Review of Ethanol Dispersion, Distribution, and Elimination from the Fetal Compartment

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Background: This study is a review of alcohol dispersion into and elimination from the fetal compartment. **Methods:** PubMed searches were conducted for all years and all languages for relevant papers. We also hand searched the reference list of papers and text books for additional references. **Results:** Alcohol concentration is determined by body water (49% for women), grams of ethanol consumed, and duration of drinking. The fetus has very limited metabolic capacity and transfer from the fetal compartment to maternal circulation is the major pathway to reduce fetal exposure. Vasoconstriction of the placenta-umbilical unit from alcohol and smoking decreases rates of alcohol elimination from the fetal compartment. By 20 weeks of gestation, keratinization of fetal skin reduces the permeability of fetal skin to very low levels, increasing the duration of fetal exposure and complicating alcohol elimination from the fetal compartment. Two reabsorption pathways, the intramembranous pathway and fetal swallowing, create a recycling system where much of the ethanol the fetus excretes will be reabsorbed back into its circulatory system. Fetal re-excretion of ethanol into the amniotic fluid occurs by means of fetal urine, breathing movements, and nasal excretions. Amniotic fluid then functions as a reservoir for ethanol, prolonging fetal exposure. **Conclusion:** While the fetus has the ability to metabolize some ethanol, removal from the fetal–maternal unit relies primarily on maternal metabolic capacity. The alcohol elimination rate from the fetal compartment is approximately 3% to 4% of the maternal rate. We conclude with examples of the clinical relevance of information from this review.

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Key words: prenatal alcohol exposure; fetal; amniotic fluid; alcohol elimination; metabolism; pregnancy; amniotic fluid

Introduction

PREVALENCE OF PRENATAL ALCOHOL EXPOSURE

In the United States, more than half of all nonpregnant childbearing-age women report alcohol use, with 15% reporting binge drinking within the past month (Centers for Disease Control and Prevention [CDC], 2012). High rates of overall reported alcohol use and binge drinking among childbearing-age women are of concern because half of all pregnancies in the United States are unintended (Forrest, 1994). As a result many women continue to drink during the early stages of pregnancy while unaware they are pregnant. Approximately 1 in 8 pregnant women (12.2%) report using alcohol during their pregnancy and nearly 2% (1 in 50) reported binge drinking (Centers for Disease Control and Prevention [CDC], 2009). Consequently, of the 4.0 million annual pregnancies in the United States, approximately 500,000 are exposed to alcohol and 80,000 pregnant women drink through all three trimesters.

Fetal alcohol spectrum disorder (FASD) is the spectrum of deficits, including neuroanatomic, craniofacial, cardiovascular, endocrine, metabolic, and behavioral, arising from prenatal alcohol exposure. FASD comprises four diagnostic categories: fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol related neurodevelopmental disorder, and alcohol related birth defects. Fetal alcohol syndrome is characterized by growth impairment, facial anomalies, and central nervous system abnormalities, often including intellectual disability, and represents 10% to 15% of all fetal alcohol spectrum disorders (Stade et al., 2009). Although a child may not fit into one of the four diagnostic categories he/she may still have FASD. Prevalence estimates vary widely, from 1 to 30 per 10,000 children (Hymbaugh et al., 2002). However, rates for school-age children using systematic screening suggest a higher prevalence of 88 per 1000 in the Northern Cape of South Africa (May et al., 2009). Current prevalence rates of FASD are estimated to be 2% to 5% in populations of younger school-age children in the United States and some Western European countries (May et al., 2009).

There is an association between prenatal alcohol exposure (PAE) and complications of pregnancy. Approximately 15% of all pregnancies end in spontaneous abortion, but among heavy drinking mothers the incidence increases to 45% (Hannigan and Armant, 2000). The occurrence of stillbirth among pregnancies exposed to ethanol has been shown to increase sixfold compared with the rate of stillbirths within the population as a whole (Cornman-Homonoff et al., 2012). PAE also increases the risk of prematurity and fetal growth impairment (Odendaal et al., 2009). Fetal alcohol spectrum disorders are the leading identifiable cause of intellectual disability and a common risk factor for birth defects, and may be one of the most preventable developmental disorders. Understanding the complex factors affecting dispersion of alcohol into the fetal compartment and the multiple factors affecting alcohol elimination

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from the fetal compartment have the potential to improve management of women who drink during pregnancy and development of new strategies to reduce morbidity and mortality associated with prenatal exposure.

Materials and Methods

SEARCH STRATEGY

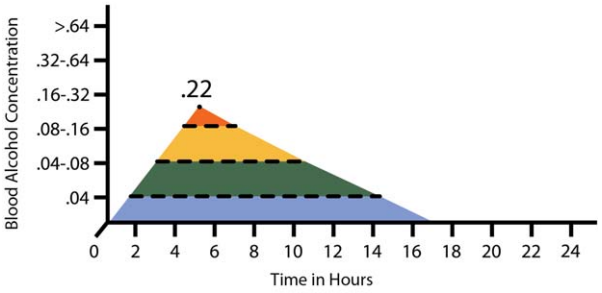
We used a search strategy on PubMed to locate articles reporting ethanol dispersion in the fetal compartment, ethanol metabolism in the placenta and fetus, and parameters of exposure episodes. We used the search terms: ethanol, fetus, placenta, fetal swallowing, fetal skin, amniotic fluid, maternal–fetal exchange, fetal alcohol spectrum disorders, fetal urine, fetal breathing, absorption, and maternal–fetal relations. The search was completed to July 2013 and placed no limits on language or publication date. Additional relevant publications were located by hand-searching articles for references.

Results

EXPOSURE EPISODES

An exposure episode is the duration of time ethanol is present in the fetal compartment. The dosimetry of prenatal alcohol exposure is assessed by using body weight to determine total body water (approximately 49% for women), the grams of ethanol consumed, and the duration of the drinking episode. Before pregnancy, a female has approximately 49% total body water (Paintner et al., 2012a). During pregnancy, the proportion of total body water varies modestly (Lukaski et al., 1994). The total body water includes both the fetus and the amniotic fluid. In a given individual, increasing blood alcohol concentrations are a result of metabolic enzyme saturation. Once alcohol consumption has stopped, metabolic enzyme capacity exceeds absorption of alcohol and blood alcohol concentration begins to fall. If a 140 pound woman consumes 4 standard drinks (14 grams of alcohol per drink) in a 4-hr period it will take approximately 8.5 hr to reach a blood alcohol concentration of 0 (Paintner et al., 2012a). If the same women consumed 3 times as many drinks (12 standard drinks) it would take 25.6 hr for blood alcohol concentrations to decline to 0. In Figure 1, we present a model of an exposure episode and estimated cumulative dosimetry parameters for weekend drinking over a term pregnancy.

Persistent alcohol use increases tolerance, which can result in very high blood alcohol concentrations for some individuals. Another key factor in determining duration of an exposure episode is the effect of drinking on consecutive days, when the second exposure episode will begin before the blood alcohol concentration from the previous drinking episode has reached zero (Paintner et al., 2012a). This will result in a higher blood alcohol concentration for the second episode and extend the period of exposure for the fetus.



Cumulative Exposure

Weekend Drinking (Friday and Saturday)

Dosimetry	4 Beers	8 Beers
Days Exposed	80	80
# Standard Drinks (14 Grams)	320	640
Binge Days	80	80
Hours Exposed	680	1360
Total Grams Ethanol	4480	8960
Total Grams Ethanol entering Fetal Comparmtment	520	1040

FIGURE 1. *Exposure episode and dosimetry parameters for a 140-pound woman drinking eight standard drinks (12 ounces of beer; 5% alcohol) over 4 hr.*

ETHANOL DISPERSION INTO AND WITHIN THE FETAL COMPARTMENT

At the beginning of pregnancy, amniotic fluid volume exceeds fetal volume. By the 20th week of gestation the two volumes are equal, but by the 30th week of gestation amniotic fluid volume is approximately half the fetal volume, and at term it is approximately a quarter of fetal volume.

By 40 weeks gestation, approximately 4 liters of water are present within the human fetal compartment, with 2800 ml in the fetus, 400 ml in the placenta, and 800 ml in the amniotic fluid (Modena and Fieni, 2004). Amniotic fluid has a turnover rate of approximately once per day (Beall et al., 2007).

Ethanol enters the fetal compartment readily across the placenta. The chemical structure of ethanol allows rapid diffusion across multiple biological membranes and dispersion throughout the body water resulting in fetal compartment ethanol levels approaching maternal levels within 1 hr and equilibrium in 2 hr (Idanpaan-Heikkila et al., 1972). Before 20 weeks of gestation, ethanol enters the amniotic fluid through the highly permeable skin of the fetus. Between 20 and 24 weeks of gestation, the fetal skin undergoes keratinization, creating a barrier to solutes (Hardman et al., 1999; Modena and Fieni, 2004). After 20 weeks, this barrier formation effectively reduces ethanol movement through the fetal skin into the amniotic fluid.

Therefore, after 20 weeks of gestation, the primary source for ethanol dispersion into the amniotic fluid is through fetal urine and fetal breathing movements. Ethanol is excreted unchanged through both pulmonary excretions and fetal urine. In a subsequent section, we provide a detailed discussion on maternal ethanol metabolism as a primary route of alcohol elimination.

ACCUMULATION OF ETHANOL IN THE FETAL COMPARTMENT

As the maternal blood alcohol concentration increases, ethanol is diffused into the fetal compartment at increasing rates. In Figure 2, we present a graphic to facilitate estimation and quantification of ethanol accumulation in the fetal compartment. The figure has two time points approximating fetal size and fluid volume at 22 weeks and 40 weeks gestation. The maternal blood alcohol level is the first key variable in ethanol accumulation in the fetal compartment. In the second column we estimate the accumulation of alcohol in the fetal compartment in grams. In this figure, we estimate the alcohol elimination rate from the fetal compartment to be approximately 3% to 4% of the maternal rate. We have also estimated the time it takes to eliminate alcohol from the fetal compartment to achieve a blood alcohol concentration of 0.

ALCOHOL ELIMINATION FROM THE FETAL COMPARTMENT

The fetus has very limited metabolic capacity and transfer of ethanol from the fetal compartment to maternal circulation is the major pathway to reduce fetal exposure. Animal studies show similar elimination rates from the maternal and fetal circulation. This suggests that there is rapid, bidirectional placental transfer between the two compartments and that elimination occurs mainly within the maternal compartment (Ng et al., 1982; Brien et al., 1985; Beall et al., 2007). Consequently, alcohol elimination from the fetal compartment is accomplished by reabsorption back into the fetal circulation where it is then transferred by means of the placenta back to the maternal circulation (Nava-Ocampo et al., 2004). Thus, reabsorption of ethanol from the amniotic fluid into the fetal circulation may be the rate-limiting step for the elimination of ethanol from amniotic fluid. Before 20 weeks of gestation, this may not be a factor, because reabsorption occurs through the fetal skin. After 20 weeks of gestation, reabsorption occurs by means of two pathways: fetal swallowing and the intramembranous pathway (Underwood et al., 2005; Beall et al., 2007).

Fetal swallowing begins during the 11th week of gestation. By term, the amount of amniotic fluid swallowed by the fetus is between 500 and 1000 ml/day (Gilbert and Brace, 1989). The second route for reabsorption into the fetal circulation is the intramembranous pathway. This pathway involves the absorption of amniotic fluid across the amnion and into the fetal vasculature driven by osmotic differences (Gilbert and Brace, 1989). The human

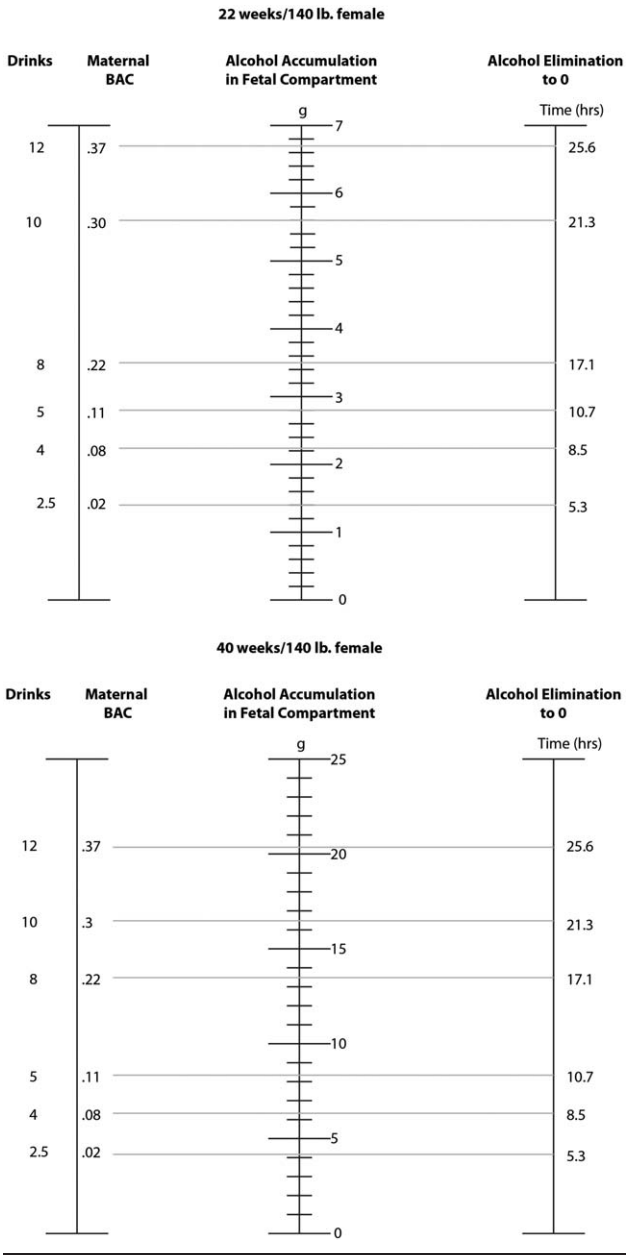


FIGURE 2. *Alcohol accumulation within the fetal compartment is closely related to maternal blood alcohol concentrations which may vary as much as fourfold between individuals of the same weight consuming the same amount of alcohol (Ramchandani et al., 2009). All calculations were based on a 140-pound woman with total body water of 31.2 liters (water concentration is 49% total body weight) drinking one standard drink of 12 ounces of beer containing 5% alcohol (14 grams of alcohol) over 4 hr. It is also assumed that maternal blood alcohol concentration and fetal compartment maternal blood alcohol concentration equilibrate, and are therefore the same.* **A:** *Graphic to estimate alcohol accumulation in fetal compartment at 22 weeks gestation. At 22 weeks, there are approximately 1.38 liters of fluid in the fetal compartment (4% total body water).* **B:** *Accumulation estimates at 40 weeks gestation in 4 liters of fluid in the fetal compartment (12% total body water).*

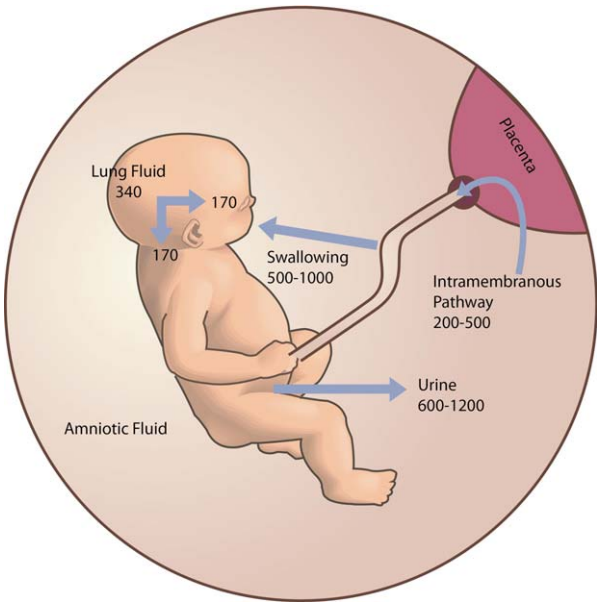


FIGURE 3. *Fluid flow rates in the fetal compartment are depicted by the schematic diagram of all known pathways for fluid and solute entry into and elimination from the fetus/amniotic fluid near term. The numbers represent volume flows in ml/day. The asterisk symbol denotes recirculating pathways. The double arrow represents the proportions of pulmonary excretions that are swallowed (50%) and those that enter the amniotic fluid (50%).*

amnion is a single layer of epithelial cells separating the amniotic cavity from the vascularized chorion. The amount of fluid that passes through the intramembranous pathway has been estimated at 200 to 500 ml/day (Wintour and Shandley, 1993; Underwood et al., 2005). Figure 3 diagrams fluid flow rates within the fetal compartment.

FACTORS THAT EXTEND EXPOSURE IN LATE PREGNANCY

Two factors increase the duration of alcohol exposure to the fetus. Ethanol is excreted unchanged into the amniotic fluid through fetal pulmonary fluid and fetal urine is partially recycled back into amniotic fluid through fetal swallowing or reabsorption through the intramembranous pathway (Nava-Ocampo et al., 2004). These two reabsorption pathways create a recycling system where much of the ethanol the fetus excretes will be reabsorbed back into its circulatory system. In addition, it is likely that vasoconstriction of the placenta-umbilical unit from alcohol and smoking may further impair alcohol elimination rates from the fetal compartment (Kay et al., 2000; Acevedo et al., 2001). Umbilical vessels react to ethanol at very low levels (50–85 mg/dl) (Altura et al., 1982). The umbilical artery is even more sensitive to ethanol exposure, with 10% of arteries demonstrating vasoconstriction at exposure levels beginning at .001 g (exposure to approximately 1 standard drink) (Savoy Moore et al., 1989). This effect may be further modified by alcohol-induced vascular maladaptations in the maternal–fetal interface (Ramadoss and Magness, 2012). The combined effect of exposure to both alcohol and smoking exerts effects that exceed the sum of the effects from both, suggesting a multiplicative risk enhancement from combined exposure (Odendaal et al., 2009). Thus, the physiology of the fetal compartment allows amniotic fluid to function as a reservoir for ethanol (Nava-Ocampo et al., 2004).

Animal studies also show that the amniotic fluid may act as a storage site for ethanol. Studies done with pregnant ewes show that alcohol concentration does not peak within the amniotic fluid until 1 to 1.5 hr after intravenous infusion of ethanol, whereas maternal and fetal blood concentrations peak at the end of infusion (Ng et al., 1982). Although the elimination rates of ethanol between the three compartments (maternal blood, fetal blood, and amniotic fluid) do not differ significantly in ewes, studies show that the concentration of ethanol in amniotic fluid is greater than maternal or fetal blood during the elimination phase (Brien et al., 1985). The higher concentrations of ethanol in and its slower elimination from amniotic fluid in comparison with maternal and fetal blood indicate that the amniotic fluid can act as a reservoir.

ETHANOL METABOLISM

Ethanol is metabolized in the placenta, fetus, neonate, and mother, but at different rates. Oxidative metabolism is the main pathway for the metabolism of ethanol in the liver and occurs through three different mechanisms. Alcohol dehydrogenase (ADH) is the primary mechanism, accounting for 90–95% of ethanol metabolism in the liver. This biotransformation reaction results in the production of acetaldehyde, a highly toxic metabolite, which is then metabolized by the mitochondrial aldehyde dehydrogenase (ALDH) to acetate and eventually to CO_2 and water, to be eliminated from the body. Hepatic catalase provides a small amount of ethanol metabolism, but it is not clinically significant. The remainder (5–10%) of ethanol metabolism is by means of microsomal p450 enzymes, namely CYP2E1 (Zakhari, 2006; Gemma et al., 2007; Pizon et al., 2007). This biotransformation results in the production of acetaldehyde, which is oxidized releasing oxygen-derived free radicals. There is also a nonoxidative pathway, which plays a minor role in elimination kinetics compared with the oxidative pathways, accounting for only 1% of total metabolism. This pathway involves the transformation of ethanol into fatty acid ethyl esters by means of FAEE synthase (Zakhari, 2006). In addition to elimination by metabolic reactions, approximately 2% to 5% of ethanol can be eliminated unchanged through maternal cutaneous, pulmonary, and renal excretions (Pizon et al., 2007).

Dispersion of alcohol through the placenta into the fetal compartment is the initial pathway for prenatal alcohol exposure. The placenta is endowed with drug-metabolizing enzymes and is, therefore, able to

biotransform xenobiotics, either activating or detoxifying them. Subsequently, the placenta may play a role in both protective and harmful consequences for the fetus. CYP2E1 protein has been detected by Western blot analysis in the human placenta. The levels of CYP2E1 protein in human placenta were directly related to prenatal alcohol consumption, but varied markedly. This result suggests that ethanol induction of placental CYP2E1 is likely under genetic control, but it is unknown what role it may play in fetal susceptibility to intrauterine ethanol exposure (Rasheed et al., 1997; Syme et al., 2004). ADH is also known to be expressed in the human placenta. The placental ADH isozyme is analogous to class III ADH enzymes, which have a low affinity and a reduced metabolic rate for ethanol compared with other classes of ADH enzymes (Burd et al., 2012). Because of the reduced ethanol oxidation capacity of placental ADH, placental CYP2E1 is likely to be more important. CYP2E1 also has a higher affinity for ethanol and is inducible (Gemma et al., 2007). The placenta also contains a low-affinity, low-activity type ALDH. If the placenta succeeds in metabolizing any ethanol, it is unlikely that the toxic metabolite, acetaldehyde, will be metabolized, and therefore, it is not prevented from entering the fetal compartment (Andersson et al., 1989). Placental enzymes activities are usually relatively lower when compared with those of the maternal and fetal liver; therefore, they do not appear to play a significant role in the oxidative metabolism of ethanol or acetaldehyde to protect the fetus against their harmful effects.

In humans, ADH is expressed in the fetal liver at 2 months of gestation. ADH is also expressed in fetal kidneys and lung, indicating that fetal tissues are able to biotransform ethanol in situ (Gemma et al., 2007). However, fetal hepatic ADH functions at a rate of no more than 3% to 4% of adult activity, which is 0.017 g%/hr (Pikkarainen and Raiha, 1967; Cowan et al., 1996). Detectable hepatic CYP2E1 levels corresponding to 10–30% of adult levels as early as 16 weeks gestation have been reported (Hines and McCarver, 2002). Fetal liver microsomes, which contain the P450 enzymes, oxidize ethanol at a rate that is 12 to 27% of adult microsomes (Carpenter et al., 1996). The decreased abundance of Cytochrome P450 enzymes as well as their decreased activity compared with adult enzymes limits fetal capacity to use microsomal oxidation to remove ethanol.

The finding of CYP2E1-mediated bioactivation of xenobiotics in prenatal human brain tissue, the target organ of alcohol teratogenesis, is of interest as one component of a causal pathway for FAS. The presence of CYP2E1 message, immunoreactive protein, and functionally active enzyme at relatively low levels in prenatal human brain tissue (gestational weeks 7–16) suggest that CYP2E1 may play an important role in alcohol teratogenesis, especially in eliciting neurotoxic effects (Brzezinkski et al., 1999). During ethanol metabolism in the fetal brain, CYP2E1 generates reactive chemical species including oxygen-derived free radicals, hydroxyethyl radical, acetaldehyde, and other aldehydes derived from lipid peroxides. Each of these chemical species is capable of contributing to alcohol-induced cellular injury that is manifested as highly prevalent and variable central nervous system dysfunction (Brzezinkski et al., 1999). While the fetus has the ability to metabolize some ethanol, the pathways that are responsible for the majority of ethanol metabolism are so modest that the burden of ethanol removal from the fetal–maternal unit relies primarily on maternal metabolic capacity.

Discussion

There are multiple variables that may increase the duration of alcohol exposure to the fetus, including exposure episode dosimetry, recycling pathways, and vasoconstriction of the placental-umbilical unit. The inefficient alcohol elimination systems present within the fetal compartment increase both levels of exposure and exposure duration. This is important as the proportion of pregnancies (especially the 50% that are unplanned) with some early exposure is very high. Early identification of PAE may be especially relevant in the management of pregnancies complicated by high levels of alcohol use. Several important management strategies could result from early detection and improved understanding of alcohol dispersion and elimination from the fetal compartment. First, is an improved appreciation of the consequences of drinking in late pregnancy. Alcohol elimination during late pregnancy is more complex than elimination before 20 weeks of pregnancy due to keratinization of the fetal skin. Second, is the need to look for multiple other co-occurring risk factors frequently associated with PAE. Smoking is one of the most prevalent and both alcohol and smoking at very low levels result in hours of vasoconstriction of the placenta and umbilical cord. Third, prenatal care providers can now provide improved explanations for their concerns about PAE at any point in pregnancy. Fourth, improved understanding of the pathophysiology may encourage providers to increase the amount of brief intervention provided during the visit which have been demonstrated to improve quit rates and to decrease exposure throughout the remainder of pregnancy (Jones, 2013). Fifth, PAE increases risk for morbidity and mortality including stillbirth, prematurity, low birth weight, infectious illness, sudden infant death syndrome, and learning and behavior disorders (Odendaal et al., 2009; Paintner et al., 2012a). This supports the need for systematic screening to detect PAE identifying these high risk pregnancies (Paintner et al., 2012a). Sixth, untreated PAE is likely to be repeated in future pregnancies (Burd et al., 2008; Paintner et al., 2012b; Burd, 2014). In these families, it is important to

note that younger siblings are often more severely affected by PAE compared with older siblings (Burd et al., 2008).

While PAE is essential for the diagnosis of fetal alcohol spectrum disorders, there is no widespread consensus of a level of ethanol exposure below which there are no observable adverse effects. Multiple variables may affect susceptibility for adverse outcomes for each individual woman and individual fetus. These factors are variably influenced by maternal genetics, fetal genetics, and the interaction of these influences. Therefore, further research to improve the understanding of the dispersion of ethanol into and out of the fetal compartment is important to improve outcomes from this common teratogen.

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