodevelopmental effects of these co-occurring exposures.

Key Words: Prenatal Alcohol Exposure, Prenatal Depression, Infant Neurodevelopment.

THE DETERMINANTS OF neurodevelopment and its functional domains, including cognition, memory, language, and motor function, have been studied across disciplines as researchers attempt to elucidate its nongenetic components. As little as 25% has been found to be hereditable in early childhood (Davis et al., 2015), directing interest toward early exposures in the intrauterine environment. Alcohol consumed during pregnancy has been well-documented as a neurotoxic agent associated with neurodevelopmental deficits. A recent meta-analysis found significant detrimental associations between binge and moderate prenatal alcohol exposure (PAE) and childhood cognition and behavior (Flak et al., 2014). Further findings have indicated that low or moderate exposure to alcohol, while inconsistent, is also adversely associated with a variety of neurocognitive outcomes (Jacobson and Jacobson, 1999; Polanska et al., 2015).

One interesting angle that to our knowledge has not been explored is whether maternal depression in pregnancy, a reported comorbidity of women with alcohol use disorders (Leis et al., 2012), modifies the detrimental effects of PAE on infant neurodevelopmental outcomes. Maternal prenatal depression, long investigated for its association with negative birth outcomes (Grigoriadis et al., 2013), has been independently explored as a risk factor for neurodevelopmental

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deficits with inconsistent results (for review, see Gentile, 2015). Primarily, this research has focused specifically on the effects of medication treatment for depression in pregnancy (most commonly with selective serotonin reuptake inhibitors) (Hanley et al., 2013). Research that has attempted to estimate the functional neurodevelopmental effects of prenatal maternal depression independent of medication to treat depression is scarce and has resulted in inconsistent, primarily null findings (Barker et al., 2013; Nulman et al., 2012, 2015; Santucci et al., 2014). However, research examining brain structure in preschoolers found women's second trimester depression scores negatively correlated with children's cortical thickness in right inferior frontal and middle temporal regions, which has been associated with negative neurodevelopmental outcomes (Lebel et al., 2015). This association remained when limited to women not taking antidepressants.

To our knowledge, while some studies have adjusted for the independent effects of maternal prenatal depression when evaluating PAE (Molteno et al., 2014), there have been no studies investigating the joint effects of the 2 exposures in pregnancy on infant neurobehavioral outcomes. There is a strong biologic rationale for this hypothesized interaction. Independently, prenatal maternal depression (Waters et al., 2014) and PAE (Macrì et al., 2007) have both been associated with hypothalamus–pituitary–adrenal (HPA) axis regulation in the mother and alternations in the developing HPA axis in the fetus, although they are hypothesized to operate through independent pathways (Waters et al., 2014; Weinberg et al., 2008). While specific mechanisms by which maternal HPA axis activity influences fetal brain development are not understood, these perturbations are hypothesized to contribute to impaired fetal brain development (Waters et al., 2014). The potential synergies and reported comorbidity of the exposures (Kessler et al., 2016; Leis et al., 2012) warrants exploration of this interaction.

We hypothesize that unmedicated maternal depressive symptoms in pregnancy will independently predict neurodevelopmental deficits in infants at ages 6 and 12 months. Furthermore, we hypothesize an additive interaction between maternal depressive symptoms and PAE will result in further neurodevelopmental deficits in the young offspring. To test these hypotheses, we used a sample collected in a randomized clinical trial of multivitamin supplements in pregnancy conducted in Ukraine. This trial, consisting of women recruited on periconceptional alcohol exposure, allowed us to examine the independent effects of unmedicated depressive symptoms in pregnancy, as well as the joint effects with PAE, on the neurodevelopmental outcomes in the infant offspring.

MATERIALS AND METHODS

Study Design and Sample

Data for this analysis are from a prospective cohort study of pregnant women in western Ukraine conducted as part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD).

The CIFASD is supported by the National Institute on Alcohol Abuse and Alcoholism and is a multidisciplinary initiative conducted in several countries throughout the world (www.CIFASD.org). This randomized trial of prenatal micronutrient supplementation has been described elsewhere in detail (Chambers et al., 2014; Coles et al., 2015; Mattson et al., 2010). Briefly, all women who presented to 1 of 2 centralized prenatal care facilities in western Ukraine between April 2008 through August 2012 were eligible for screening. A total of 11,909 women were screened during this period (approximately 25% of the total eligible population) (Chambers et al., 2014). Women were queried about their previous and current alcohol consumption and moderate to heavy drinkers in the month around conception and/or in the most recent month of pregnancy and low or unexposed control women were recruited for participation. Half of the women in each group were randomly assigned to take a multivitamin mineral supplement with or without an additional choline supplement provided by the study site; the other half in each group were assigned standard of care, in which multivitamin supplementation was recommended but not provided. Women were interviewed about demographics, behaviors, and pregnancy characteristics, including use of medications, using standard questionnaires upon enrollment and again at approximately 32 weeks of gestation. Medical records for birth outcomes were provided from the birth. Mothers of live born infants were also invited back to be interviewed twice postpartum (6 and 12 months) at which time neurodevelopmental testing was conducted with the infant.

From the 2 sites, 754 women were enrolled into the study at a median gestational age at enrollment of 18.4 weeks (standard deviation 6 weeks, range 2 to 39 weeks). Of these, 422 subjects (56.0%) completed the second maternal pregnancy interview that included a Beck Depression Inventory (BDI) score at approximately 32 weeks to categorize the depression exposure. Women who enrolled after 32 weeks of gestation were not required per the protocol to complete the second pregnancy visit, resulting in this attrition. From those with exposure information, 364 singleton live born infants returned for the neurodevelopmental testing (86.3%). After excluding 20 participants whose reported alcohol consumption was judged by investigators to be unreliable, the final sample for this analysis consisted of 344 subjects with Bayley Scales of Infant Development scores at 6 months and/or 12 months. The protocol was approved by the institutional review boards at the University of California, San Diego and the Lviv National Medical University in Ukraine. All participants signed informed consent.

Measures

Depressive Symptoms and Treatment. The BDI-1A (Beck and Steer, 1993) was administered at the follow-up enrollment visit at approximately 32 weeks of gestation (median gestational age at administration: 32.0 weeks, interquartile range [IQR] 1.8 weeks). This version of the scale was created from a direct translation from English and administered in Ukrainian. The standard cutoff for the 21-item version is ≥19 for moderate to severe depressive symptoms; however, in our population only 8 women met this criterion (median BDI-1A: 5.0, IQR 5.0). Thus, we employed a cutoff of ≥10 corresponding to mild, moderate, or severe depressive symptoms for this analysis.

Maternal screening and in-pregnancy interviews queried the mother about all medications she was currently taking, including prescription and nonprescription products, and these were reviewed for evidence of any use of antidepressant medication during pregnancy. None of the participants reported any medication use for depression during pregnancy.

Alcohol Exposure. Criteria for inclusion in the study were defined as moderate to heavy alcohol consumption in the periconceptional period for the alcohol exposed group and low to no alcohol consumption for the contrast group. Eligibility for enrollment was determined at the screening visit with a questionnaire adapted from Barr and Streissguth (2001) to assess usual patterns of alcohol consumption both in the month around conception and in the most recent month. Moderate to high alcohol intake was defined as at least weekly binge-drinking episodes (5+ drinks), at least 5 episodes of 3 to 4 standard drinks, or at least 10 episodes of 1 to 2 standard drinks either in the month around conception or in the most recent month of pregnancy. Comparison women were defined as no binge episodes, minimal or no alcohol (no more than 2 drinks on any occasion) in the month around conception, and no continued drinking in pregnancy. Upon enrollment, women in the alcohol exposed and contrast groups completed an interview that included a timeline follow-back assessment of day-by-day alcohol consumption by type, quantity, and frequency in both a week around conception and in the most recent 2 weeks (Sobell and Sobell, 2000). From the enrollment interview, absolute ounces of alcohol consumed by the mother in the week around conception and in the most recent 2 weeks of pregnancy were calculated per day and per drinking day.

For these analyses, we chose to estimate the effects of alcohol dose using absolute ounces of alcohol at conception as opposed to enrollment as women enrolled at different gestational time points, potentially confounding the effect estimates by exposure duration.

Neurodevelopmental Outcomes. We evaluated neurocognitive development with the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993). As detailed in a recent publication from this project (Coles et al., 2015), the BSID-II is widely used worldwide and is preferable to the third edition for this population (Lowe et al., 2013). Additionally, the scale is accessible in Russian, which is preferable to English in this Ukrainian population. Testing was administered by 2 Ukrainian psychologists blinded to the mother's alcohol exposure group. If mothers missed the 6-month assessment they were still eligible to complete the 12-month assessment.

We focused our analyses on the Mental Development Index (MDI) and Psychomotor Development Index (PDI), both of which were standardized to a scale with a mean of 100 and a standard deviation of 15. The MDI assesses early cognitive and language development through measures of knowledge, problem solving, and memory. The PDI evaluates body control, manipulation of large muscles, and fine manipulation skills. All scores were age standardized and age corrected for births prior to 37 weeks (n = 15).

Covariates. Demographic and pregnancy characteristics were obtained from maternal report. Potential confounders for model adjustment were selected from direct acyclic graphs (DAGs) (Greenland et al., 1999). Using subject matter knowledge, we constructed DAGs to identify confounders and mediators by mapping the hypothesized causal mechanism. Pregnancy vitamin use was operationalized as randomization to a multivitamin supplement for the trial and/or self-report of multivitamin use in pregnancy at the time of enrollment. In a recent publication from this study, Coles and colleagues (2015) found no difference in performance on the Bayley Scales between those who took only multivitamins or those who took multivitamins plus choline. Therefore, we collapsed our vitamin exposure over choline status for these analyses. Hollingshead category (socioeconomic status [SES]) was calculated from maternal reported familial employment and education (Hollingshead, 2011). Additional covariates included cohabitation status (married or cohabitating vs. single, separated, divorced, widowed), maternal education, maternal age at enrollment, prepregnancy body mass index (BMI), and maternal smoking status. Previous studies have associated maternal depression, independent of medication use, with preterm birth (Staneva et al., 2015). Accordingly, we did not adjust for gestational age at delivery or preterm birth in our models as they may mediate the pathway of interest. However, BSID-II scores were age standardized and corrected for prematurity as described.

Statistical Analyses

Generalized linear models were constructed to estimate beta coefficients for depressive symptoms (dichotomized Beck scale) and neurological development (MDI, PDI) at 6 and 12 months (resulting in 4 separate models), and subsequently an interaction term between depressive symptoms and alcohol group was added to assess joint effects. We then stratified the models by alcohol exposure group to better explore the effects of maternal depressive symptoms. Full models and models of the alcohol exposed stratum were adjusted for daily alcohol consumption (absolute ounces/d) at conception. Models were further adjusted for vitamin use in pregnancy, cohabitation status, Hollingshead SES, maternal education, maternal age at enrollment, prepregnancy BMI, gestational age at enrollment, and maternal smoking status.

To explore effect modification by infant gender, we stratified models by infant gender and constructed joint effects models in each alcohol exposure stratum with a sex*depressive symptoms interaction term.

Finally, in sensitivity analyses, censoring variables were created for attrition from initial enrollment to completion of the BDI, and from BDI to completion of the BSID-II at 6 months. Maternal pregnancy and demographic characteristics were regressed on these censoring variables in logistic regression models to estimate the extent of group differences in attrition on our estimates.

RESULTS

Due to the timing of enrollment, only 56.0% of the full enrollment cohort completed the BDI. After 32 weeks of gestation, women were not required to complete the second pregnancy visit, although 10 women did, resulting in a range of gestational age at enrollment through 39 weeks. In sensitivity analyses (data not shown), women who did not complete the BDI had lower SES than those who completed the measure. They did not differ on vitamin use in pregnancy, alcohol exposure group, marital status, education level, age, or prepregnancy BMI. Furthermore, women who completed the BDI but did not return for neurodevelopmental testing at either 6 or 12 months postpartum were less educated and younger than those who did return. Importantly for internal validity, those that did not return for the follow-up evaluations did not differ by alcohol exposure group or depression level. Thus, while we experienced moderate attrition from study entry, censoring was only differential by age and select socioeconomic indicators. This may slightly reduce external generalizability, but is generally representative of our original cohort.

From 344 enrolled women with BDI and BSID-II scores, 304 singleton infants participated in neurodevelopment testing at 6 months, 304 infants completed testing at 12 months, and 264 completed neurodevelopmental testing at both visits.

In the full sample, 21.0% had mild-severe depressive symptoms; 25.5% in the alcohol exposed stratum and 13.3% in the contrast stratum. Independent of alcohol

status, women with higher depressive symptoms were less likely to be cohabitating with a partner, had less education and lower SES, and were more likely to continue smoking in pregnancy (Table 1).

In generalized regression models of the full sample, periconceptional alcohol use (absolute oz/d) predicted each of the BSID-II measures at both 6- and 12-month time points. Unmedicated maternal depressive symptoms did not predict either the MDI or PDI at 6 or 12 months, although it had negative effect estimates at each observation (Table 2). Maternal depressive symptoms were more strongly associated with deficits in the MDI at 6 and 12 months and PDI at 6 months in the alcohol exposed strata, and the depressive symptoms*alcohol group interaction term was statistically significant for the PDI at 6 months ($p = 0.05$) and marginally significant for the MDI at 12 months ($p = 0.09$). Additionally, not taking multivitamin supplements in pregnancy was associated with deficits in both BSID-II tests at 12 months in the alcohol exposed stratum. In exploratory analysis, when alcohol exposure group was included in the full model instead of periconceptional alcohol use, the group effects were not statistically significant (data not shown).

When stratified by both alcohol exposure group and infant gender (Table 3), negative associations between maternal depressive symptoms and infant neurodevelopmental outcomes were much stronger in females, although interaction terms for infant sex*depressive symptoms only reached statistical significance in the MDI and PDI at 6 months within the alcohol exposed stratum. Similar disparities between the genders were also observed at 12 months in this stratum, although interaction terms failed to reach statistical significance. Among the alcohol exposed stratum, periconceptional alcohol consumption was associated with decrements in all BSID-II measures in males, but not in females.

Table 1. Demographic and Descriptive Characteristics of Participants by Alcohol Exposure Group and Pregnancy Depression ($n = 344$)

	Alcohol exposed			Contrast		
	No-minimal depressive symptoms	Mild-severe depressive symptoms		No-minimal depressive symptoms	Mild-severe depressive symptoms	
	$n = 111$ (32.3%)	$n = 38$ (11.1%)	p-value	$n = 169$ (49.1%)	$n = 26$ (7.6%)	p-value
Maternal characteristics						
Maternal age at enrollment (mean [SD])	26.3 (5.5)	26.1 (6.0)	0.89	26.2 (4.2)	27.0 (5.7)	0.50
Gestational age at delivery (mean [SD])	39.3 (1.8)	38.3 (2.4)	0.02	39.7 (1.3)	39.8 (1.2)	0.74
Parity (mean [SD])	0.5 (0.8)	1.1 (1.2)	0.01	0.7 (1.0)	1.2 (1.8)	0.18
Prepregnancy body mass index (mean [SD])	22.0 (3.9)	22.9 (4.2)	0.23	21.5 (3.2)	21.2 (3.4)	0.69
Gestational age at enrollment (mean [SD])	17.7 (5.9)	21.9 (7.6)	0.002	17.2 (5.1)	19.2 (6.8)	0.16
Cohabitation status						
Single, separated, or divorced	13 (11.7)	6 (15.8)	0.52	2 (1.2)	2 (7.7)	0.03
Maternal education						
Less than high school	10 (9.0)	7 (18.4)	0.05	5 (3.0)	3 (11.5)	0.02
High school diploma	66 (59.5)	26 (68.4)		64 (37.9)	14 (53.9)	
College	35 (31.5)	5 (13.2)		100 (59.2)	9 (34.6)	
Socioeconomic status						
Hollingshead >39	45 (40.5)	6 (15.8)	0.03	111 (65.7)	11 (42.3)	0.04
Hollingshead 30 to 39	39 (35.1)	15 (39.5)		40 (23.7)	8 (30.8)	
Hollingshead 20 to 29	13 (11.7)	8 (21.1)		16 (9.5)	7 (26.9)	
Hollingshead 8 to 19	14 (12.6)	9 (23.7)		1 (0.6)	0 (0.0)	
Missing	0 (0.0)	0 (0.0)		1 (0.6)	0 (0.0)	
Vitamin use in pregnancy						
No	28 (25.2)	11 (29.0)	0.65	37 (21.9)	4 (15.4)	0.45
Offspring gender						
Male	57 (51.4)	17 (44.7)	0.48	90 (53.3)	16 (61.5)	0.43
Maternal smoking						
Active pregnancy smoking	32 (28.8)	15 (39.5)	0.40	1 (0.6)	2 (7.7)	0.04
Former pregnancy smoking	29 (26.1)	9 (23.7)		5 (2.9)	0 (0.0)	
Past smoking (prior to pregnancy)	8 (7.2)	4 (10.5)		7 (4.1)	2 (7.7)	
Never smoked	41 (36.9)	9 (23.7)		152 (89.9)	22 (84.6)	
Missing	1 (0.9)	1 (2.6)		4 (2.4)	0 (0.0)	
Maternal exposures						
Beck score (mean [SD])	4.4 (3.0)	14.2 (5.3)	<0.001	3.9 (2.4)	13.8 (5.5)	<0.001
Alcohol use at conception (absolute oz/d) (mean [SD])	0.8 (1.0)	1.0 (1.1)	0.33	0.0 (0.0)	0.0 (0.0)	0.42
6-month Bayley outcomes						
Mental Development Index (MDI) (mean [SD])	88.5 (9.9)	83.3 (12.7)	0.02	90.9 (6.8)	90.5 (9.2)	0.81
Missing	13 (11.7)	4 (10.5)		19 (11.2)	4 (15.4)	
Psychomotor Development Index (PDI) (mean [SD])	87.8 (12.9)	82.6 (13.6)	0.05	89.7 (9.5)	93.0 (11.6)	0.15
Missing	13 (11.7)	4 (10.5)		19 (11.2)	4 (18.2)	
12-month Bayley outcomes						
MDI (mean [SD])	88.6 (11.6)	82.5 (15.9)	0.05	90.8 (10.0)	93.0 (11.6)	0.38
Missing	13 (11.7)	5 (13.2)		16 (9.5)	6 (23.1)	
PDI (mean [SD])	96.3 (12.8)	90.1 (18.8)	0.08	99.9 (10.5)	97.2 (14.4)	0.41
Missing	13 (11.7)	5 (13.2)		16 (9.5)	6 (23.1)	

Table 2. Beta Estimates (Bs) of Alcohol, Mild-Severe Depressive Symptoms, and Vitamin Use on Neurocognitive Outcomes

	Independent effects of exposures	Stratified analyses by alcohol group		
	Full model	Alcohol exposed	Contrast	*p* for interaction
6-month outcomes	*n* = 296	*n* = 129	*n* = 167	
MDI				
Alcohol use at conception (absolute oz/d)	−2.91 (−4.18, −1.64)	−3.08 (−4.75, −1.41)	n/a	
Depressive symptoms	−1.96 (−4.44, 0.52)	−2.62 (−6.34, 1.09)	−1.16 (−4.37, 2.06)	0.13
No vitamin use	−1.95 (−4.20, 0.31)	−3.10 (−7.10, 0.89)	−1.94 (−4.48, 0.59)	
PDI				
Alcohol use at conception (absolute oz/d)	−2.18 (−3.88, −0.48)	−1.80 (−4.05, 0.44)	n/a	
Depressive symptoms	−0.64 (−3.95, 2.68)	−2.48 (−7.49, 2.52)	1.14 (−3.16, 5.45)	0.05
No vitamin use	−3.22 (−6.23, −0.20)	−4.86 (−10.25, 0.52)	−2.32 (−5.71, 1.07)	
12-month outcomes	*n* = 296	*n* = 127	*n* = 169	
MDI				
Alcohol use at conception (absolute oz/d)	−2.67 (−4.38, −0.96)	−2.26 (−4.25, −0.27)	n/a	
Depressive symptoms	−0.16 (−3.54, 3.22)	−0.73 (−5.36, 3.89)	2.91 (−2.09, 7.91)	0.09
No vitamin use	−2.46 (−5.48, 0.56)	−5.18 (−9.91, −0.45)	0.31 (−3.64, 4.26)	
PDI				
Alcohol use at conception (absolute oz/d)	−2.58 (−4.44, −0.72)	−1.78 (−4.07, 0.50)	n/a	
Depressive symptoms	−1.65 (−5.34, 2.02)	−0.98 (−6.29, 4.33)	−2.28 (−7.56, 3.00)	0.82
No vitamin use	−3.29 (−6.58, −0.01)	−6.66 (−12.09, −1.23)	−0.88 (−5.04, 3.28)	

MDI, Mental Development Index; PDI, Psychomotor Development Index, BMI, body mass index.
Adjusted for vitamin use, cohabitation status, Hollingshead category, maternal education, maternal age at enrollment, prepregnancy body mass index, gestational age at enrollment, and maternal smoking status.

Table 3. Main effects (Bs) of Mild-Severe Depressive Symptoms and Vitamin Use on Neurodevelopmental Outcomes Stratified by Gender and Alcohol Use

	Alcohol exposed		*p* for interaction	Contrast		*p* for interaction
6-month outcomes	Male (*n* = 62)	Female (*n* = 67)		Male (*n* = 91)	Female (*n* = 76)	
MDI						
Alcohol use at conception (absolute oz/d)	−4.73 (−6.82, −2.65)	−0.28 (−2.79, 2.23)		n/a	n/a	
Depressive symptoms	0.68 (−4.58, 5.94)	−8.28 (−13.06, −3.49)	0.04	−0.90 (−4.65, 2.84)	−0.49 (−6.73, 5.75)	0.79
No vitamin use	5.28 (−0.87, 11.44)	−6.76 (−11.63, −1.88)		−1.20 (−4.78, 2.38)	−3.17 (−6.76, 0.43)	
PDI						
Alcohol use at conception (absolute oz/d)	−3.28 (−6.35, −0.22)	0.57 (−2.84, 3.99)		n/a	n/a	
Depressive symptoms	2.52 (−5.22, 10.25)	−10.30 (−16.81, −3.78)	0.01	0.21 (−4.67, 5.11)	2.48 (−5.56, 10.52)	0.23
No vitamin use	2.85 (−6.20, 11.90)	−8.80 (−15.43, −2.16)		−2.09 (−6.77, 2.60)	−2.48 (−7.41, 1.85)	
12-month outcomes	Male (*n* = 62)	Female (*n* = 65)		Male (*n* = 92)	Female (*n* = 77)	
MDI						
Alcohol use at conception (absolute oz/d)	−3.13 (−5.52, −0.75)	0.18 (−3.53, 3.88)		n/a	n/a	
Depressive symptoms	0.79 (−5.24, 6.82)	−6.88 (−14.26, 0.50)	0.17	5.25 (−1.29, 11.79)	−0.92 (−9.50, 7.65)	0.51
No vitamin use	0.47 (−6.18, 7.13)	−7.76 (−14.68, −0.84)		−0.54 (−6.44, 5.35)	0.44 (−4.55, 5.44)	
PDI						
Alcohol use at conception (absolute oz/d)	−3.28 (−6.35, −0.22)	−0.18 (−4.60, 4.24)		n/a	n/a	
Depressive symptoms	2.52 (−5.22, 10.25)	−6.82 (−15.63, 1.99)	0.20	−1.07 (−7.93, 5.78)	−3.38 (−12.80, 6.03)	0.56
No vitamin use	2.85 (−6.20, 11.90)	−8.71 (−16.96, −0.45)		−2.51 (−8.68, 3.67)	1.25 (−4.24, 6.74)	

MDI, Mental Development Index; PDI, Psychomotor Development Index.
Adjusted for alcohol use at conception (where applicable), Beck Depression Inventory, vitamin use, marital status, Hollingshead category, maternal education, maternal age at enrollment, prepregnancy body mass index, gestational age at enrollment, and maternal smoking status.

DISCUSSION

In this prospective cohort study of pregnant women selected for enrollment on the basis of periconceptional alcohol use, we did not find evidence of unmedicated maternal depressive symptoms independently predicting neurodevelopmental outcomes as measured by the BSID-II up to

12 months of age. We did, however, find some evidence of an interaction between prenatal depressive symptoms and PAE on measures of the PDI at 6 months and the MDI at 12 months. Additionally, there was some evidence of gender dependence within the alcohol exposed stratum, with female infants exhibiting larger neurodevelopmental deficits associated with maternal depressive symptoms than males. There was no interaction between gender and depressive symptoms in the contrast group.

To date, research on unmedicated prenatal depression and neurodevelopment has been rare, and results are inconsistent (Casper et al., 2003; Lebel et al., 2015; Nulman et al., 2012, 2015; Santucci et al., 2014). Barker and colleagues (2013) found prenatal depressive symptoms were negatively associated with cognitive function in 8-year-old offspring, which was partially mediated through prenatal nutrition. These results were robust to postnatal depression and nutrition, although were modest in effect size (Barker et al., 2013). Santucci and colleagues (2014) did not find evidence of an association between unmedicated prenatal depressive disorder (diagnosed with the Structured Clinical Interview for DSM-IV) and the MDI or PDI scales of the BSID-II at any point between 12 and 78 months postnatally. However, the sample of unmedicated women with major depressive disorder was small (n = 27). Additionally, their sample of infants had higher BSID-II scores than did our sample at both 6 months (MDI-105.5, PDI-102.5) and 12 months (MDI-107.3, PDI-99.7). The stronger group performance on the BSID-II may be a result of differences in sociodemographic characteristics between the 2 samples, potentially limiting comparability. Ultimately, however, the lack of evidence in support of a main effect of maternal depressive symptoms on infant neurodevelopment is largely consistent with previous reports.

Similar to the previous analysis of this cohort led by Coles and colleagues (2015), our data supported a modest reduction in neurodevelopmental outcomes associated with higher levels of periconceptional alcohol use. Additionally, neither analysis resulted in group level alcohol effects over the broader range of exposure patterns (Coles et al., 2015). Our lack of main effects of alcohol group as opposed to alcohol dose at conception is likely a result of the heterogeneity of alcohol intake that met the group definition. The alcohol exposed group consisted of women consuming moderate to high alcohol intake around the time of conception and/or at enrollment, and there was variability in quantity and duration of alcohol consumption after that time point.

Our lack of main effects of depression may be due to the depression measure selected, which was not validated in a Ukrainian population and may not have been familiar to this population. Additionally, due to the small sample that met the cutoff for moderate-severe depression, we employed a lower cutoff for mild depression which may have attenuated results. However, the correlates generally observed with depression, such as comorbid alcohol use, lower education and SES were observed here, increasing our confidence in the reliability of the measure in our sample. Finally, the main scales of the BSID-II, considered the gold standard for evaluation of neurodevelopment at this age, may lack the specificity to detect subtle differences in infant development resulting from pregnancy depression. We did not explore subscales of the BSID-II that measure orientation/engagement, emotional reactivity, and motor quality, as the sample that completed the subscales was further reduced. These subscale scores had large variance making interpretation with a small sample difficult. This cohort is currently being reassessed at 3.5 to 5 years with a more comprehensive preschool age testing battery, allowing us to reassess our hypothesis at that time. These later neurodevelopmental batteries, in addition to more refined emotional regulation and behavioral testing, may result in differences that the main scales of the BSID-II cannot yet detect (Coles et al., 2015; Santucci et al., 2014).

To our knowledge, this is the first study in humans to explore the joint effects of depressive symptoms and PAE. In a study of macaques, offspring exposed to a combination of PAE and maternal stress in pregnancy had the highest levels of adrenocorticotropic hormone after stress challenge, and consequently displayed cognitive deficits not observed from prenatal stress alone (Schneider et al., 2004). Conversely, in a study of the offspring of rat dams exposed to PAE and stress, PAE was associated with reduced learning and prenatal stress with increased anxiety. However, the authors found no interaction on either measure between the exposures (Staples et al., 2013). Both exposures are hypothesized to alter maternal and fetal HPA functioning, although they do not appear to share the same mechanisms (Lan et al., 2015; Lee and Rivier, 1992). Using adrenalectomized rats, Lee and Rivier (1992) demonstrated that corticosterone, which appears to mediate HPA changes in the offspring from prenatal stressors (including depression), does not mediate the changes in HPA function resulting from PAE. While questions therefore remain about the etiology of the synergism, our findings of a joint effect suggest that it warrants further exploration. Researchers often adjust for co-exposures such as alcohol use, tobacco use, and prenatal distress (stress, anxiety, and depression) depending on the exposure of interest; however, given the commonality of the co-exposures and potential implications for HPA axis development by each of them (Stroud et al., 2014; Waters et al., 2014; Weinberg et al., 2008), we argue that the joint effects should be more carefully considered.

Our findings of differential effects of maternal depressive symptoms by infant gender in those with PAE were intriguing. Sexual dimorphism was also reported in this sample by Coles and colleagues (2015), who found that males exposed to PAE without vitamin supplementation fared worse than their female counterparts. Our analyses, which adjusted for vitamin supplementation, found that females exposed to maternal depressive symptoms and PAE had greater measured neurodevelopmental deficits than their male counterparts. In a recent study using magnetic resonance imaging, female offspring had stronger negative correlations between

cortical thinning and maternal depressive symptoms in pregnancy than male offspring (Lebel et al., 2015). We too found greater evidence of female susceptibility to maternal depressive symptoms, but only in those with concurrent PAE. Recently, a few studies in humans have examined gender-dependent changes from maternal pregnancy stress. Male offspring had higher risks of attention deficit hyperactivity disorder and schizophrenia, while females had higher risks of anxiety or depression following prenatal stress exposure (reviewed in Weinstock, 2015). Although infrequently reported in human studies, there is a larger literature on gender-dependent outcomes in studies of pregnant rats. In general, female rats exposed to prenatal stress are more likely to display anxiety and learned helplessness while male rats were more likely to have deficits in spatial learning, although the results are inconsistent (Weinstock, 2007). Sexually dimorphic outcomes have also been reported with PAE. Haley and colleagues (2006) found females exposed to PAE had greater heart rate and negative affect than males; who conversely had greater changes in cortisol. Given the scarcity of human literature on gender-dependent outcomes with either exposure, and the inconsistency of results from animal models, our results should be interpreted with caution. However, the mounting suggestion of differential risk from prenatal distress by gender invites further investigation.

In discussing our findings, it is important to consider the limitations of the study. As discussed earlier, there is potential exposure misclassification resulting from the BDI, 1A in this Ukrainian speaking population. For sample size considerations, we selected a lower cutoff on the BDI-1A than typically used, resulting in a more heterogeneity in our depression exposed group. However, we would expect this potential misclassification to be nondifferential and therefore to attenuate results. Another limitation is that we do not have a measure of prenatal stress, which may co-occur with both prenatal alcohol consumption and maternal depressive symptoms, and has been independently associated with neurodevelopmental deficits (Kingston et al., 2012). Also, we do not have mental health measures postnatally. Maternal postpartum depression has been well studied for its effects on neurodevelopment in the offspring (Azak, 2012; Grace et al., 2003). Measures of postpartum depression, anxiety, or stress would have allowed for mediation analyses or examination of the joint effects of these measures pre- and postpartum. Finally, we would have liked to explore the BSID-II outcomes at 6 and 12 months longitudinally with repeated measures, however, our sample size and attrition between visits would not allow for this analysis.

Despite these limitations, we are intrigued by the findings of synergism between maternal depressive symptoms in pregnancy and PAE, particularly in the female offspring. Prenatal depression and alcohol use are both potentially detrimental to the behavioral and developmental well-being in the offspring. Their synergies may further jeopardize the offspring of women who struggle with both, a comorbidity that tends to be associated with other socioeconomic disadvantages. By recognizing the importance of maternal mental health in our aims of mitigating the deleterious effects of PAE, we hope to increase the effectiveness of our efforts.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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