OBSTETRICS

First trimester alcohol exposure alters placental perfusion and fetal oxygen availability affecting fetal growth and development in a non-human primate model

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BACKGROUND: Prenatal alcohol exposure leads to impaired fetal growth, brain development, and stillbirth. Placental impairment likely contributes to these adverse outcomes, but the mechanisms and specific vasoactive effects of alcohol that links altered placental function to impaired fetal development remain areas of active research.

OBJECTIVE: Recently, we developed magnetic resonance imaging techniques in nonhuman primates to characterize placental blood oxygenation through measurements of T_2* and perfusion using dynamic contrast-enhanced magnetic resonance imaging. The objective of this study was to evaluate the effects of first-trimester alcohol exposure on macaque placental function and to characterize fetal brain development in vivo.

STUDY DESIGN: Timed-pregnant Rhesus macaques (n=12) were divided into 2 groups: control (n=6) and ethanol exposed (n=6). Animals were trained to self-administer orally either 1.5 g/kg/d of a 4% ethanol solution (equivalent to 6 drinks/d) or an isocaloric control fluid from preconception until gestational day 60 (term is G168). All animals underwent Doppler ultrasound scanning followed by magnetic resonance imaging that consisted of T_2* and dynamic contrast-enhanced measurements. Doppler ultrasound scanning was used to measure uterine artery and umbilical vein velocimetry and diameter to calculate uterine artery volume blood flow and placental volume blood flow. After noninvasive imaging, animals underwent cesarean delivery for placenta collection and fetal necropsy at gestational day 110 (n=6) or 135 (n=6).

RESULTS: Fetal weight and biparietal diameter were significantly smaller in ethanol-exposed animals compared with control animals at gestational day 110. By Doppler ultrasound scanning, placental volume blood flow was significantly lower (P=.04) at gestational day 110 in ethanol-exposed vs control animals. A significant reduction in placental blood flow was evident by dynamic contrast-enhanced magnetic resonance imaging. As we demonstrated recently, T_2* values vary throughout the placenta and reveal gradients in blood deoxyhemoglobin concentration that range from highly oxygenated blood (long T_2*) proximal to spiral arteries to highly deoxygenated blood (short T_2*). Distributions of T_2*throughout the placenta show significant global reduction in T_2* (and hence high blood deoxyhemoglobin concentration) in ethanol-exposed vs control animals at gestational day 110 (P=.02). Fetal brain measurements indicated impaired growth and development at gestational day 110, but less so at gestational day 135 in ethanol-exposed vs control animals.

CONCLUSION: Chronic first-trimester ethanol exposure significantly reduces placental perfusion and oxygen supply to the fetal vasculature later in pregnancy. These perturbations of placental function are associated with fetal growth impairments. However, differences between ethanol-exposed and control animals in placental function and fetal developmental outcomes were smaller at gestational day 135 than at gestational day 110. These findings are consistent with placental adaptation to early perturbations that allow for compensated placental function and maintenance of fetal growth.

Key words: alcohol, imaging, nonhuman primate, oxygenation, placental perfusion

In the United States, approximately 40% of women consume alcohol in pregnancy,[1] and >3 million women are at risk of exposing their fetus to alcohol because more than one-half of all pregnancies are unplanned and most women do not recognize they are pregnant until 4–6 weeks after conception.[2-4] Of significance, ethanol readily crosses the placenta and accumulates in the fetus at concentrations proportionate to maternal blood levels within an hour.[5] Previous pregnant ovine,[6] baboon,[7] and perfused human placenta[8] models have shown that uterine blood flow decreases after acute exposure to ethanol.[6,7,9] In addition, other studies have demonstrated that prenatal ethanol exposure negatively affects fetal growth[10] and increases the risk of stillbirth, fatty hepatic degeneration, and fetal alcohol syndrome.[11] However, the mechanisms and specific vasoactive effects of alcohol exposure early in gestation that link placental perfusion and oxygenation to impaired fetal development are not known.

Alcohol exposure has been shown in vitro to produce dose-dependent placental vasoconstriction that increases fetal-placental vascular resistance and placental perfusion pressure that results in impaired oxygen transport.[9] The existing literature is limited and consists mostly of in vitro studies of the placenta. Furthermore, human studies are limited by current imaging capabilities to assess placental function in vivo in human subjects.[12] Traditionally, Doppler ultrasound (Doppler-US) has been used to query major maternal vessels that support the placenta for clinical antenatal surveillance. However, this

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TABLE 1
Fetal biometry

Parameter	Gestational day 110, mean±standard deviation		Gestational day 135, mean±standard deviation	
	Control (n=3)	Ethanol (n=3)	Control (n=3)	Ethanol (n=3)
Biparietal diameter, mm	39±0.9	35±1.1[a]	45±0.6	44±1.4
Abdominal circumference, cm	12±0.2	11±0.8	14±0.4	13±1.9
Femur length, mm	29±0.4	26±0.9[b]	37±1.9	36±0.5

Nonpaired *t*-test used.

[a] $P<.01$; [b] $P<.05$.

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method cannot be used to assess blood flow within the placental intervillous space, which is the site of maternal-fetal oxygen and nutrient exchange. Recent work with pregnant nonhuman primates (NHP) has identified magnetic resonance imaging (MRI)–based methods to characterize maternal blood flow and oxygen exchange in the placenta with the fetal vasculature.[13,14] Maternal perfusion of the placenta can be quantified with the use of dynamic contrast-enhanced MRI (DCE-MRI), which requires intravenous administration of an MRI contrast reagent.[13] Although we have shown that maternal gadolinium (Prohance) administration in Rhesus macaques results in minimal fetal exposure,[15] methods for antenatal in vivo hemodynamic assessment that does not require gadolinium-based contrast reagents are clinically desirable. Another method, which involves the analysis of endogenous MRI contrast provided by water T_2^* values, can quantify maternal blood oxygenation through the blood oxygen level-dependent effect.[16] This provides a safe alternative to standard MRI contrast agents for future clinical use in human subjects.

The NHP model provides a powerful translational model for human pregnancy studies; NHPs have a gestational term and developmental ontogeny similar to humans, which includes its placental structure and function.[17,18] Further benefits to studying NHPs are the similar rates of absorption and metabolism of ethanol to humans[19] and the ability to induce oral self-administration of preset doses of ethanol. Maternal smoking, nutritional inadequacy, medication or illicit drug use, which are all factors that can have a synergistic effect on alcohol exposure, often confound human studies of placental impairment. Modeling human drinking behavior with NHP models provides the added advantage of a precise alcohol history[20,21] while retaining the normal route of alcohol administration as opposed to strategies that are used to study fetal ethanol exposure in rodents. Further, voluntary ethanol self-administration also obviates the need for procedures such as gavage, which introduce confounders that are associated with increased maternal stress.[22] This study focuses on the effects of chronic early alcohol exposure on placental perfusion and fetal oxygen availability and development in a relevant translational model. We hypothesized that alcohol exposure early in pregnancy would impair maternal perfusion of the placenta and would result in decreased tissue oxygenation.

Materials and Methods

Experimental design

A cohort of time-mated pregnant control Rhesus macaques (n=12) were divided into 2 groups: control (n=6)

TABLE 2
Maternal, fetal birth, and placental weights

Parameter	Gestational day 110		Gestational day 135	
	Control (n=3)	Ethanol (n=3)	Control (n=3)	Ethanol (n=3)
Maternal weight, kg[a]	7.5±1.7	8.3±1.4	7.5±0.9	8.5±1.1
Fetal weight, g[a]	217±21	175±8.4[b]	333±6.5	318±3.6[b]
Placental weight, g[a]	75±17	65±4.1	78±2.3	83±10.3
Fetal sex (male:female)	1:2	0:3	1:2	1:2

Nonpaired *t*-test used.

[a] Data are given as mean±standard deviation; [b] $P<.05$.

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