Fatty Acid Ethyl Esters in Meconium are Associated with Poorer Neurodevelopmental Outcomes to Two Years of Age

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Objective To determine the relationship between fatty acid ethyl esters (FAEE) in meconium and neurodevelopment in infants exposed to alcohol in utero at 6.5 months, 1 year, and 2 years of age.

Study design A secondary analysis of a prospective cohort of mothers at high risk and their infants recruited after admission to a labor and delivery unit. Mothers were screened for drug and alcohol use during pregnancy by clinical interview and urine screening. Meconium was analyzed for FAEE in 216 newborn infants. Outcome measures included the Bayley Scales of Infant Development Mental (MDI) and Psychomotor (PDI) Developmental Index scores in infants at 6.5 months, 1 year, and 2 years of age.

Results After controlling for prenatal visits and maternal factors, increasing concentrations of FAEE were significantly associated with poorer mental and psychomotor development ($\beta \pm$ standard error) at all follow-up visits: ethyl myristate (MDI -2.46 ± 1.24, $P = .05$; PDI -3.88 ± 1.67, $P = .02$), ethyl oleate (MDI -1.94 ± 0.65, $P < .01$; PDI -2.60 ± 0.93, $P < .01$), ethyl linoleate (MDI -1.92 ± 0.60, $P < .01$; PDI -2.28 ± 0.84, $P < .01$), ethyl linolenate (MDI -1.99 ± 0.74, $P < .01$; PDI -2.98 ± 1.04, $P < .01$), and ethyl arachidonate (MDI -2.40 ± 1.11, $P = .03$; PDI -3.32 ± 1.51, $P = .03$).

Conclusion FAEE in meconium may be a marker for identifying newborns at risk for neurodevelopmental delay from alcohol exposure in utero. *(J Pediatr 2008;152:788-92)*

Fetal alcohol syndrome (FAS) represents a wide range of developmental disabilities resulting from alcohol exposure in utero and is the leading cause of mental retardation.[1] Children with FAS are also at risk for psychiatric problems, criminal behavior, unemployment, and incomplete education. Even low to moderate levels of prenatal maternal alcohol exposure are associated with impairments in cognitive and behavioral functioning including lower IQ, attention deficits, decreased executive functioning, balance deficits, and visual-spatial deficits.[2-4] Identification of children exposed to alcohol in utero is critical to facilitating early intervention and minimizing secondary disabilities.[5] However, recognizing children who may have cognitive impairments from prenatal alcohol exposure can be challenging when the characteristic facies of FAS are absent.[6]

Fatty acid ethyl esters (FAEE), the nonoxidative metabolites of ethanol in meconium, may be useful biologic markers for measuring alcohol exposure in utero. Increased concentrations of FAEE in meconium correlate with prenatal alcohol exposure.[7-9] To our knowledge, no studies have demonstrated an association between FAEE in meconium and neurodevelopment. The objective of this report was to determine whether a relationship exists between specific FAEE and neurodevelopmental outcome at 6.5 months, 1 year, and 2 years of age in infants enrolled in a longitudinal neurobehavioral study.[7,9,10] We hypothesized that increasing concentrations of FAEE in meconium would be associated with poorer mental and psychomotor performance.

FAEE	Fatty acid ethyl esters	MDI	Mental Developmental Index
FAS	Fetal alcohol syndrome	PDI	Psychomotor Developmental Index
GSI	General Severity Index	PPVT	Peabody Picture Vocabulary Test

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METHODS

Subjects

Eligible mothers included those presenting to the labor and delivery unit and considered at high risk for drug use. Mothers and their infants were enrolled between 1994 and 1996 from a large urban county teaching hospital. All mothers provided informed consent to participate. Detailed descriptions of study methods including inclusion and exclusion criteria, methods of enrollment, baseline evaluation, and meconium analysis were previously reported.[7,9,10] Mothers were included if they received no prenatal care; appeared to be intoxicated or taking drugs; had a previous history of involvement with the Department of Human Services; were at least 19 years of age; and had no history of psychiatric or chronic illness, primary heroin use, human immunodeficiency virus–positive status, or low maternal IQ. Infants and their respective mothers were excluded if meconium was not available or they had evidence of Down syndrome, fetal alcohol syndrome, or infant illness.

Study nurses approached all mothers shortly before or after birth. The method of quantifying maternal alcohol and drug use by questionnaire has been previously described.[9,10] Briefly, subjects underwent a standardized interview within 1 month postpartum to estimate the amount and frequency of maternal alcohol use during each trimester of pregnancy and the month before delivery. The number of drinks of beer, wine, or hard liquor each day was determined. A drink was equivalent to 0.5 mL of absolute alcohol.[11]

Demographic and medical characteristics were obtained from the medical records of the mothers and their infants. Measures of maternal vocabulary, nonverbal intelligence, and psychological distress were obtained from all mothers via the Peabody Picture Vocabulary Test—Revised (PPVT),[12] block design and picture completion subscales of the Wechsler Adult Intelligence Scales—Revised,[13] and the Brief Symptom Inventory,[14] respectively. Overall distress was measured by use of the Brief Symptom Inventory and is summarized by use of a General Severity Index (GSI). Infants were considered small for gestational age if their birth weight was more than 2 standard deviations below the mean for gestational age.[15] The Hobel Neonatal Risk score was computed for all infants to obtain a measure of neonatal risk.[16]

FAEE Analysis

Meconium was collected from the newborn infant shortly after birth and stored at −70°C until analysis. The following FAEE were analyzed: (1) ethyl myristate, (2) ethyl palmitate, (3) ethyl oleate, (4) ethyl linoleate, (5) ethyl linolenate, and (6) ethyl arachidonate.[9] Detailed methods for meconium collection have been previously reported.[7,9] Meconium analyses were performed by investigators blinded to questionnaire results.

Neurodevelopmental Outcomes

The primary outcome of this report was neurodevelopmental outcomes of infants at 6.5 months, 1 year, and 2 years corrected age born to high risk mothers. Neurodevelopment was assessed with Bayley Scales of Infant Development (2nd edition).[17] Bayley Scales examine mental and psychomotor development with 2 scales: the Mental Development Index (MDI), which measures memory, language, and problem-solving abilities, and the Psychomotor Developmental Index (PDI), which measures gross and fine motor control and coordination. Interrater reliabilities for examiners for the scales averaged 93% for the MDI and 94% for the PDI.[10] Assessors were blinded to mother and infant drug and alcohol exposure.

Statistical Analysis

Concentrations for each FAEE were transformed with $\log_{10}$ plus 100. Log transformations are routinely used to convert values, which increase exponentially to a scale where the increase is linear, thus allowing for standard parametric statistical testing to be used. A constant value of 100 was added, which effectively set the value of the samples with values below the limit of detection at 100 to allow for log transformation.

The relationships of FAEE values to corrected Bayley scores at each time period were described with Spearman correlation coefficients (ρ). Mixed linear regression models with an unstructured covariance structure were used to estimate the association between transformed values of FAEE in meconium and corrected Bayley scores, after controlling for potential confounding and demographic factors, in a longitudinal analysis using data from all three visits (6.5 months, 1 year, and 2 years of age). The models initially included terms for FAEE, visit, and the interaction between FAEE and visit. The interaction was included to test for visit-specific FAEE associations with MDI and PDI. If the interaction was not significant, it was then excluded from the model, implying that the associations do not significantly vary over time.

Variables that were significantly associated with FAEE measures and were known to be related to the outcome measures were considered as potential confounders and entered into the model using a backward elimination approach. Variables under consideration are listed in Tables I and II. Each FAEE was considered separately. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. A sample size calculation was performed and has been previously reported.[10] All analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Four hundred fifteen subjects were enrolled in the study by Singer et al.[10] Of these infants, 216 had adequate analysis of meconium (0.5 g or more of meconium available and 50% or greater recovery of internal standard[9]). Twenty-two subjects had missing maternal data, and 4 had no developmental

Table I. Maternal characteristics

Variable	
Age at birth (years)	27.6 ± 5.4
Education (years)	11.8 ± 1.5
Gravidity	4.0 (2.0-5.0)*
Parity	3.0 (2.0-4.0)*
Prenatal visits	8.0 (3.0-11.0)*
Average drinks of alcohol per week	0.4 (0.0-3.0)*
Average cocaine units per week	0.0 (0.0-5.2)*
Average marijuana dose per week	0.0 (0.0-0.6)*
Average cigarettes per day	3.9 (0.0-12.5)*
PPVT standard score	76.8 ± 13.2
Block design score	7.0 ± 2.1
Picture completion scale	6.8 ± 2.3
General Severity Index score	0.4 (0.2-0.9)*
Married	24 (12.6%)
African American	155 (81.6%)
Currently employed	34 (17.9%)
Low socioeconomic status	190 (100%)

*Median (interquartile range).

Table II. Infant characteristics

Variable	Mean ± SD
Gestational age (weeks)	38.4 ± 2.9
Birth weight (grams)	2989 ± 661
Birth length (cm)	48.7 ± 3.9
Birth head circumference (cm)	33.1 ± 2.4
1-minute Apgar score	8.0 ± 1.4
5-minute Apgar score	8.8 ± 0.7
Hobel Neonatal Risk score	0.0 (0.0-5.0)*
Males	84 (44.2%)
Premature (<37 weeks gestation)	40 (21.1%)

*Median (interquartile range).

testing, leaving 190 subjects from the original study cohort available for analysis. Maternal and infant demographic data are presented in Tables I and II. One hundred thirty-eight (73%) mothers reported alcohol use, and 52 (27%) mothers denied using alcohol during pregnancy. Mean (±SD) maternal age at delivery was 27.6 (±5.4) years old, and most of the women were African American (82%), single (87%), and of low socioeconomic status (100%). Mean (±SD) gestational age was 38.4 (±2.9) weeks and birth weight was 2989.4 (±661.3) g. Of the subjects, 89% completed follow-up at 6.5 months, 95% at 1 year, and 96% at 2 years corrected age.

Associations between demographic data and FAEE concentrations are shown in Table III. Maternal measures associated with increasing FAEE were gravidity, parity, alcohol use, and General Severity Index score. For the infants, gestational age, birth weight, and birth length were associated with increasing FAEE.

Correlations between FAEE concentrations and mental (MDI) and psychomotor (PDI) development were investigated. An increasing concentration of ethyl linolenate was associated with lower MDI at 6.5 months of age ($\rho = -0.156$, $P < .05$). At 2 years of age, increasing concentrations of ethyl myristate ($\rho = -0.205$, $P < .01$) and ethyl oleate ($\rho = -0.151$, $P < .05$) were associated with lower MDI. Significant correlations were only seen at 2 years with PDI. Increasing concentrations of ethyl myristate ($\rho = -0.155$, $P < .05$), ethyl oleate ($\rho = -0.156$, $P < .05$), ethyl linoleate ($\rho = -0.160$, $P < .05$), and ethyl arachidonate ($\rho = -0.153$, $P < .05$) were associated with lower PDI. There were no significant associations between any FAEE and MDI or PDI at 1 year corrected age.

In the longitudinal analysis with linear mixed models, none of the FAEE × visits or age interactions were significant. This implied that the effect of FAEE on MDI or PDI scores did not significantly vary over time. After controlling for cocaine exposure, sex, maternal nonverbal intelligence at birth, gestational age, and birth weight, increasing levels of 5 FAEE were associated with significantly lower MDI at all follow-up visits (Table IV). After controlling for parity, maternal GSI score, maternal nonverbal intelligence, prenatal cigarette exposure, and maternal PPVT standard score, increasing levels of 5 FAEE were also associated with significantly lower PDI at all follow-up visits (Table IV).

DISCUSSION

Elevated FAEE in meconium may be a marker for identifying newborn infants at risk for neurodevelopmental delay from alcohol exposure in utero. We found that increasing levels of 5 FAEE were significantly associated with poorer mental and psychomotor development during the first 2 years of age. These findings have significant implications because prenatal exposure to alcohol is one of the leading preventable causes of birth defects, mental retardation, and neurodevelopmental disorders in the United States.[18]

Several findings merit further discussion. A positive relationship was found between several maternal characteristics and FAEE. Increasing gravidity and parity were associated with increasing FAEE. Higher gravidity and parity have been reported as risk factors for FAS.[19] The results would indicate either heavier drinking by these mothers or a difference in their metabolism such that more FAEE are formed. This observation may explain their increased risk. The average consumption of alcohol during pregnancy was also positively correlated with FAEE with the exception of ethyl myristate and ethyl linolenate. Our previous report showed that each of the FAEE in meconium was greater in nonabstainers versus abstainers.[9] The lack of a positive correlation with these 2 FAEE may be due to the method of statistical analysis. In this case, we only took the mother's self report of alcohol use. In our previous study, we considered women as nonabstainers if they admitted to using cigarettes, marijuana, or cocaine. Because ethyl myristate and ethyl linolenate have not been the strongest predictors of maternal drinking,[9] this change in the definition of abstainers may account for the loss of a significant correlation. Maternal GSI was also positively correlated with FAEE. The simplest explanation is that mothers who experience more stress also drink more.[20]

Table III. Maternal and infant characteristics associated with fatty acid ethyl esters*

	Ethyl myristate	Ethyl palmitate	Ethyl oleate	Ethyl linoleate	Ethyl linolenate	Ethyl arachidonate
Maternal data						
Age	0.06	0.11	0.04	0.04	0.04	0.10
Education	−0.03	−0.04	−0.05	−0.06	−0.04	0.00
Gravidity	0.09	0.10	0.15†	0.13‡	0.10	0.12‡
Parity	0.14‡	0.12‡	0.19§	0.16†	0.10	0.10
Prenatal visits	−0.05	−0.01	−0.05	−0.01	−0.02	−0.06
Alcohol (drinks/wk)	0.11	0.18†	0.14†	0.12†	0.06	0.15†
Cocaine (times/wk)	0.09	0.10	0.06	0.04	0.05	0.09
Marijuana (joints/wk)	0.13‡	0.11	0.09	0.11	0.08	0.09
Cigarette use (cig/day)	0.06	0.03	0.03	0.04	0.01	0.04
PPVT	−0.07	−0.06	−0.07	−0.03	−0.05	−0.02
Block Design	0.00	−0.09	−0.03	−0.02	−0.02	−0.02
Picture Completion	−0.03	−0.03	0.01	0.02	0.04	0.04
General Severity Index	0.12	0.14‡	0.14‡	0.13‡	0.08	0.08
Infant data						
Gestational age	0.12‡	0.16†	0.08	0.14‡	0.12‡	0.16†
Birth weight	0.12‡	0.16†	0.11	0.16†	0.17†	0.17†
Birth length	0.09	0.14†	0.10	0.15†	0.14†	0.17†
Birth head Circumference	−0.02	−0.01	−0.05	0.00	0.03	0.06
Apgar score at 1 minute	0.04	0.00	0.00	0.04	0.03	0.00
Apgar score at 5 minutes	0.04	0.06	0.03	0.05	−0.03	0.04
Hobel Neonatal Risk score	0.04	−0.01	0.04	0.06	0.10	0.05

*Data presented as Spearman correlation coefficients. †$P < .10$. §$P < .05$. ‡$P < .01$.

Table IV. Associations of fatty acid ethyl esters (FAEE) with Mental (MDI) and Psychomotor (PDI) Developmental Index

	MDI*†		PDI‡	
FAEE	$\beta \pm$ SE	*P* value	$\beta \pm$ SE	*P* value
Ethyl myristate	−2.46 ± 1.24	.05	−3.88 ± 1.67	.02
Ethyl palmitate	−1.61 ± 1.14	.16	−2.89 ± 1.60	.07
Ethyl oleate	−1.94 ± 0.65	<.01	−2.60 ± 0.93	<.01
Ethyl linoleate	−1.92 ± 0.60	<.01	−2.28 ± 0.84	<.01
Ethyl linolenate	−1.99 ± 0.74	<.01	−2.98 ± 1.04	<.01
Ethyl arachidonate	−2.40 ± 1.11	.03	−3.32 ± 1.51	.03

*After controlling for cocaine exposure, gender, and maternal nonverbal intelligence.
†Additional controlling for gestational age for ethyl oleate and birth weight for ethyl linoleate.
‡After controlling for parity, maternal GSI score, maternal nonverbal intelligence, prenatal cigarette exposure, and maternal PPVT standard score.

Of the infant measures, only gestational age, birth weight, and birth length correlated with the amount of FAEE. It is not surprising that there were no negative correlations because the study population did not drink heavily. The mean alcohol drinks per week was 0.4 or 5.2 g/wk. In a study reviewing the effects of low-moderate (less than 84 g/wk) alcohol exposure on pregnancy outcome, no consistent effect on gestational age or birth weight was found.[21] Indeed, some studies reported greater mean birth weight at 12 to 24 g of alcohol consumption per week and less prematurity with drinking up to 72 g per week. Our results are consistent with these studies. We anticipate neurobehavioral changes to occur at doses of ethanol less than those required for effects on growth.[22]

In the correlation analysis, very few FAEE correlated to MDI or PDI. However, in the regression analysis, all but one, ethyl palmitate, did correlate. Ethyl palmitate was not strongly associated with maternal drinking in our prior study.[9] The children in this study are exposed to multiple risk factors for poor neurodevelopmental outcome including poor socioeconomic status, maternal cocaine use, and low maternal IQ. When investigating the effects of ethanol on neurodevelopment, it may be necessary to account for the uneven distribution of these other risk factors in this highly exposed population.[23]

Two of the FAEE (ethyl myristate and ethyl linolenate) were significantly associated with MDI and PDI but were not significantly related to admission of alcohol use by the mother. We are concerned that the alcohol histories given by the mother are not always accurate, even though the method of obtaining such histories is state of the art. Our concerns lie with the known stigma of reporting alcohol use, the difficulty in recall over 9 months of pregnancy, and the sometimes ambiguous answers on our questionnaire. For example, in our patient population, 95 mothers reported no drinking in the month before pregnancy. However, only 52 mothers reported no drinking during pregnancy. To overcome these difficulties in our previous study on this patient population,[9] abstainers

were defined as women who answered no to all questions about drinking, cocaine, tobacco, and marijuana. In that analysis, all of the FAEE reported here were significantly different between the abstainers and nonabstainers. This report's analysis of the 2 more-objective measures, that of FAEE and outcome, is likely to be more accurate (ie, outcome is a better "gold standard" than maternal self report).

The prevalence rate of FAS is between 0.5 to 2 cases per 1000 births,[24] with the total lifetime cost of caring for a typical child with FAS as high as $1.4 million.[5] Prenatal alcohol exposure warrants referral for early intervention and access to educational agencies providing services under the provisions of the Individuals with Disabilities Education Act.[25] The American Academy of Pediatrics Committee on Substance Abuse and Committee on Children with Disabilities recommends that infants and children with a suspected diagnosis of FAS or fetal alcohol spectrum disorder should undergo evaluation for neurodevelopmental and psychosocial problems.[26] In the future, the meconium analysis described in this article could be used as an early identifier at birth of such at-risk children.

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