

MECONIUM FATTY ACID ETHYL ESTERS AND PREDICTION OF FETAL ALCOHOL EFFECTS

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Measurement of fatty acid ethyl esters (FAEE) in meconium is a relatively novel biomarker to detect heavy prenatal alcohol exposure. As a biomarker of exposure, FAEEs have been shown to have high sensitivity and specificity.^{1,2,3,4}

Recent studies have also evaluated the ability of FAEEs in meconium to predict adverse outcomes associated with fetal alcohol spectrum disorder (FASD). This article will review the current literature concerning the predictive value of FAEEs in meconium in identifying adverse fetal effects. Analysis of the ability of FAEEs in meconium to predict fetal alcohol effects is critical in evaluating the qualities of this new screening tool in the general population.

In the first report, a population based study in Hawaii (n=422), Derauf *et al.* performed multiple logistic regression analysis to assess the association between FAEEs in meconium and different fetal outcomes.⁵ The regression allowed for control of factors that may affect fetal outcome such as other illicit drug use, which was also tested for in meconium. Total FAEE present in meconium was associated with lower one-minute Apgar scores measured at one-minute (p=0.003).

Additionally, ethyl oleate was associated with decreased birth weight (<2500g) (p=0.006). No association was found between other fetal outcomes such as head circumference, birth weight (as a continuous variable), gestational age, or recumbent length. The positive cutoff for cumulative FAEEs used in this study was 50ng/gram meconium. This value is tenfold lower than the current cutoff of 500ng/gram meconium that is currently used by the US Drug Testing Laboratory, the laboratory where the meconium samples were analyzed for this study. Using the current, higher positive cutoff could possibly result in stronger associations since it would increase the specificity of the test.

In a second report, a prospective study by Noland *et al.*, 316 children completed executive functioning (EF) tasks at 4 years of age.⁶ The test included working memory, ability to plan, focus

attention, and inhibitory control and relies on the functioning of the frontal-subcortical circuit. The three EF tasks performed in this study included category fluency, motor planning, and tapping inhibition. A child was considered alcohol exposed if FAEE levels were significantly greater than levels reported in an abstaining population from Jordan. Alcohol exposed children had a significantly lower tapping inhibition score (t=2.34 df=171) than non-exposed (defined by both a negative meconium test and maternal self-report). There was no difference regarding the motor-planning and category fluency tasks but the authors propose that the abilities required for these two tasks may not be developed enough by the age of 4 to detect differences between the groups. Alcohol exposure remained a significant predictor of tapping inhibition performance after determining potential confounders, including current home environment and other prenatal drug exposures. The alcohol-exposed group also had lower birth weight, birth length, and head circumference. Furthermore, lower means for full-scale, verbal, and performance IQs were implied, although these did not reach statistical significance (p<0.08, p<0.1, p<0.1 respectively).

An additional paper and abstract have been published reporting outcomes measured in the same cohort of children as the previous study by Noland *et al.* Performance on attention tasks that are under control of the frontal-striatal system was not affected by alcohol exposure (n=330).⁷ However, Peterson *et al.* determined a significant association between specific FAEEs and decreased psychomotor performance in children at age 2 (n=202) (p=0.01-0.04).⁸ Psychomotor performance was measured by the psychomotor developmental index scores of the Bayley Scales of Infant Development. No association was shown at 6.5 months and 1 year assessments.

In a recent abstract by Jacobson *et al.*, ethyl oleate had a stronger relation to infant cognitive performance on recognition memory and processing speed on the Fagan Test of Infant Intelligence than did maternal self report (n=55).⁴

The same observation was made between ethyl oleate and complexity of spontaneous and elicited symbolic play. Furthermore, higher levels of ethyl oleate were found in infants who received a diagnosis of fetal alcohol syndrome (FAS) or partial FAS at the age of 5 ($p < 0.005$).

Using an animal model, Brien *et al.* determined the relationship of FAEEs in meconium of the fetal guinea pig pups to outcome.⁹ The guinea pig is a useful animal model for studying ethanol-induced neurodevelopmental toxicity because, compared to other rodent models such as the rat and mouse, the guinea pig is more similar to human prenatal brain development. Pregnant guinea pigs were treated with either 4g ethanol/kg maternal body weight/day ($n=8$), isocaloric-sucrose/pair feeding ($n=8$), or water ($n=2$) from gestational day 2 to 64.

Meconium was collected from the term fetal large intestine. Total FAEEs in meconium had an inverse relationship with both fetal body weight ($r = -0.37$, $p < 0.05$) and brain weight ($r = -0.66$, $p < 0.05$). Interestingly, total FAEE did not correlate with maternal blood ethanol concentration measured at gestational day 57 or 58, supporting the hypothesis that FAEE concentration in meconium reflects fetal ethanol exposure since FAEEs do not cross the placenta.¹⁰

Three peer-reviewed papers and 2 abstracts report on the relationship of FAEEs in meconium and outcomes related to FASD. When evaluating current and future studies on this topic, the power of the study to detect differences in the alcohol-exposed group must be considered. Fetal alcohol exposure does not always lead to adverse effects in offspring. In fact, only 40% of children will be affected, and only 4% will have the full features of FAS.¹¹ Studies must therefore have a sufficiently sample size to account for this low incidence of fetal alcohol effects.

Associations between elevated FAEEs in meconium and growth restrictions, decreased executive function, specific cognitive performance, and psychomotor performance have been described. It is evident that FAEEs are a useful tool to assist in early identification of children with prenatal alcohol exposure that may develop deficits associated with FASD. Because early identification of children with prenatal alcohol exposure is needed to prevent secondary problems associated with FASD¹², FAEEs in meconium should be used as a clinical tool to assist in detecting or even screening for prenatal alcohol exposure.

TABLE 1 Evidence to support the association between elevated FAEEs in meconium and fetal alcohol effects.

Study Population	Association with elevated FAEEs in meconium*	Reference
Honolulu, Hawaii population (n=422)	<ul style="list-style-type: none"> lower one-minute Apgar scores ($p=0.003$) ethyl oleate associated with low birth weight ($<2500g$) ($p=0.006$) 	Derauf <i>et al.</i> ⁵
Infants enrolled in longitudinal neurobehavioural study (n=316)	<ul style="list-style-type: none"> Lower score on executive functioning task assessed through tapping inhibition at age 4 ($t=2.34$ $df=171$) Lower birth weight, birth length, and head circumference Lower (non-significant) means for full-scale, verbal, and performance IQs, ($p < 0.08$, $p < 0.1$, $p < 0.1$ respectively) 	Noland <i>et al.</i> ⁶
	<ul style="list-style-type: none"> Decreased psychomotor performance in children at age 2 ($p=0.01 - 0.04$ for different esters) 	Peterson <i>et al.</i> ⁸
Cape Town, South Africa cohort (n=55)	<ul style="list-style-type: none"> Elevated ethyl oleate in infants given a diagnosis of FAS or pFAS at age 5 ($p < 0.005$). Correlation between ethyl oleate with recognition memory, processing speed, and complexity of symbolic play stronger than maternal self-report 	Jacobson <i>et al.</i> ⁴
Fetal Guinea Pig <ul style="list-style-type: none"> Alcohol- exposed (n=25) Sucrose pair-fed (n=23) Water (n=3) 	<ul style="list-style-type: none"> Inverse correlation with fetal body weight ($r = -0.37$, $p < 0.05$) and brain weight ($r = -0.66$, $p < 0.05$) 	Brien <i>et al.</i> ⁹

*Results are discussed as total FAEEs measured in meconium unless otherwise stated.

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