Vascular effects of maternal alcohol consumption

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Ramadoss J, Magness RR. Vascular effects of maternal alcohol consumption. Am J Physiol Heart Circ Physiol 303: H414–H421, 2012. First published June 22, 2012; doi:10.1152/ajpheart.00127.2012. —Maternal alcohol consumption during pregnancy is a significant field of scientific exploration primarily because of its negative effects on the developing fetus, which is specifically defined as fetal alcohol spectrum disorders. Though the effects on the mother are less explored compared with those on the fetus, alcohol produces multiple effects on the maternal vascular system. Alcohol has major effects on systemic hemodynamic variables, endocrine axes, and paracrine factors regulating vascular resistance, as well as vascular reactivity. Alcohol is also reported to have significant effects on the reproductive vasculature including alterations in blood flow, vessel remodeling, and angiogenesis. Data presented in this review will illustrate the importance of the maternal vasculature in the pathogenesis of fetal alcohol spectrum disorders and that more studies are warranted in this field.

fetal alcohol spectrum disorders; pregnancy; uterine; endothelium

Introduction

Maternal alcohol consumption during pregnancy is a significant field of scientific exploration primarily because of its negative effects on the developing fetus, specifically defined as fetal alcohol spectrum disorders (FASD) (82). These deficits span numerous organ systems, but the most studied effects are on the developing brain neuronal losses and its related behavioral abnormalities with learning and memory impairment (74). The Surgeon General of the United States released a warning in 1981 and again in 2005 urging women who are or may become pregnant to abstain from drinking (86). Despite these specific and clear public health initiatives, it is currently estimated that about 2–5% of young school children in the United States and some West European countries may be affected by FASD (53), showing that a large number of pregnant women consume alcohol during pregnancy. A main reason to be concerned about these statistics is that fetal alcohol deficits are considered to last for a lifetime, and there are no approved drug therapies for treatment of FASD, nor are there established diagnostic or therapeutic tools to be able to prevent and/or ameliorate some of these deficits.

The focus of research on the effects of maternal alcohol consumption has historically been on the developing fetal brain due to the obvious manifestations of craniofacial and behavioral impairments in fetal alcohol syndrome (FAS, an extreme manifestation of FASD including craniofacial deficits, central nervous system dysfunction, and growth restriction). Although alcohol (ethanol) is a simple molecule (C2H5OH), it has posed considerable difficulties to scientists in identifying converging candidate mechanisms underlying alcohol-mediated deficits because of diverse effects of alcohol based on the timing (first, second, or last third or throughout pregnancy), pattern (acute, chronic, or binge), and dose of exposure (50). Furthermore, there are organ/region-specific developmental differences in vulnerability (44, 49–51, 96); for example, alcohol produces differential effects on brain regions depending on whether the cells are proliferating or differentiating (52). In addition, it has been noted in animal model studies that binge drinking, wherein a lower dose of alcohol is consumed in a short intermittent pattern to generate a higher-peak blood alcohol concentration (BAC), produces significantly greater deficits than a higher dose of alcohol continuously administered that generates an lower-peak BAC (8, 50). Finally, one should also carefully address the animal model system that is used to understand the mechanistic perspectives underlying alcohol-induced deficits (15, 16); for instance, the developing brain in the humans has its peak growth velocity (first derivative of brain weight with reference to time) peak at parturition, whereas in rats or mice, this event occurs shortly after parturition (15).

Alcohol freely permeates through all body fluid compartments including the vasculature, interstitial fluid, and intracellular space; thus the alcohol concentration is the same in any body fluid compartment in the mother and the fetus. In contrast to numerous fetal studies, very few studies have focused on the effects of alcohol on the mother during pregnancy. This is...
important from the perspective of both the mother’s and the offspring’s health since it has been suggested that alcohol may lead to FASD partly via its effects on the mother, maternal-fetal interface, as well as events like parturition (15). In this review, we will specifically focus on the effects of maternal alcohol consumption during pregnancy on the maternal vascular system.

Effects of Alcohol on Maternal Systemic Hemodynamics

In men and nonpregnant women, different alcohol-dose and blood pressure relationships have been described including linear (with and without threshold), J shaped, U shaped, etc., as a function of age, sex, smoking habits, race, and drinking pattern/frequency of drinking, with high levels of alcohol consumption being a risk factor for hypertension (24, 76, 78, 90, 99). Since most alcohol studies have been traditionally conducted mainly in men (25), it is important to note that women metabolize alcohol distinctly different from men because the first pass metabolism and gastric alcohol dehydrogenase activity are both as low as 23 and 59% of those of men, respectively resulting in much higher BACs (23). In an early study, Barker had demonstrated that moderate (men ≤ 280 g, and women ≤ 168 g) and heavy (men > 280 g, and women > 168 g) alcohol consumption is reported to produce an increase in mean systolic and diastolic pressures by 4 mmHg compared with those with low intake (men ≤ 168 g, women ≤ 112 g) (4). However, there are no reports of maternal alcohol effects during pregnancy on systemic hemodynamic parameters in humans. In sheep, binge alcohol exposure during the third trimester equivalent of human brain development showed dose-dependent increases in the maternal heart rate and blood pressure with 0.75, 1.25, 1.5, and 1.75 g/kg of alcohol, generating peak BACs of about 80.8 ± 6.5, 182.5 ± 13.5, 224.4 ± 13.9, and 260.6 ± 20.0 mg/dl respectively (Fig. 1) (17). These alterations were attributed to direct alcohol effects on peripheral vascular resistance that will be discussed in the subsequent sections as well as from reflexes such as chemoreflex arising from maternal hypoxia and acidosis (17, 33). However, studies on the effects of alcohol on systolic and diastolic pressures in women as well as in animal models like rats, the most widely used model to study FASD, are highly warranted.

Effects of Alcohol on Maternal Endocrine and Paracrine Systems Regulating Vascular Resistance

Numerous studies have investigated alcohol effects on maternal hormones that are known to have substantial effects on maternal resistance vessels. Herein, we will review what is known about alcohol effects on the major endocrine axes that regulate total peripheral resistance. The hypothalamic pituitary adrenal (HPA) axis has immense effects on vascular system accompanied by sodium retention and enhanced vascular reactivity, leading to vasoconstriction via glucocorticoid receptors mediated by suppression of nitric oxide (NO) system (41). In humans, it has been reported that alcohol exposure during pregnancy increases basal cortisol levels in the offspring (36); however, no information is available on the mother. Even animal studies have predominantly concentrated on the fetus or the neonate with only few studies on the maternal HPA axis wherein alcohol is reported to increase maternal basal and stress HPA activity (18, 94). Furthermore, these alcohol-induced increases in HPA signaling may be important not only for normal parturition but also for maturation of fetal organ systems in preparation for birth (10, 12, 13, 18, 57, 81, 100). The hypothalamic pituitary thyroid axis modulates HPA activity and has been implicated in FAS because of the similarities in developmental behavioral and neuroanatomical deficits in maternal thyroid deficient disorders and FAS (31, 74). Numerous reports exist on maternal alcohol effects on fetal, neonatal, and young offspring hypothalamic pituitary thyroid axis (19, 65, 97, 98). Alcohol-exposed rat dams have suppressed levels of T3 and T4, and maternal T4 supplementation ameliorates certain learning deficits in FASD offspring (97, 98). In ewes, alcohol exposure results in decreased maternal T3, but not T4, toward the end of gestation (19). More work has been performed on the hypothalamic pituitary gonadal axis. The androgens and estrogens have profound effects on the vascular system (46, 77). Alcohol consumption in women during pregnancy that has led to FAS has been noted to lead to lower levels of sex hormone-binding globulin throughout pregnancy and total testosterone concentrations at 16–20 wk of gestation (term is roughly 285 days) (25, 102). These early studies also showed that free testosterone was higher between 16 and 20 wk of gestation, whereas a lower level of dehydroepiandrosterone sulfate was observed between 16 and 32 wk of gestation (102). Furthermore, recent studies have shown a nearly 25% decrease in serum testosterone levels in women who drink a median of one glass a day (85). Furthermore, in rats, alcohol exposure in utero has been reported to lead to decreased testosterone levels in the male fetuses and neonates that may be attributed to increased aromatase activity in the whole hypothalamus in the fetus and the hypothalamic preoptic area tissue postnatally (54, 55, 92, 93). In the field of estrogens, although earlier studies have reported decreases in 17β-estradiol and estriol levels in mothers with FAS infants (32), more recent studies focusing on lower alcohol consumption (median of 0.2, 1.1, and 4.4 oz/wk)

Fig. 1. Maternal heart rate (in beats/min, left) and mean arterial pressure (in mmHg, right) on gestational day (GD) 118 (top) and 132 (bottom) experimental days in response to saline [pair-fed control (PFC)] and 1.75 g/kg ethanol doses in sheep. Alcohol was intravenously delivered to ewes beginning on GD 109 for 1 h on 3 consecutive days each week followed by 4 days without exposure, and the pattern was repeated till GD 132. For clarity, the 0.75-, 1.25-, and 1.5-dose plots were not presented but fell between the PFC and 1.75-dose groups in a dose-dependent manner. Maternal heart rate on GD 118 and GD 132 were significantly higher in all ethanol treatment groups compared with PFC. Maternal mean arterial pressure was progressively higher with increasing doses of ethanol on both GD 118 and 132. All values are means ± SE. Adapted with permission from Cudd et al. (17).
showed that estradiol levels are not associated with occasional/light/moderate alcohol consumption (85). Another hormone critical in maintaining the vascular tone is the potent vasoconstrictor arginine vasopressin (AVP) that also has antidiuretic properties. Virtually nothing has been reported about AVP levels in mothers consuming alcohol during pregnancy; however, in the offspring, one study showed that alcohol [35% calories derived from alcohol, gestational day (GD) 6–20] leads to increased neurohypophysis activity and higher AVP levels, a reason cited for alcohol-induced increased HPA activity, whereas another study using 36% alcohol-derived calories throughout gestation showed no difference in offspring AVP mRNA levels compared with the controls, though males exhibited higher mRNA levels than females (20, 43, 103). Another study again using 35% calories derived from alcohol (GD 7–21) demonstrated 30% decrease in AVP mRNA and decreases in plasma AVP levels in response to 20% hemorrhage in rats by adulthood (5). Another system that has significant effects on the systemic vascular resistance is the renin angiotensin system for which there are no studies on the maternal effects of alcohol in either the mother or the fetus. The last system that we will discuss herein is the effects of alcohol on the catecholamines produced by the sympathetic division of the autonomic nervous system and the adrenal medulla. Early studies have shown acute alcohol (4 g/kg, GD 21)-induced increases in plasma norepinephrine concentrations in pregnant mothers in the rat (56). In men, acute alcohol consumption (0.5 ml/kg) increased plasma catecholamine levels and chronic alcohol exposure (BAC, ~192 mg/dl) increased their excretion (35, 58), and in rats, chronic alcohol (80 mM for 15–18 days) potentiates α1-adrenergic receptor-mediated vasoconstriction (64). Despite these observations, studies that directly test the effects of alcohol-induced endocrine changes on the maternal vascular system are still warranted. The role of major paracrine factors that regulate vascular resistance is also of importance to the effects of alcohol on changes in gestational physiology. We will first review the effects of alcohol on the prostanoid system that is activated during pregnancy. In one study, pregnant women who were consuming ≥48 g alcohol per day and those who abstained were studied and no significant differences in levels of urine 8-isoprostane F2α (oxidative stress marker), 2,3-dinor-6-keto-prostaglandin F1α (a vasodilator metabolite of prostaglandin I2), and 11-dehydro-thromboxane B2 (a vasoconstrictor metabolite of thromboxane A2) were detected, and the authors concluded against a significant role for eicosanoids markers of oxidative stress (79). In contrast, an earlier study conducted in drinking pregnant women who consumed higher amounts of alcohol (5- to 20-yr history of alcohol abuse; consumption, −140–840 g/wk during first half of gestation or beyond) showed the ratio of the urinary combined prostacyclin metabolites (vasodilator) and thromboxane B2 (vasoconstrictor) to be significantly lower compared with that in the controls (101). Similar observations were found in the fetoplacental compartment; alcohol perfusion (240 min or 60 min; 200 or 300 mg%) of single human cotyledons increased the ratio of thromboxane to prostacyclin at few time points (80). Randall and Saulnier (72) have demonstrated that perfusion (100 mM) in human umbilical veins showed an increased thromboxane-to-prosta- cycclin ratio at all time points. Next, we will discuss oxygen free radicals as redox balance impairment produces vasocostric- tion. Substantial evidence exists to demonstrate maternal alco- hol exposure increases oxidative stress markers in the fetus (11), fetoplacental compartment (40), maternal ovine uterine artery endothelial cells (69), etc., via multiple mechanisms that are discussed in other excellent review articles (9, 11, 27), whereas there is a paucity of human clinical studies especially in pregnant women (79). Another paracrine factor that is critical in gestational adaptations is NO. More is known about alcohol effects in adult nonpregnant humans and animals; one report showed that in vitro acute treatment of alcohol (0.1%, 3 h) increased basal and stimulated bovine aortic endothelial cell NO release (91), whereas alcohol (4 g/kg for 12 wk) given to male rats decreased aortic endothelial NO synthase expression, NO levels, and impaired vasorelaxation (34). However, Barona et al. (3) showed that in male rats, chronic alcohol (increasing alcohol levels in diet from 30–50 g/l over 5 days) increased hepatic inducible NO synthase activity and NO levels. Again, in male rats, alcohol (BAC, ~41 mM) produced vessel-specific increases in blood flow only in the coronary, mesenteric, and renal arteries, and the authors have attributed this to increased NO and inducible NO synthase (2). In con- trast, intravenous infusion of alcohol in nonpregnant male and female rabbits (3–30 mmol/kg) (62) as well as in healthy human volunteers (0.25 and 1.0 g/kg) (61) dose-dependently decreased exhaled NO. Similarly, extensive human, animal, as well as cell culture studies that show increased or decreased NO, depending on the dose, duration, and pattern of exposure in nonpregnant adults (88), are extensively reviewed elsewhere, where which are beyond the focus of the current review on pregnant mothers. In one study, alcohol administered in the diet (GD 6–18, peak BAC, 0.11 g/dl) to pregnant C57BL/6J mice showed reduced NO modulation of the mesenteric artery vascular response (14). In vitro chronic binge-like alcohol treatment (300 and 600 mg/dl) to uterine artery endothelial cells derived from third trimester pregnant ewes decreased excitatory serine-635 endothelial NO synthase phosphorylation levels at both concentrations (67). In placental villi, in vitro acute alcohol exposure for 2 h (100 and 200 mM) decreased tissue NO concentrations and cGMP levels and increased superoxide dismutase activity (39). In the fetus, similarly, it is reported that alcohol induces impairments in neuronal NO system as well as decreases in NO synthase-positive neurons, possibly leading to teratogenesis (6, 7, 63). Thus it appears that alcohol effects on these paracrine factors during pregnancy involve multiple variables including alcohol dose, sex, duration, enzyme isoforms, pattern of alcohol exposure, gestational programming of enzyme expression/activity, as well as regional differences among the organ vascular beds. However, despite these advances, studies that test the cause and effect relationship between alcohol-induced alterations in these paracrine/intrinsic factors and vascular function and/or uterine vascular development during pregnancy are highly warranted. Maternal Alcohol Effects on Vascular Reactivity Few studies have been conducted on the effects of alcohol during pregnancy on the systemic vascular reactivity to different vasoconstrictive and dilatory agonists. Assessment of vessel function and their mechanical properties using myography (84) in various maternal vascular beds provide the basis for understanding gestational programming characterized by dra-
motic vascular adaptations including increases in heart rate and cardiac output as well as decreases in mean arterial pressure (45). Furthermore, the most substantial adaptation takes place in the uterine artery; uterine artery diameter is reported to increase from about 1.4 mm in nonpregnant state to 2.8 mm by week 21 and to 3.4 mm in the third trimester, and the mean blood velocity increases from 8.4 cm/s in the nonpregnant state to 61.4 cm/s in the third trimester (59). Similarly, in the sheep, the uterine blood flow during the third trimester increases between 30- to 50-fold compared with the nonpregnant state (45, 75). Such organ-specific vascular effects are further substantiated by vessel functional studies using myography; in one study uterine artery had decreased sensitivity to thromboxane compared with the carotid artery during pregnancy (95), whereas in another study myometrial vessels were less responsive to bradykinin compared with omental vessels (1). With reference to maternal alcohol consumption, in one study alcohol was administered in the diet between GD 6 and 18 in C57BL/6J mice to generate a peak BAC of around 110 mg/dl (14). The authors report reduced maximal relaxation response to methacholine in maternal mesenteric artery and found that alcohol reduced the NO component of modulation of the vascular response (Fig. 2) (14). These effects were further specific to pregnancy, an expected finding as the endothelium is programmed during pregnancy. To date, however, there is only one study examining alcohol-induced maternal vascular reactivity and that too on a systemic vascular bed. Thus it is highly warranted that more functional studies be conducted to assess effects of gestational alcohol exposure on vascular responses to vasoconstrictors and dilators on reproductive vasculature, especially the uterine and the placental resistance arteries, since these data would give important insights into the effects of alcohol on nutrient and gas delivery from the mother to the fetus.

Maternal Alcohol Effects on Reproductive Vasculature

Major adaptations occur in the uteroplacental circulation during pregnancy. For instance, in animal model systems, it has been shown that the uterine vascular resistance drops significantly from 4.91 mmHg/min·ml in the nonpregnant state to 0.198 mmHg/min·ml in the second trimester and 0.07 mmHg/min·ml in the third trimester of gestation (75). The percentage of cardiac output perfusing the uterus increases from 0.5% in the nonpregnant state to around 7.65 and 15.7% in the second and third trimesters of gestation, and the blood flows to the uterus and the mammary gland alone account for nearly one fifth of the cardiac output by term (75). These changes are critical to meet the growing requirements of the developing fetus. In pregnant sheep, intravenous infusion of 1 g alcohol/min over 1 h decreased uterine as well as placental blood flow, and the reductions were maintained for at least 2 h after the end of alcohol treatment; uterine blood flow significantly decreased from 1,477 ± 169 to 1,180 ± 195 ml/min, whereas the umbilical blood flow significantly decreased from 572 ± 74 to 391 ± 74 ml/min (21). Another pattern of alcohol administration was followed in a subsequent study where four intermittent 2 or 4 g/kg body wt doses were administered over 28 min with a 56-min interval between doses, leading to a progressive increase in the BAC to around 332 and 538 mg/dl, respectively (73). Although absolute uterine blood flows were not reported in this study, it was observed that with time, an increase in the uterine blood flow was observed (73). This contrast could be attributed to this intermittent pattern of infusing alcohol over more than 4 h, generating higher BACs or a compensatory change in uterine resistance or perfusion pressure. In another study in rats, progressively increasing concentrations of alcohol, 10% and 20% vol/vol, was fed via diet for a month before pregnancy followed by 30% vol/vol during gestation (38). Microsphere analysis was then used to assess placental blood flow which decreased by around 52% in the alcohol treatment group compared with the controls (38). More studies are needed to understand the effects of alcohol on chronic exposure that mimics human binge drinking, for example during all three trimesters of gestation compared with for instance the third trimester of gestation.

Because angiogenesis and vessel remodeling are major contributing mechanisms defining the uteroplacental circulation during gestation, we will now review what is known about the effects of alcohol on these adaptations. More is known about the effects of alcohol in the nonpregnant state; for instance, alcohol (1%, every night for 4 wk) increased tumor angiogenesis in male mice (87), whereas Radek at al. (66) demonstrated in nonpregnant female mice that acute alcohol exposure (100 mg/dl) impaired wound angiogenesis. Again, during gestation, more is known about the effects of alcohol on fetal angiogenesis compared with the mother; for example, angiogenic measures such as vessel perimeter and absolute cross-sectional area are decreased in human embryonic and fetal brain (83), and region-specific microvascularity is altered in the rat fetal brain (42). In the mother, chronic alcohol (37% of caloric content, GD 6–16) impairs the physiological conversion of the maternal uterine vasculature within the mesenteric triangle in rats, a necessary step for delivery of nutrients and gas to the fetus; for instance, the spiral artery vascular muscular layer was disrupted in the control dams, whereas the thickness was 12–15 µm in the alcohol-exposed mothers (30). In a chick extraembryonic model, moderate and heavy alcohol doses (30% or 50%, 24 or 48 h) impaired vascular development, and the authors (89) have attributed these deficits to angiogenic growth factors, associated receptors, and oxidative stress, whereas Gu et al. (29), again using the chick extraembryonic model, showed that administration of alcohol (0.25 g·kg⁻¹·day⁻¹, 7 days) induced greater branching of blood vessels (29). In uterine
artery endothelial cells derived from pregnant ewes, in vitro chronic binge-like alcohol exposure (300 or 600 mg/dl) inhibits estradiol 17β-induced endothelial proliferation (67). In a more recent study, biotinylated capture and color-coded reporter probes were used to digitally characterize 85 angiogenesis-associated genes in the uterine vasculature following chronic binge alcohol exposure (22, 26). In this study, 20 angiogenesis-associated genes were downregulated and two upregulated (71). The downregulated genes included angiogenic growth factors/receptors (placental growth factor), adhesion molecules (angiopoietin-like-3, collagen-18A1, endoglin), proteases/matrix proteins/inhibitors (alanyl aminopeptidase, collagen-4A3, heparanase, plasminogen, platelet factor-4, plexin domain containing-1, tissue inhibitor of metalloproteinases-3), transcription/signaling molecules (heart and neural crest derivatives-2, DNA-binding protein inhibitor-1, NOTCH4, ribosomal protein-L13a, ribosomal protein large-P1), cytokines/chemokines (interleukin-1β), and miscellaneous growth factors [leptin, platelet-derived growth factor-α, transforming growth factor-α], whereas plasminogen activator urokinase and transforming growth factor-β receptor-1 were upregulated (71). In summary, these studies show that alcohol affects vascular adaptations during pregnancy by altering angiogenic indexes.

Now, we will review the mechanistic perspectives underlying alcohol-induced angiogenesis and vascular remodeling via its effects on the endothelial proteome. This is an important area of exploration since the vascular endothelium is programmed during pregnancy (47, 48); for example, we reported that 17β-estradiol and its metabolites induce proliferation of uterine endothelial cells only during pregnancy and not in the nonpregnant state (37). In one study, uterine artery endothelial cells were isolated from pregnant ewes, fluorescence-activated cell sorted, validated, and maintained in culture and treated with chronic in vitro binge-like alcohol (300 mg/dl, 3-h treatment on 3 consecutive days followed by 4 days without exposure for 2 wk) (69). Two-dimensional differential in gel electrophoresis separation followed matrix-assisted laser desorption time-of-flight mass spectrometry tandem mass spectrometry was then used to demonstrate that alcohol significantly decreased 30 proteins and increased 19 others in the uterine endothelium (Fig. 3). Gene enrichment and functional annotation cluster analysis was then used to show significant enrichment in three categories: oxidative stress-associated glutathione S-transferase and thioredoxin, as well as vesicle transport-related pathways (69). It has also been demonstrated that alcohol significantly alters the protein expression in the uterine artery endothelial caveolar lipid rafts where numerous receptors, signaling molecules, ion channels, etc., reside (28, 60, 68). Subsequently, using a similar binge-like alcohol exposure paradigm, a study using isobaric tags for relative and absolute quantitation-labeled proteomic approach reported that 14 maternal uterine endothelial proteins were significantly upregulated and 17 significantly downregulated by alcohol, including those related to cell structure, transcription and translation regulation, histones, Ca2+/NO, and redox balance (J. Ramadoss and R. R. Magness, in review). Alcohol altered processes at multiple levels including epigenetic, transcriptional, and translational (J. Ramadoss and R. R. Magness, in review). Thus these reports demonstrate that alcohol has specific and possibly detrimental effects on the uteroplacental compartment at the level of the vasculature.

Future Directions and Perspectives

It is evident that alcohol alters maternal systemic and reproductive circulatory adaptations during pregnancy (Fig. 4). Furthermore, studies are warranted to investigate how varying patterns of alcohol consumption (chronic, binge, etc.) during different temporal periods of pregnancy affect systemic hemo-
dynamic variables such as blood pressure and total peripheral resistance and how these variables are altered by baro- and chemoreflexes. Further studies are warranted evaluating focused interaction between alcohol and reproductive hormones such as testosterone and 17β-estradiol. An area where hardly any work has been performed is on the vascular reactivity of the uteroplacental vasculature in response to vasoconstrictors and dilators following maternal alcohol exposure during pregnancy. These studies will provide immense insights on the role of the maternal uteroplacental vasculature in the pathogenesis of FASD. These studies will also demonstrate the importance of the mother, the maternal vasculature, and the maternal-fetal interface in addition to the direct effects of alcohol on the developing fetal brain in the pathogenesis of FASD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

J.R. and R.R.M. drafted manuscript; J.R. and R.R.M. edited and revised manuscript; J.R. and R.R.M. approved final version of manuscript.

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