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Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn

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Fetal alcohol spectrum disorders (FASDs) are a common cause of intellectual impairment and birth defects. More recently, prenatal alcohol exposure (PAE) has been found to be a risk factor for fetal mortality, stillbirth and infant and child mortality. This has led to increased concern about detection and management of PAE. One to 2 h after maternal ingestion, fetal blood alcohol concentrations (BACs) reach levels nearly equivalent to maternal levels. Ethanol elimination by the fetus is impaired because of reduced metabolic capacity. Fetal exposure time is prolonged owing to the reuptake of amniotic-fluid containing ethanol by the fetus. Alcohol elimination from the fetus relies on the mother's metabolic capacity. Metabolic capacity among pregnant women varies eightfold (from 0.0025 to 0.02 $g\,dl^{-1}\,h^{-1}$), which may help explain how similar amounts of ethanol consumption during pregnancy results in widely varying phenotypic presentations of FASD. At birth physiological changes alter the neonate's metabolic capacity and it rapidly rises to a mean value of 83.5% of the mother's capacity. FASDs are highly recurrent and younger siblings have increased risk. Detection of prenatal alcohol use offers an important opportunity for office-based interventions to decrease exposure for the remainder of pregnancy and identification of women who need substance abuse treatment. Mothers of children with FAS have been found to drink faster, get drunk quicker and to have higher BACs. A modest increase in the prevalence of a polymorphism of alcohol dehydrogenase, which increases susceptibility to adverse outcomes from PAE has been reported. Lastly, detection of alcohol use and appropriate management would decrease risk from PAE for subsequent pregnancies.
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Introduction

Ethanol is a well-known fetal teratogen, which can cause a range of pathophysiological consequences termed fetal alcohol spectrum disorder (FASD). It is likely that both the duration of teratogen exposure and dosimetry have an important role in the development of FASD. Understanding the maternal, fetal and neonatal alcohol elimination rates (AER) and the mechanisms of elimination is important for management of ethanol exposure in the fetus and neonate.

Prenatal alcohol exposure (PAE) is a pandemic health problem. In the United States, the prevalence of alcohol use by non-pregnant women during their childbearing years was 54.6% in 2001.[1] Approximately 50% of pregnancies in the United States are unplanned, and therefore many will have early exposure before pregnancy can be confirmed.[2]

In 2001, 12.5% of pregnant women reported at least some alcohol use during their pregnancy and 1.6% reported frequent use of alcohol while pregnant.[1] As a result, for the four million pregnancies each year in the United States, 500 000 have experienced some level of PAE and 64 000 had high levels of exposure. Current prevalence estimates of FASD from worldwide studies of school-age-children range from 20 to 50 per 1000 live births.[3] Current prevalence estimates of FASD within the US range from 0.5 to 9.1 cases for every 1000 live births.[3,4] Siblings of children with FASD have an increased rate for FASD.[5,6] Fetal alcohol syndrome (FAS) is the most readily identifiable category of FASD. In 2010, the prevalence of FAS in the United States was reported to be 0.2–1.5 cases per 1000 live births,[7] a review paper of more recent studies reports rates of FAS of 2 to 7 per 1000 live births.[3] This would equate to an annual incidence of FAS between 8000–28 000 cases each year in the United States alone.[7]

There is an association between maternal consumption of alcohol and unsuccessful pregnancies. Approximately 15% of all pregnancies end in spontaneous abortion, but among heavy drinking mothers the prevalence increases to 45%.[8] The occurrence of stillbirth among pregnancies exposed to ethanol has been shown

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to increase sixfold compared with the rate of stillbirths within the population as a whole.[9]

Although PAE is teratogenic to multiple organ systems, it is especially harmful to the central nervous system because of its extended developmental period. PAE is the most common identifiable and preventable cause of intellectual disability in the United States.[7]

Knowledge of the pathophysiological mechanisms of PAE is incomplete. Conflicting reports of correlations regarding blood alcohol concentrations (BACs) and AERs for maternal, fetal and newborn levels complicates treatment of mothers and the exposed fetus or neonate.

For this review we utilized a search strategy designed to locate articles reporting perinatal alcohol exposure, BACs and AER. We utilized the search terms: alcoholism, blood, blood alcohol, blood concentration, blood level, ethanol, fetal, FAS, fetus, foetal, gestational age, maternal-fetal exchange, neonate, newborn, pregnancy and prenatal exposure delayed effects. The search was completed to June 2011 and placed no limits on language or publication date. Only reports on human studies were included. Additional relevant publications were located by hand-searching articles for references. This review was organized into six topical areas: (1) pathophysiology of exposure, (2) maternal metabolism of ethanol, (3) transfer of ethanol across the placenta, (4) fetal metabolism, (5) dispersion in amniotic fluid and (6) newborn elimination.

Pathophysiology of exposure

Following a rise in maternal BAC, ethanol can be detected in the fetus within 1 min.[10] However, the rise in the BAC of the fetus is slower than the rise in maternal BAC, but eventually the two values reach or come close to equilibrium (Figure 1).

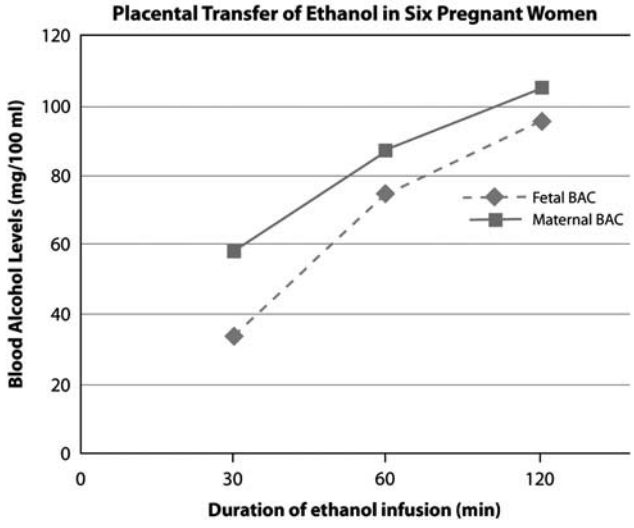

Figure 1 Rate of ethanol transfer from mother to fetus. This figure illustrates the delay in rising fetal blood alcohol concentration and the progressive equilibrium between the two compartments.[18]

Reports of maternal BACs at the time of delivery, range from 0.005 to 0.210 g dl^{-1}. The neonates' BACs varied between 0.005 and 0.212 g dl^{-1}. The mean BAC of neonates at the time of delivery exceeded the mean BAC of the mothers (Table 1). The 10 cases, which included data for both maternal and newborn AER (Table 2), showed a mean neonatal AER of 0.0059 g dl^{-1} h^{-1} and a mean maternal AER of 0.0093 g dl^{-1} h^{-1} (Figures 2 and 3). The data for the 47 newborns revealed an AER ranging from 0.0025 to 0.020 g dl^{-1} h^{-1}, an eightfold variation with a mean AER of 0.0083 g dl^{-1} h^{-1} (Table 1).

The reported maternal AERs ranged from 0.0025 to 0.020 g dl^{-1} h^{-1}. The mean value of the maternal AERs was 0.010 g dl^{-1} h^{-1}. Most of the reports did not provide peak BAC for mother and neonate, but rather provided BACs at time of delivery.

A comparison of the AERs between the pairs of mothers and neonates found the neonates' AER ranged from 1/3 of the mothers' to twice that of the mothers'. The newborns' mean AER was 83.5% of the mothers' mean AER with a median rate of 57% (Table 2).

Among the 10 pairs of maternal-newborn data sets, the case study by Jung *et al*.[11] contained a report of a newborn who died of alcohol poisoning who also had outlier data values and unusual elimination kinetics (non-zero order). For these reasons the data from this case was excluded from the mean values of the maternal-newborn pairs in Table 2. If the data from this study had been included, the mean maternal AER would have been 0.0112 g dl^{-1} h^{-1} and the neonatal AER would have been 0.0071 g dl^{-1} h^{-1}.

Maternal metabolism of ethanol

The enzymes used to metabolize ethanol in the placenta, fetus and neonate are the same as those for the mother, but are found at different concentrations and levels of activity. Ethanol is metabolized through oxidative and non-oxidative pathways. Oxidative metabolism is the main pathway for the metabolism of ethanol in the liver and occurs through three different mechanisms. The enzyme alcohol dehydrogenase (ADH) metabolizes ethanol to acetaldehyde and accounts for 90–95% of the metabolism by the liver.[12,13] In a controlled field drinking trial mothers of children with FAS were found to drink faster, get drunk quicker, obtain higher BACs and to have an increased prevalence of an ADH polymorphism. The mothers also weighed less and had more children.[14] Some research has suggested that polymorphisms in the enzymes responsible for ethanol metabolism may have a role in why some children develop FAS while others do not. The studies suggest that the ADH2*2 allele in either the mother or the fetus may have a protective effect.[13]

The remaining 5–10% of liver oxidation is catalyzed by Cytochrome P450 enzymes, most notably by CYP2E1, in a microsomal system.[12,13] When the ADH enzymes are saturated ethanol exposure increases CYP2E1 metabolism by four to 10-fold.

Table 1 Cumulative maternal and/or neonatal data BACs and/or AERs of all included studies

Reference	*Case*	*Maternal BAC at delivery*	*Neonate BAC at delivery*	*Maternal AER g dl^{-1} h^{-1}*	*Neonate AER g dl^{-1} h^{-1}*
Seppala, 1971	1	0.058	0.067	0.014	0.008
—(Twins)	2	0.058	0.053	0.014	0.007
Idanpaan, 1972	3,4,5,6,7,8	0.099 (mean)[a]	0.102 (mean)[a]	0.014 (mean)	0.0077 (mean)
Jung, 1980	9	0.629[a]	0.8[a]	0.026[a]	0.017[a]
Cook, 1975	10	0.098	0.15	No data	0.008[a]
Wagner, 1970	11	No data	0.035	No data	0.0068
	12	No data	0.05	No data	0.0048
	13	No data	0.07	No data	0.0075
	14	No data	0.071	No data	0.0068
	15	No data	0.086	No data	0.011
	16	No data	0.1	No data	0.01
Gartner, 1972	17	0.06	0.072 (umbilical vein)	No data	0.012
	18	No data	No data	No data	0.008
	19	0.082	0.102 (umbilical vein)	No data	0.02
	20	No data	0.183 (umbilical vein)	No data	0.009
Beattie, 1986	21	0.21	0.212	0.0175[a]	0.0088[a]
Fuchs, 1967	22	0.15	0.18	No data	No data
—(Twins)	23	0.15	0.17	No data	No data
Waltman, 1972	24	0.045	0.02 (umbilical artery)	0.006	0.00375
	25	0.03	0.02 (umbilical artery)	0.005	No data
	26	0.05	0.035 (umbilical artery)	0.010	0.00375
	27	0.05	0.03 (umbilical artery)	0.009	No data
	28	0.02	No data	0.0025	No data
	29	0.03	0.02 (umbilical artery)	0.02	No data
	30	0.02	0.015 (umbilical artery)	No data	No data
	31	0.015	0.005 (umbilical artery)	0.01	No data
	32	0.02	0.015 (umbilical artery)	0.01	No data
	33	0.02	0.01 (umbilical artery)	0.005	No data
	34	0.02	0.01 (umbilical artery)	0.01	No data
	35	0.04	0.04 (umbilical artery)	0.01	0.0075
	36	0.03	0.01 (umbilical artery)	0.0075	Insufficient data
	37	0.035	0.01 (umbilical artery)	No data	Insufficient data
	38	0.03	0.03 (umbilical artery)	0.0025	0.005
	39	0.02	0.02 (umbilical artery)	0.0025	0.0025
	40	0.005	0.005 (umbilical artery)	0.005	Insufficient data
	41	0.05	0.02 (umbilical artery)	Insufficient data	Insufficient data
	42	0.01	0.01 (umbilical artery)	Insufficient data	Insufficient data
	43	0.01	0.01 (umbilical artery)	Insufficient data	Insufficient data
	44	0.01	0.05 (umbilical artery)	Insufficient data	0.0075
	45	0.025	0.02 (umbilical artery)	Insufficient data	Insufficient data
	46	0.04	No data	Insufficient data	Insufficient data
Puschel, 1979	47	No data	0.2	No data	0.008
Mean:		0.0672	0.0796	0.0100	0.0083
Range:		0.005–0.210	0.005–0.212	0.0025–0.02	0.0025–0.02

Abbreviations: AER, alcohol elimination rates; BAC, blood alcohol concentrations.
Cited from:[10,11,18,34–40].
[a]Derived estimate from data given.

In the presence of chronic exposure CYP2E1 is likely related to the development of tolerance observed in people with chronic alcohol abuse.[13,15] Placental CYPE2E1 is inducible by ethanol exposure and has a higher affinity for ethanol than placental ADH. Although induction by PAE is variable, CYP2E1 may have important roles in placental pathways influencing fetal susceptibility to PAE.[13,16]

Table 2 Mother and newborn pairs: blood alcohol concentrations (BAC) and alcohol elimination rates (AER)

Reference	N	*Maternal BAC @ delivery (g dl^{-1})*	*Neonate BAC @ delivery (g dl^{-1})*	*Maternal AER (g dl^{-1} h^{-1})*	*Neonate AER (g dl^{-1} h^{-1})*	*Neonatal AER ÷ maternal AER*
Seppala (twins)	1	0.058	0.067	0.014	0.008	0.57
	2	0.058	0.053	0.014	0.007	0.50
Jung[a]	3	0.629[a]	0.8[a]	0.026[a]	0.017[a]	0.65[a]
Beattie	4	0.21	0.21	0.017[b]	0.008[b]	0.47[b]
Waltman	5	0.045	0.04	0.006	0.009	1.50
	6	0.05	0.045	0.01	0.004	0.40
	7	0.04	0.035	0.01	0.0075	0.75
	8	0.03	0.02	0.0075	0.0025	0.33
	9	0.03	0.025	0.0025	0.005	2.00
	10	0.02	0.02	0.0025	0.0025	1.00
Mean:		0.0601	0.0572	0.0093	0.0059	0.8355
Range:		0.02–0.629	0.02–0.8	0.0025–0.026	0.0025–0.017	0.33–2.00
Magnitude:				(10 fold)	(6 fold)	(6 fold)

[a]Data excluded from mean values because of its outlier status and unusual elimination kinetics.
[b]Derived estimate from data given.

A third oxidative reaction involving the enzyme catalase does not have significant ethanol metabolizing capacity *in vivo*.[15] The non-oxidative pathway, which transforms ethanol into fatty acid ethyl esters by FAEE synthase, has a minor role in elimination kinetics when compared with the oxidative pathways.

In addition to biotransformation by metabolic reactions, ethanol can be eliminated unchanged through cutaneous, pulmonary and renal excretions. Cutaneous elimination is usually small (0.1%) and can be impacted by hydration status and activity level.[13,17] The percent of ethanol eliminated through pulmonary excretions in an adult ranges from 0.7 to 3% at low ethanol concentrations and 6 to 8% at higher concentrations; elimination by renal excretion is between 0.3 to 10%.[13,17]

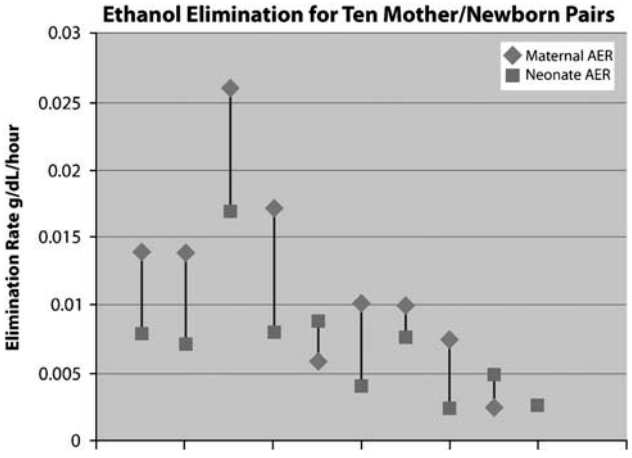

Figure 2 Comparison with mother (diamond)–newborn (square) AER for 10 cases demonstrating newborns decreased capacity for alcohol elimination.[10,11,34,38]

Transfer of ethanol across the placenta

The dispersion of alcohol through the placenta into the fetal compartment is the initial pathway of PAE. The chemical structure of the ethanol molecule enables rapid diffusion across biological membranes, such as the placenta, and dispersion throughout the body water resulting in fetal circulation levels close to maternal levels within 1 h and equilibrium in 2 h[18] (Figure 1). Although the placenta is a metabolically active organ, it is capable of only a minute amount of ethanol metabolism and does not appreciably reduce the amount of ethanol reaching the fetus.

ADH is present in various isoforms throughout the human body and is the most active enzyme in ethanol oxidation; however, there is only one ADH isozyme found 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.[19] The alcohol oxidation rate of the placenta is estimated at 45.6 nmol h^{-1} g^{-1} of tissue, whereas the oxidation rate of the alcohol in the adult liver is increased over 3900 fold at 178 μmol h^{-1} per g of tissue.[20] Because of the reduced ethanol oxidation capacity of placental ADH, the placenta does not appear to have a significant role in the oxidative metabolism of ethanol. While the placenta contains FAEE synthase activity,[21] the limited role of FAEE synthase in the normal metabolism of ethanol suggests that the non-oxidative pathway does not make a significant contribution to the ability of the placenta to metabolize alcohol. The ineffectiveness of both the oxidative and non-oxidative pathways within the placenta results in the unrestricted diffusion of ethanol across the placenta into the fetal compartment.

Fetal metabolism

Once ethanol has entered into the fetal circulation, the fetus attempts to metabolize it through the same pathways seen in the adult.

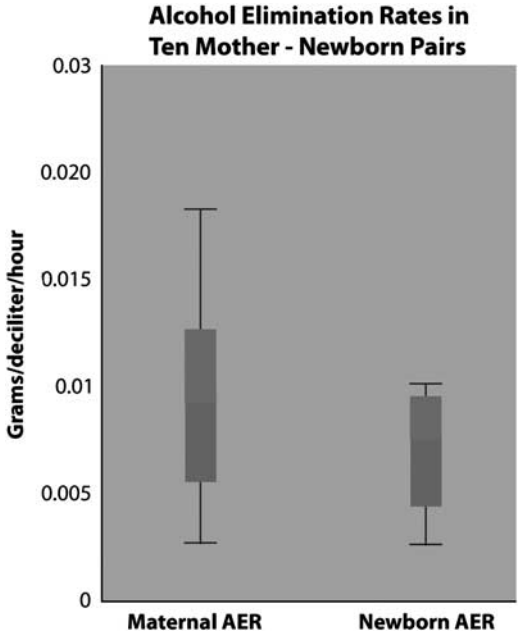

Figure 3 Midline of bar indicates mean value; ends of each bar indicate s.d.; the ends of the whiskers indicate the high and low values for the AER for the same 10 mother-newborn pairs in Figure 2.

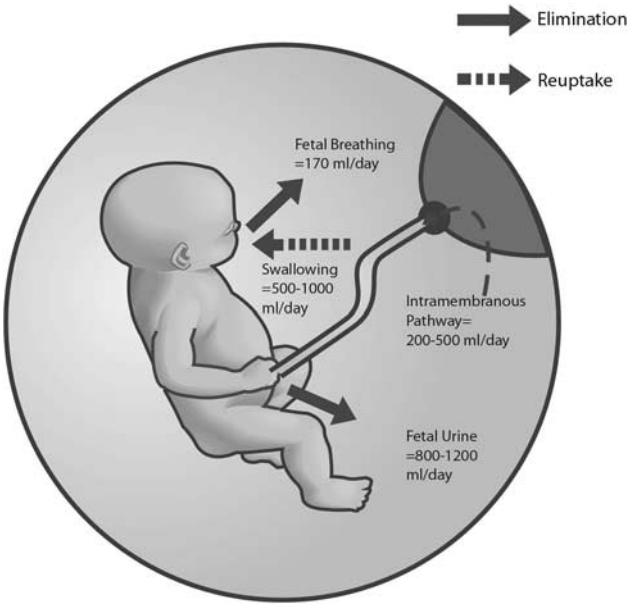

Figure 4 Pathways of amniotic fluid recirculation.[27] Production and reuptake are usually near equilibrium and therefore alcohol elimination through these pathways is highly ineffective.

Although the understanding of the metabolic capacity of the fetal liver is limited, available studies show that the major enzyme involved in ethanol oxidation, ADH, is detectable in the fetus at 2 months gestation.[22] Metabolic capacity in the fetus is severely diminished, functioning at a rate of about 5 to 10% of adult activity.[23]

CYP2E1, the P450 enzyme with the greatest capacity to oxidize alcohol, was not present in 10 week fetuses but was present in fetal livers at 19, 23 and 24 weeks gestation.[24] The reduced capacity of the fetus to metabolize ethanol is in part because of the lower abundance of P450 enzymes in the fetal liver (0.2 to 0.4 nmol mg^{-1}) compared with the adult liver (0.4 to 0.8 nmol mg^{-1}).[25] Also, fetal liver microsomes, which contain the P450 enzymes, have been shown to oxidize ethanol at a rate that is 12 to 27% of adult microsomes.[26] While the concentration of CYP2E1 was shown to double during *in vitro* exposure of fetal hepatocytes to ethanol,[26] the decreased abundance of Cytochrome P450 enzymes as well as their decreased activity compared with adult enzymes limits fetal capacity to utilize microsomal oxidation to remove ethanol.

While the fetus has the ability to metabolize some alcohol, 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.

Dispersion in amniotic fluid

The origin of the amniotic fluid during the first half of gestation is not fully understood but diffusion of water and substrates across unkeratinized fetal skin may contribute to its formation. During the second half of gestation, fetal urinary and pulmonary excretions are the main contributors to fluid volume. Ethanol can be excreted unchanged through pulmonary excretions and in fetal urine, where it accumulates in the amniotic fluid. The amniotic fluid can be reabsorbed back into the fetal circulation through two pathways: fetal swallowing and the intramembranous pathway.

Fetal swallowing begins by the 11 week of gestation and becomes the major component of reabsorption providing a route for ethanol reentry into the fetal circulation. The amount of amniotic fluid swallowed by the fetus (500 to 1000 ml per day) does not account for the amount of urine and pulmonary secretions (970 to 1370 ml per day) that enter the amniotic fluid.[27]

An alternate route of fluid absorption must account for the difference, with the intramembranous pathway having the most support in the literature. The pathway details the absorption of amniotic fluid across the amnion and into the fetal vasculature driven by osmotic differences.[27] The absorption of the amniotic fluid through fetal swallowing and the intramembranous pathway creates a recycling system where much of the ethanol that the fetus excretes will be reabsorbed back into its circulatory system (Figure 4). This increases the duration of each exposure episode.

Upon exposure the fetus removes the ethanol through two different mechanisms. The limited capability of the fetus to metabolize ethanol does little to reduce the duration of exposure. Despite the fetus' ability to eliminate ethanol as renal and pulmonary excretions, it remains trapped in the amniotic fluid leading to reabsorption by the fetus and prolonging exposure time[28] (Figure 5).

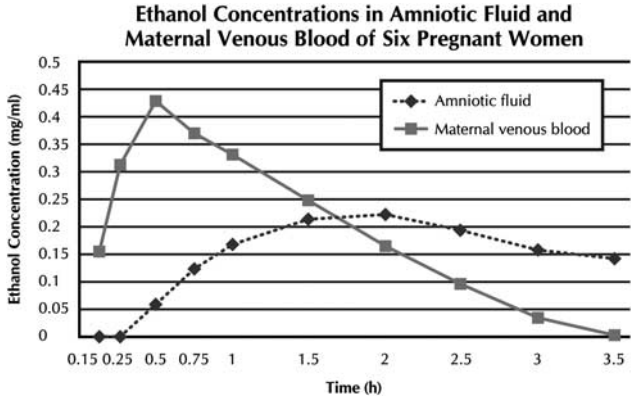

Figure 5 Line chart displaying the mean values of ethanol concentration in the blood versus the amniotic fluid of six pregnant women.[28] Blood ethanol concentrations peak at a value nearly twice that of the amniotic fluid. Ethanol within the amniotic fluid remains at a significant level as maternal blood concentrations decrease.

Newborn elimination

The ethanol elimination capacity of the fetus changes from a small fraction of maternal capability *in utero* to a mean of 83.5% of the maternal capability in the newborn. Although the changes underlying the increase in elimination capacity are not fully understood, there are a number of physiological and environmental changes around the time of birth that contribute to the increased AER of the newborn. The postnatal development of oxidation enzymes, increase in glomerular filtration rate and an environment where renal and pulmonary excretions are not recirculated through the amniotic fluid contribute to the increased AER.

The increased metabolic capability of the newborn is not fully understood. However, there are a number of reports examining the ontogeny of newborn liver enzymes. The level of CYP2E1 enzyme was found to increase significantly at birth, regardless of gestational age with notable increase on the first post natal day.[29]

The capacity of the kidneys to excrete ethanol also increases after birth. Hemodynamic changes occur around the time of birth that causes a 50 to 100% increase in glomerular filtration rate during the 1st week of life.[30,31] As the glomerular filtration rates increase, a greater amount of ethanol is removed from circulation. Renal excretion by the newborn is also more effective than renal excretion by the fetus, because there is no amniotic fluid reservoir to trap and recycle the ethanol back into the newborn.

Limitations

We identified several limitations in the available literature. We were unable locate data to estimate the potential effects of chronic exposure on the development of tolerance and resulting changes in metabolic rates for the fetus or newborn. The accuracy and comparability of the methodologies used to determine the BAC values is unknown. Most studies, which sampled umbilical cord blood, did not differentiate between the umbilical vein and the umbilical artery. Potential differences in BAC within these different vessels could explain some of the wide variations seen in this review.

Smoking is a common comorbid exposure among women who use alcohol or have children with FASD.[32] Smoking is a potent vasoconstrictor of the maternal vasculature, placenta and umbilical cord, which may modify dispersion rates of alcohol into the fetal compartment. Ethanol is also a potent vasoconstrictor and combined exposure likely results in long time windows of constriction.[33] We did not locate studies reporting on effects of vasoconstriction in relation to either BAC or AER in the fetus or newborn.

Discussion

The BAC of the fetus in early pregnancy may be quite high as the elimination factors described above are inefficient or absent. This is important as the proportion of pregnancies (especially the 50% that are unplanned pregnancies) with some early exposure is very high. BAC levels at delivery can be elevated and based on the prevalence of alcohol use in the last trimester it appears that most of these babies are not identified. Early identification of PAE may be especially relevant in the management of pregnancies complicated by high levels of alcohol use. The case report of a newborns death from alcohol poisoning by Jung *et al*.[11] is a reminder of the potential benefits of identification of PAE and intervention at any time point in pregnancy. As many of these pregnancies will also have maternal smoking as an accompanying comorbidity, management pathways for this population are urgently needed. The safety of abrupt discontinuation of smoking and alcohol use in pregnancies with high levels of long-term use is as yet unknown. Development of evidence-based strategies for management of pregnancies complicated by substance abuse is a compelling research issue for perinatologists who are likely to be an important component of the medical care team for these women and their fetuses. Similar evidence-based care pathways need to be developed for infants with third trimester PAE exposure managed in the NICU. Research to determine if PAE is under-identified in NICU populations should be a priority given the prevalence of exposure, continued alcohol use throughout pregnancy and the increased risk of stillbirth, prematurity, growth impairment and birth defects. Identification of PAE and intervention can prevent exposure in all subsequent pregnancies and as a result should be a routine consideration for perinatologists who are likely to be among the professionals who encounter this problem most frequently.

Further research to improve understanding of the relationship between gestational age and the fetal or newborn AER would be useful. There is limited data regarding differences in AER for term and preterm newborns or by gender. These differences may have

important clinical applications. Additional research on correlation of maternal, fetal and newborn BAC and metabolic rates is needed. PAE results in three generations of exposure (mother, fetus and oocytes). Generational alcohol use during pregnancy, which is common, results in three developmental epochs of PAE. The developmental and epigenetic consequences of multi-generational exposure to ethanol are poorly understood. Future studies should also consider the role of epigenetic changes from PAE and the functional impact of exposure on placental and umbilical cord physiology, effects on metabolic pathways for alcohol and importantly maternal, fetal and newborn AER.

PAE provides a compelling opportunity for important research by clinicians within the context of appropriate clinical care. Improving our understanding of PAE and the adverse consequences from exposure provides an important opportunity for prevention, improved clinical management and mortality reduction for the mother, the fetus, the newborn and the siblings.

Summary

Understanding the mechanisms and rates of neonatal elimination will help clinicians determine how long a neonate should be monitored after alcohol exposure and if a clinical intervention is necessary. Fetal AER is severely diminished because of reduced metabolic activity and recirculating pathways of ethanol excretions. Although this paper presents mean values it is important to appreciate the impressive variation in AER of pregnant women and neonates (Table 2). The summary data demonstrate that the neonate's ability to metabolize alcohol compared with their mother is reduced by 16.5%.

Strategies for improved detection of PAE and ongoing patient education about alcohol use should be routinely implemented by perinatologists. The surgeon general's warning about alcohol use during pregnancy notes that alcohol-related birth defects are completely preventable: the cognitive deficits and behavioral problems resulting from PAE are lifelong and that no amount of alcohol consumption during pregnancy can be considered safe. Pregnant women should not drink and if they are drinking they should stop. Every pregnant woman should be screened for alcohol use and offered advice and ongoing support to quit if they are drinking. The complete warning is available at http://www.surgeongeneral.gov/news/2005/02/sg02222005.html.

Conflict of interest

The authors declare no conflict of interest.

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References

1 Floyd RL, Sidhu JS. Monitoring prenatal alcohol exposure. *Am J Med Genet C Semin Med Genet* 2004; **127**(1): 3–9.
2 Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998; **30**(1): 24–29, 46.
3 May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M *et al*. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Dev Disabil Res Rev* 2009; **15**(3): 176–192.
4 Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P *et al*. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology* 1997; **56**(5): 317–326.
5 Abel EL. *Fetal Alcohol Abuse Syndrome*. Plenum Press: New York, 1998.
6 Burd LJ, Roberts D, Olson M, Odendaal H. Ethanol and the placenta: a review. *J Matern Fetal Neonatal Med* 2007; **20**(5): 361–375.
7 de la Monte SM, Wands JR. Role of central nervous system insulin resistance in fetal alcohol spectrum disorders. *J Popul Ther Clin Pharmacol* 2010; **17**(3): e390–e404.
8 Hannigan JH, Armant DR. Alcohol in pregnancy and neonatal outcome. *Semin Neonatol* 2000; **5**(3): 243–254.
9 Cornman-Homonoff J, Kuehn D, Aros S, Carter TC, Conley MR, Troendle J *et al*. Heavy prenatal alcohol exposure and risk of stillbirth and preterm delivery. *J Matern Fetal Neonatal Med*; e-pub ahead of print 5 July 2011.
10 Waltman R, Iniquez ES. Placental transfer of ethanol and its elimination at term. *Obstet Gynecol* 1972; **40**(2): 180–185.
11 Jung AL, Roan Y, Temple AR. Neonatal death associated with acute transplacental ethanol intoxication. *Am J Dis Child* 1980; **134**(4): 419–420.
12 Pizon AF, Becker CE, Bikin D. The clinical significance of variations in ethanol toxicokinetics. *J Med Toxicol* 2007; **3**(2): 63–72.
13 Gemma S, Vichi S, Testai E. Metabolic and genetic factors contributing to alcohol induced effects and fetal alcohol syndrome. *Neurosci Biobehav Rev* 2007; **31**(2): 221–229.
14 Khaole NCO, Ramchandani V, Viljoen D, Li T. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol Alcohol* 2004; **39**(6): 503–508.
15 Zakhari S. Overview: how is alcohol metabolized by the body? *Alcohol Res Health* 2006; **29**(4): 245–254.
16 Rasheed A, Hines RN, McCarver May DG. Variation in induction of human placental CYP2E1: possible role in susceptibility to fetal alcohol syndrome? *Toxicol Appl Pharmacol* 1997; **144**(2): 396–400.
17 Dossevi L, Marfaing-Jallat P, Campfield LA, Le Magnen J. Blood removal and renal elimination of a constant dose of ethanol as a function of volumes and concentrations of solutions administered to rats. *Pharmacol Biochem Behav* 1983; **18**(3): 333–339.
18 Idanpaan-Heikkila J, Jouppila P, Akerblom HK, Isoaho R, Kauppila E, Koivisto M. Elimination and metabolic effects of ethanol in mother, fetus, and newborn infant. *Am J Obstet Gynecol* 1972; **112**: 387–393.
19 Jelski W, Szmitkowski M. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases. *Clin Chim Acta* 2008; **395**(1–2): 1–5.
20 Karl PI, Gordon BH, Lieber CS, Fisher SE. Acetaldehyde production and transfer by the perfused human placental cotyledon. *Science* 1988; **242**(4876): 273–275.
21 Bearer CF, Santiago LM, O'riordan MA, Buck K, Lee SC, Singer LT. Fatty Acid ethyl esters: quantitative biomarkers for maternal alcohol consumption. *J Pediatr* 2005; **146**(6): 824–830.
22 Lieber CS, DeCarli LM. Hepatic microsomal ethanol-oxidizing system. *In vitro* characteristics and adaptive properties *in vivo*. *J Biol Chem* 1970; **245**(10): 2505–2512.
23 Pikkarainen PH. Metabolism of ethanol and acetaldehyde in perfused human fetal liver. *Life Sci II* 1971; **10**(23): 1359–1364.

24 Hakkola J, Pelkonen O, Pasanen M, Raunio H. Xenobiotic-metabolizing cytochrome P450 enzymes in the human feto-placental unit: role in intrauterine toxicity. *Crit Rev Toxicol* 1998; **28**(1): 35–72.

25 Pelkonen O. Biotransformation of xenobiotics in the fetus. *Pharmacol Ther* 1980; **10**(2): 261–281.

26 Carpenter SP, Lasker JM, Raucy JL. Expression, induction, and catalytic activity of the ethanol-inducible cytochrome P450 (CYP2E1) in human fetal liver and hepatocytes. *Mol Pharmacol* 1996; **49**(2): 260–268.

27 Gilbert WM. Amniotic fluid dynamics. *NeoReviews* 2006; **7**(6): 292–295.

28 Brien JF, Loomis CW, Tranmer J, McGrath M. Disposition of ethanol in human maternal venous blood and amniotic fluid. *Am J Obstet Gynecol* 1983; **146**(2): 181–186.

29 Gow PJ, Ghabrial H, Smallwood RA, Morgan DJ, Ching MS. Neonatal hepatic drug elimination. *Pharmacol Toxicol* 2001; **88**(1): 3–15.

30 Aperia A, Broberger O, Broberger U, Herin P, Zetterstrom R. Glomerular tubular balance in preterm and fullterm infants. *Acta Paediatr Scand Suppl* 1983; **305**: 70–76.

31 Aperia A, Broberger O, Herin P, Thodenius K, Zetterstrom R. Postnatal control of water and electrolyte homeostasis in pre-term and full-term infants. *Acta Paediatr Scand Suppl* 1983; **305**: 61–65.

32 Odendaal HJ, Steyn DW, Elliott A, Burd LJ. Combined effects of cigarette smoking and alcohol consumption on perinatal outcome. *Gynecol Obstet Invest* 2009; **67**(1): 1–8.

33 Altura BM, Carella A, Chatterjee M, Halevy S, Tejani N. Alcohol produces spasms of human umbilical blood vessels: relationship to fetal alcohol syndrome (FAS). *Eur J Pharmacol* 1982; **86**(2): 311–312.

34 Seppala M, Raiha NC, Tamminen V. Ethanol elimination in a mother and her premature twins. *Lancet* 1971; **1**(7710): 1188–1189.

35 Cook LN, Shott RJ, Andrews BF. Acute transplacental ethanol intoxication. *Am J Dis Child* 1975; **129**(9): 1075–1076.

36 Wagner L, Wagner G, Guerrero J. Effect of alcohol on premature newborn infants. *Am J Obstet Gynecol* 1970; **108**(2): 308–315.

37 Gartner U, Ryden G. The elimination of alcohol in the premature infant. *Acta Paediatr Scand* 1972; **61**(6): 720–721.

38 Beattie JO. Transplacental alcohol intoxication. *Alcohol Alcohol* 1986; **21**(2): 163–166.

39 Fuchs F, Fuchs AR, Poblete VF, Risk A. Effect of alcohol on threatened premature labor. *Am J Obstet Gynecol* 1967; **99**(5): 627–637.

40 Puschel K, Seifert H. Effects of alcohol in the embryo, fetus, and newborn infant (author's transl). *Z Rechtsmed* 1979; **83**(1): 69–76.