IS MILD-MODERATE DRINKING IN PREGNANCY HARMLESS? NEW EXPERIMENTAL EVIDENCE TO THE OPPOSITE

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ABSTRACT

During the last decade a growing number of studies have failed to detect adverse neurodevelopmental effects of mild –to moderate maternal drinking in the exposed child, supporting a climate that "some drinking in pregnancy is OK".

A recent experimental study in sheep, mimicking conditions of moderate drinking in the third trimester of pregnancy, provides powerful evidence that there are serious lifelong risks to fetal exposure to alcohol. These should serve as an alarm call to those who legitimize mild-moderate maternal drinking based on incomplete data.

Alcohol consumption during pregnancy is associated with fetal alcohol syndrome disorder (FASD) – a spectrum of effects in newborns including physical malformations, behavioural disturbances, and neurological damage.[1] The most severe form of FASD is Fetal Alcohol Syndrome (FAS), which is diagnosed by characteristic facial malformations including short palpebral fissures, flat philtrum, and thin upper lips, as well as growth retardation and cognitive and neurological deficits.[2] Other forms of FASD, however, are more difficult to diagnose due to the absence of the pathognomonic facial malformations. Thus, the majority of these cases go undetected until later in the child's life since maternal self-report of alcohol consumption is often unreliable.[3] This is a major challenge because early diagnosis and intervention are associated with better outcomes and decreased secondary disabilities in individuals with FASD.[4] To overcome this problem, establishing a reliable biological marker of fetal alcohol exposure is crucial for early diagnosis of the less severe forms of FASD.

During the last decade a growing number of studies have failed to detect adverse neurodevelopmental effects of mild to moderate maternal drinking, supporting a climate that "some drinking in pregnancy is OK".[4]

A recent experimental study in sheep, mimicking conditions of mild drinking in the third trimester of pregnancy, provides powerful evidence that there are serious lifelong risks to fetal exposure to alcohol.[5] These should serve as an alarm call to those who legitimize maternal drinking based on incomplete data.

FAEE as a Biological Marker of Fetal Alcohol Exposure

Ethanol undergoes non-oxidative metabolism to produce fatty acid ethyl esters (FAEE). FAEEs can accumulate in fetal meconium and have been validated as sensitive and specific biological markers of heavy maternal drinking during the second and third trimesters of pregnancy in humans.[6-8] The sensitivity and specificity of meconium FAEEs in detecting lower levels of fetal alcohol exposure has yet to be elucidated. The ability of meconium FAEEs to identify newborns at risk for of more subtle organ dysfunctions are also not yet clear.

The Study

A recent study conducted by Zelner et al.[5] investigated whether meconium FAEE concentrations can serve as a biological marker of moderate alcohol consumption in the third-trimester-equivalent of pregnant sheep. The

investigators also assessed the relationship between meconium FAEE concentration and fetal organ injury. Fetal sheep is a useful animal model due to the similarities in organ development and ethanol disposition with humans. Moreover, the pharmacokinetics of maternal-fetal distribution and elimination are similar in both sheep and humans. Previous studies have also shown that the ability to produce FAEEs are comparable in sheep and humans.

In this study, 8 pregnant ewes were infused with ethanol daily for one hour during the third-trimester-equivalent producing maternal and fetal plasma ethanol concentrations (PEC) of 0.11 -0.12 g/dL (blood ethanol concentration approximately equivalent to a 55 to 70 kg woman consuming 3 to 4 standard alcohol drinks over one hour). Another 8 pregnant ewes were infused with saline daily for one hour and 6 additional pregnant ewes served as untouched controls. At 134 days gestational age (DGA) (full term ~147 DGA), the pregnant ewes and their fetuses were euthanized. The fetuses and their kidneys, lungs, heart, and brain were weighed. Fetal meconium was also collected and FAEE concentrations were quantified by headspace solid-phase microextraction gas chromatography-mass spectrometry. The investigators found that the meconium FAEE concentrations were significantly higher in the sheep exposed to ethanol than in the control groups (saline-only and untouched sheep). Subsequent ROC analysis demonstrated that a positive cut-off value of 0.0285 nmol FAEE/g meconium had a 93% specificity and sensitivity for detecting fetal ethanol exposure. This cut-off value was then used to assess the relationship between meconium FAEE and fetal organ abnormalities.

All major fetal organs investigated (kidneys, lungs, heart, and brain) were adversely affected by the moderate alcohol exposure. In the ethanol-exposed fetuses, there was no change in overall kidney growth; however, there was an 11% decrease in nephron endowment. There was also a negative correlation between meconium FAEE concentration and nephron number. When the positive cut-off value of 0.0285 nmol FAEE/g meconium was used, sheep that tested above this value had lower nephron numbers compared to those that tested below. These data suggest that ethanol exposed fetuses may have impaired renal function post-natally.

Examination of the fetal lungs showed significantly increased collagen deposition. Using the positive cut-off value, fetuses that tested above had significantly increased collagen deposition compared to those that tested below. Furthermore, mRNA levels of surfactant protein (SP)-A and SP-B and pro-inflammatory cytokines interleukin (IL)-1β and IL-8 were decreased in fetuses exposed to alcohol, which may have implications in lung function and predispose ethanol-exposed fetuses to lung infections.

When investigating the ethanol-induced pathology on the fetal heart, the investigators found an increase in relative heart weight and left ventricle wall volume in fetuses exposed to alcohol. The relationship between meconium FAEE concentration and relative heart weight showed a significant positive correlation. Additionally, advanced cardiomyocyte maturation was seen in the left ventricle of ethanol exposed sheep. There was a significantly higher proportion of binucleated cardiomyocytes and lower proportion of mononucleated cardiomyocytes with in the left ventricle and septum in sheep that tested above the positive cut-off value, suggesting earlier maturation in cardiomyocytes and possible cardiac dysfunction in sheep exposed to ethanol.

In the fetal brain, there was an increase in tropoelastin and collagen I α1 mRNA in the cerebral vasculature of ethanol-exposed fetuses. Subarachnoid hemorrhages and/or cerebellar parenchyma associated with cell death and gliosis with were also seen in 3 out of the 8 ethanol-exposed fetuses. These three fetuses also had meconium FAEE concentrations above the positive cut-off value.

Inspection of the placenta in the ethanol-exposed sheep showed elevated mRNA levels of tumor necrosis factor (TNF)-α. There was a significant positive association between meconium FAEE concentration and mRNA expression of TNF-α, suggesting a chronic inflammatory response in the placenta.

CONCLUSIONS

Taken together, these data suggest that even moderate amounts of alcohol exposure during late pregnancy can cause abnormalities in fetal organs despite the misconception that alcohol consumption in late pregnancy is less harmful to the fetus. Furthermore, meconium FAEE concentrations may serve as biological markers of chronic ethanol exposure in the third trimester and identify newborns at risk of ethanol-induced organ dysfunction, who may not be exhibiting the obvious physical abnormalities associated with heavy maternal drinking. Importantly, the PEC levels of the sheep in this study were approximately equivalent to the PEC levels in women who drink socially and are not necessarily heavy alcohol consumers.

This study sheds light for the first time on multi organ fetal damage by alcohol, not limited only to the brain. These may add substantially to the burden of morbidity of exposed individuals later in life, adding a chilling meaning to the concept of "fetal origins of adult diseases".

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