

## CLINICAL REVIEW

## Preventing Alcohol-exposed Pregnancies

Mark B. Mengel, MD, MPH, H. Russell Searight, PhD, and Keely Cook, MPAS, PA-C

**Fetal alcohol exposure affects approximately 1% to 3% of live births in the United States. Family physicians are in a unique position to reduce the incidence of alcohol-exposed pregnancy. Fetal alcohol exposure can be minimized through 2 general approaches: reducing alcohol consumption or increasing effective contraception among childbearing-aged women who engage in “at-risk” drinking and encouraging pregnant women to abstain from alcohol. Although no safe level of alcohol consumption during pregnancy is established, women who binge drink are more likely to deliver infants with physical and cognitive-developmental anomalies. Screening tools, such as quantity/frequency questions, the TWEAK and the T-ACE, developed specifically for prenatal care, are more useful with women than the CAGE and Michigan Alcohol Screening Test (MAST). Screening alone seems to reduce alcohol use among pregnant women. Brief interventions, including education about alcohol’s effects on the developing fetus, are effective among women not responding to screening. Unfortunately, many barriers exist to effective implementation of alcohol-exposed pregnancy (AEP) prevention in the clinical setting. Designing effective office base systems so the entire burden of implementing AEP prevention activities does fall solely on the family physician is critical. (J Am Board Fam Med 2006;19:494–505.)**

Effects of alcohol on the developing fetus are multifocal, incurable, pernicious, and extremely costly; however, these effects are eminently preventable.<sup>1–3</sup> Despite the federal government warning that drinking alcohol during pregnancy is unsafe,<sup>4</sup> and the fact that a safe threshold for alcohol consumption during pregnancy has not been demonstrated to exist either in human or animal studies,<sup>5–8</sup> a substantial proportion of women self-report that they continue to drink during pregnancy (10.1% in 2002, with 1.9% engaged in heavy drinking and 1.9% engaged in binge drink-

ing).<sup>9</sup> Due to the continued high prevalence of drinking alcohol during pregnancy, the US Department of Health and Human Services has established a Healthy People 2010 goal to increase the number of pregnant women who report abstinence from alcohol use during the past month from a baseline rate in 1996 to 1997 of 86% to a 2010 target of 94%.<sup>10</sup> In 2004, the US Preventive Services Task Forces recommended screening and counseling intervention in primary care settings to reduce alcohol misuse in adults, including pregnant women.<sup>11</sup>

Given the emphasis on prevention of adverse alcohol effects in the fetus through abstinence or drinking reduction in the mother, the term alcohol-exposed pregnancy (AEP) has been coined to help clinicians judge exposure status. AEP is defined as any pregnancy during which a woman drank any amount of alcohol at any time during her pregnancy. All fertile, sexually active, childbearing-aged women are at risk for an AEP if they drink alcohol, are sexually active, and do not use contraception effectively. Preventing an AEP can be accomplished through 2 mechanisms: 1) engaging in abstinence from alcohol use before and during pregnancy, or 2) preventing pregnancy entirely by engaging in effective methods of contraception or abstaining from sexual activity.

This article was externally peer-reviewed.

Submitted 19 October 2005; revised 17 March 2006; accepted 20 March 2006.

From the Department of Community and Family Medicine (MBM), St. Louis University; Behavioral Scientist, Forest Park Family Medicine Residency Training Program (HRS), St. Louis; Physician Assistant Education, Doisy College of Health Sciences (KC), St. Louis University, MO.

**Funding:** This publication was made possible through a cooperative agreement between the Association of Teachers of Preventive Medicine (ATPM) and the Centers for Disease Control and Prevention (CDC), award number U50/CCU 300860 TS-0799; its contents are the responsibility of the authors and do not necessarily reflect the official views of the ATPM or the CDC.

**Conflict of interest:** none declared.

**Corresponding author:** Mark B. Mengel, MD, Department of Community and Family Medicine, St. Louis University School of Medicine, 1402 S. Grand Blvd., St. Louis, MO 63104 (E-mail: [mengelmb@slu.edu](mailto:mengelmb@slu.edu)).

Family physicians can play a significant role in preventing AEP. Family physicians provide a significant portion of the primary care to childbearing-aged women in this country, and many family physicians continue to care for pregnant women.<sup>12,13</sup> Prevention is recognized as one of the core tenets of family medicine,<sup>14</sup> and family medicine physicians are generally among the best trained primary care physicians in dealing with issues of substance abuse and mental health.<sup>15</sup> In surveys, many family physicians believe that dealing with substance use and abuse issues is within their purview as primary care physicians.<sup>16,17</sup> By working to prevent AEP, family physicians can play a significant role in preventing the adverse effects of alcohol exposure, on the developing fetus.

### ***Potential Outcomes of Alcohol Use During Pregnancy***

Alcohol exposure during pregnancy has been shown to result in a spectrum of birth defects that can negatively affect a child's growth, cognition, physical appearance, and behavior over the lifespan.<sup>1,2,18,19</sup> This spectrum of disorders is referred to as fetal alcohol spectrum disorders (FASD). FASD is not intended to be used as a clinical diagnosis, but rather as a descriptor to include the many adverse effects that alcohol can have on the developing fetus. Fetal alcohol syndrome (FAS) is the most serious disorder within this spectrum.<sup>1,2,18</sup> Individuals affected with FAS have severe, permanent growth retardation, neurobehavioral abnormalities, and specific facial abnormalities. FAS is the leading cause of preventable birth defects and mental retardation in the United States.<sup>1</sup>

Unfortunately children with FAS represent only the tip of the iceberg of affected children, as numerous children exposed to alcohol in utero have significant physical or neurodevelopmental abnormalities without all the features of FAS.<sup>20</sup> Alcohol-related neurobehavioral disorder (ARND) refers to a constellation of neurobehavioral and central nervous system effects occurring in the absence of the characteristic facial and growth abnormalities associated with FAS. These abnormalities include: head circumference  $\leq 10\%$ , learning disabilities, poor impulse control, seizures, deficits in higher level receptive and expressive language, and problems with mathematical skills, memory, attention, and judgment. Individuals that exhibit the typical FAS facies along with specific structural anomalies that

are known to be associated with alcohol exposure such as low set ears, micrognathia, epicanthal folds, low nasal bridge, short upturned nose, strabismus, clinodactyly, "hockey stick" palmar crease, radioulnar synostosis, renal anomalies, and cardiac defects, but have normal growth and development, are classified as having alcohol-related birth defects (ARBD).

The prevalence of ARND and ARBD is estimated to be at least 4 times more common than FAS.<sup>1,21-23</sup> Combining prevalence rates for FAS, ARND, and ARBD, 1% to 3% of all children born in the United States are affected by alcohol. This combined prevalence of FAS, ARND, and ARBD in the United States is probably underestimated because primary care providers and others who care for children do not routinely screen for FASD.<sup>24</sup>

### ***Alcohol Exposure Issues during Pregnancy***

Alcohol freely crosses the placenta and in most cases the blood alcohol level of the fetus is consistent with the blood alcohol level of the mother.<sup>1,25</sup> Although all organ systems seem to be sensitive to alcohol's effects, the brain is particularly vulnerable.<sup>26</sup> Alcohol's detrimental effects on the brain have been documented since the first report of FAS in the United States.<sup>1,4,17</sup> Microcephaly; migration anomalies; agenesis or thinning of the corpus callosum and anterior commissures; cerebellar, brainstem, and basal ganglia anomalies; and neuroglial heterotropias have all been demonstrated.<sup>26-28</sup> Animal studies demonstrate that even low dose alcohol affects numerous aspects of brain structure and function, including neurogenesis, cell proliferation, and migration of cells, including connectivity, synaptosis, maturation, and apoptosis.<sup>27,28</sup> On MRI studies, persons with FAS exhibit increased gray matter density, altered gray matter in portions of the temporal lobe, asymmetry, displacement, and reduction in the size of the corpus callosum, reduced brain growth in portions of the frontal lobe, and narrowing and reduction in the size of the temporoparietal regions.<sup>26</sup> These regionally specific abnormalities in brain morphology suggest a causal relationship between the brain abnormalities consistently noted and the development of neurocognitive and behavioral effects typically seen in those prenatally exposed to alcohol.<sup>26,29</sup> In addition, it was found that with higher levels of prenatal alcohol exposure, most morphologic findings were more pronounced in those individuals who exhib-

ited FAS rather than those exhibiting the less severe phenotypes, ARND and ARBD.<sup>29,30</sup>

### ***Prevalence of Drinking in Childbearing-aged Women***

The Centers for Disease Control (CDC) monitors the prevalence of alcohol use among US women of childbearing age (18 to 44 years of age). In 2002, 54.9% of childbearing-aged women admitted to drinking.<sup>9</sup> Unplanned pregnancies may occur when these women are drinking and do not use effective birth control.<sup>31</sup> Up to 50% of women who become pregnant will not realize that they are pregnant until after their 6th week of pregnancy, exposing their fetus to alcohol at a particularly vulnerable time.<sup>32</sup> This fact is especially important because 1 in 8 women of childbearing age reports binge drinking in the past month.<sup>9</sup> Binge drinking seems to be more harmful to the developing fetus than low-level daily drinking.<sup>1,33</sup> It is thus imperative to take a preconceptual approach to advising women about alcohol intake. Any childbearing-aged women who are sexually active and not using effective methods of birth control should be advised to abstain from alcohol intake. In addition, when women drink, they are more likely to participate in risky behavior including having multiple partners and engaging in unprotected intercourse, increasing the likelihood of an AEP.<sup>34</sup>

### ***Risk Factors for an Alcohol-Exposed Pregnancy***

Many studies have identified factors that increase the risk of having an AEP, including advanced age, low socioeconomic status, and having a previous child with FAS (Table 1). Identification of these women with risk factors should cause the family physician to have a higher index of suspicion for a potential AEP.

### ***Screening for Prenatal Alcohol Use***

Because some pregnant women continue to drink alcohol despite beverage warning labels, prenatal care should include repeated assessment of alcohol intake. Given the link between unprotected sex, unplanned pregnancy, and alcohol consumption, routine health maintenance visits for all women of childbearing age should address safe sex, alcohol use, and contraception.<sup>35–37</sup>

Although the Institute of Medicine and US Preventive Services Task Force advocates routine alcohol screening for pregnant women, recent esti-

**Table 1. Risk Factors for an Alcohol-exposed Pregnancy**

	References
Age: >30	89, 103
Caucasian	103
Hx binge drinking or long history of drinking	91–93
College educated	103
Low or high SES	94, 97
Special Education populations	90
Poor Native Americans	90
Hx of physical/sexual abuse ever	51
Hx of physical abuse in past year	103, 105
Heavy drinking by male partner or any family member	95, 97, 98
Loss of children to foster/adoptive care	94, 95, 99
Poly-drug use/cigarette smoking	92, 93, 96, 104
Previous child with FAS	95
Major depressive disorder	51, 100, 104
Post traumatic stress disorder	51
Unmarried	89, 98
Early age of drinking onset	101, 102

Hx, history.

mates suggest that only approximately one third of pregnant women are assessed for alcohol use during routine prenatal care.<sup>11,38</sup> When screening does occur, it is frequently confined to the initial prenatal visit instead of occurring at every prenatal visit. Even women who delay alcohol abstinence until the second trimester reduce the likelihood of an adverse birth outcome.<sup>39</sup>

Although physicians often order liver function tests, such as gamma glutamyltransferase (GGT) and aspartate aminotransferase (ALT), to obtain objective evidence of alcohol use disorders, they are less sensitive and specific than other assessment tools for identifying women at risk.<sup>40–42</sup>

### ***Screening Tools***

In assessing alcohol use in pregnant women, questionnaires, such as those listed in Table 2, may be particularly useful. The quantity/frequency questions developed by the National Institute on Alcohol Abuse provide information about current drinking patterns and may alert physicians to recent heavy or binge drinking.<sup>43</sup> If clinicians detect heavy or binge drinking (>7 drinks/week or more than 3 drinks on any one occasion in females, respectively), follow-up questions about problems associated with alcohol use should be undertaken to

**Table 2. Screening Tools for Alcohol Use during Pregnancy**

	Content	Time Required	Scoring and Cut-Off Score	Sensitivity	Specificity
Quantity/Frequency Questions (3)	Days per week of drinking Average number of drinks per day Maximum number of drinks consumed in 1 day during the past month	2 minutes	>7 drinks per week or >3 drinks per day	N/A	N/A
TWEAK <sup>47</sup>	<u>Tolerance</u> : (a) How many drinks does it take before you feel high (the first effects of alcohol)? or (b) How many drinks can you hold? (How many drinks does it take before the alcohol makes you fall asleep or pass out? If you never pass out, what is the largest number of drinks you have?) <u>Worried</u> : Have your friends or relatives worried about your drinking in the past year? <u>Eye opener</u> : Do you sometimes take a drink in the morning when you first get up? <u>Amnesia</u> : Are there times when you drink and afterwards can't remember what you said or did? <u>K/Cut Down</u> : Do you sometimes feel the need to cut down on your drinking?	3 to 5 minutes	Tolerance: (a) 3 drinks or more or (b) 5 drinks or more + 2 points Positive response to other questions = 1 point each Cut-off = 2 points	0.79–0.91	0.77–0.83
T-ACE <sup>48</sup>	<u>Tolerance</u> : How many drinks does it take to make you feel high? <u>Annoyed</u> : Have people ever annoyed you by criticizing your drinking? <u>Cut Down</u> : Have you ever felt that you needed to cut down on your drinking? <u>Eye opener</u> : Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hang over?	2 to 3 minutes	Tolerance: 2 points if requires more than 2 drinks Other questions: 1 point each Cut off: 2 points	0.70–0.89	0.79–0.85

determine whether the patient meets DSM-IV criteria for alcohol dependence or abuse. Although quantity/frequency questions are easy to include in the clinical interview, this straightforward approach has limitations. On learning of their pregnancy, many women will temporarily reduce alcohol consumption. Information about prenatal drinking before pregnancy confirmation is likely to be more predictive of alcohol use over the entire prenatal period.<sup>44</sup> Pregnant drinkers are likely to underreport their actual alcohol consumption with up to 40% of pregnant women underreporting their actual alcohol use. Women reporting consumption of as few as 1.3 drinks/week are, in reality, probably consuming greater quantities, placing them at risk for ARBD.<sup>45,46</sup>

Unfortunately, the CAGE questions and the Michigan Alcohol Screening Test (MAST) have

poor specificity in prenatal populations.<sup>43,44</sup> Both methods were developed primarily in males and emphasize social consequences of heavy, long-term alcohol use. In addition to inquiring about recent quantity and frequency of alcohol use, 2 screening measures developed for pregnant women, the T-ACE and the TWEAK, have been found to be particularly sensitive and specific (see Table 2).

The TWEAK and T-ACE are often seen as superior to direct inquiry about alcohol use because these instruments focus on indirect effects of drinking and may reduce patients' defensiveness.<sup>8</sup> Administered as part of the clinical interview, the TWEAK includes 3 questions adapted from the CAGE and MAST found to identify obstetric patients using alcohol. The TWEAK adds questions about tolerance to detect at-risk drinking specifically among pregnant women. Because tolerance to



alcohol may develop fairly rapidly, this addition may improve detection of pregnant drinkers.<sup>47</sup>

The T-ACE was developed specifically for obstetric-gynecologic settings.<sup>48</sup> The scale features items from the CAGE along with a tolerance question. Because most patients do not know socially desirable responses to the tolerance question, this dimension, given double weight in the T-ACE, may be particularly useful. Two slightly different questions have been used to assess alcohol tolerance: "How many drinks does it take to get you high?" and "How many drinks can you hold?" The "hold" question was found to be more sensitive but less specific than the "high" question. Because these measures are for initial screening, the "hold" version is preferred.<sup>48</sup> By asking about alcohol problems indirectly, the tendency to deny or under-report alcohol use by pregnant drinkers may be circumvented.

The Alcohol Use Disorder Identification Test (AUDIT) is a 10-item tool designed to detect early stages of problem drinking.<sup>49</sup> In comparison to other measures that mix items dealing with past and present drinking, the AUDIT focuses on drinking patterns during the past year. An advantage of the AUDIT, in addition to its broader coverage, is that patients complete the scale on their own, and the physician can use the completed form to guide follow-up questions.

### ***Clinical Issues with Screening Measures***

Because of social desirability, some pregnant women, particularly heavy drinkers, may be more likely to reliably report their actual alcohol use in a computerized or "pencil and paper" task rather than through a face-to-face interview.<sup>50</sup>

Because of concerns about patients' minimization of alcohol use on quantity/frequency questions, some physicians also interview collateral informants such as a spouse. Although nearly all research to date has focused on male drinkers and female collateral informants, available studies suggest that these informants also under-report the patient's alcohol consumption.<sup>51</sup>

These screening tools do not replace careful clinical interviewing. A positive response to these scales is not diagnostically specific and only indicates that a woman is at-risk for alcohol problems. Last, responses to these measures may be influenced by ethnicity. For example, White women, compared with African-American women, are

much more likely to report morning drinking. In addition, White women report a much greater tolerance for alcohol and typically indicate that they can "hold" a larger number of drinks, requiring more drinks to feel "high."<sup>52</sup>

### ***Overview of Brief Intervention in Primary Care***

Brief physician intervention successfully reduces alcohol use among primary care patients among heavy and binge drinkers.<sup>53,54</sup> The content of brief intervention typically includes advice, feedback, goal setting, and additional contacts as necessary. Whitlock et al labels these elements as the 5 "A"s: assess, advise, agree, assist, and arrange.<sup>54</sup>

Brief interventions for alcohol abuse have been classified into 3 types: 1) very brief (one 5-minute session); 2) brief (one session up to 15 minutes duration); 3) multicontact brief sessions (an initial session of up to 15 minutes followed by several time-limited contacts, either by phone or in the clinic).<sup>53</sup> These brief treatments are often equally effective as longer-term therapy.<sup>54</sup> When compared with "usual" care, multiple contact brief interventions lead to 10% to 19% of patients changing to recommended or safe drinking levels. The overall absolute risk reduction associated with brief treatments is 10.5%.<sup>53</sup> Multicontact interventions are associated with greater risk reduction than single contact treatment. Because pregnant women are scheduled for multiple, closely spaced office visits, brief multicontact alcohol counseling can be readily incorporated into prenatal care. In addition, there are suggestions that these brief treatments may be more effective with women than men. Fleming et al found that 1 year after a brief intervention, women had reduced their weekly alcohol consumption by 47% compared with 37% for men.<sup>53</sup> Binge drinking was also reduced to a greater extent among women compared with men receiving a brief intervention.

### ***Brief Intervention among Pregnant Women***

Assessment alone seems to reduce alcohol consumption. Fleming et al's control group, which was asked about their alcohol use at 4 different time points throughout the year, reduced consumption by 20%.<sup>53</sup> Among pregnant women, formal screening with tools such as the T-ACE alone, reduces prenatal consumption.<sup>48</sup> Physician advice or written educational information improves patients' knowledge of the risks of drinking during pregnan-

cy.<sup>55–57</sup> Providing information alone may reduce the risk of an alcohol-exposed pregnancy through reduced consumption or increased use of effective contraception. Information's beneficial effects on reducing risk may persist for up to 9 months.<sup>57</sup> It is likely that when coupled with education and advice, assessment may be adequate to prevent further drinking during pregnancy among most patients.<sup>46</sup>

After completing an initial screening and providing general information about the risks for drinking during pregnancy, at-risk patients should receive individualized feedback. The physician explains how the patient's drinking compares with other pregnant women or those of childbearing age. If possible, the physician then describes risks specific to the patient. Next, the physician and patient establish drinking goals, complete cessation of drinking during pregnancy is recommended. After establishing drinking goals; the patient is encouraged to "brainstorm" environmental triggers (eg, socializing with friends who are drinking) and develop behavioral alternatives for these at-risk periods. Counseling is augmented by written patient educational material such as self-paced workbooks.<sup>53</sup> Keeping a drinking diary, recording the number of alcoholic drinks, and drinking circumstances each day, is often recommended.

Motivational interviewing (MI), a counseling model developed for health risk behavior, has also demonstrated success in reducing prenatal alcohol use—particularly among heavier drinkers.<sup>58,59</sup> MI, combining education and reflective questions, in a supportive context, has also been effective in increasing contraceptive use in female drinkers who could become pregnant.<sup>59</sup>

### ***Brief Intervention: Evidence for Effectiveness in Reducing AEP***

Although brief alcohol intervention has a reasonable evidence basis, there are only limited investigations involving pregnant patients. The Trial for Early Alcohol Treatment (Project TrEAT) involved four 2- to 15-minute office counseling sessions and a self-paced workbook directed toward women of childbearing age.<sup>60</sup> The intervention led to a 48% reduction in average alcohol intake with 25% fewer women engaging in binge drinking. Although Project TrEAT's benefits were still pronounced at 48 months, the largest decline in alcohol use occurred within 6 months after the intervention.<sup>60</sup>

A more intensive intervention, Project CHOICES, targeted women at-risk for an alcohol-exposed pregnancy.<sup>61</sup> Risk status included a week of low level daily drinking and/or binge episode in the past 3 months, recent sexual activity, and no or ineffective contraception. Women participated in 4 motivational interviewing sessions and received individualized information about their risk of an AEP. Risk reduction included decreased alcohol use (18%), effective contraception (34%), or both (48%) with 68% of the participants reducing their risk of an AEP. In a further analysis comparing only education about drinking during pregnancy with education plus counseling, 54.8% receiving education alone reduced their risk of an AEP with a 68.9% risk reduction for education with added counseling.<sup>58</sup>

Chang et al provided brief treatment to women in the 16th week of pregnancy who screened positive on the T-ACE and examined motivational factors associated with risk reduction.<sup>48</sup> The intervention included a review of the patient's general health status, and lifestyle changes along with education about alcohol abstinence, goal-setting, brainstorming, and an alcohol prevention manual for individual use.<sup>62</sup> Women articulating specific concerns about preventing FAS rather than general statements about their baby's health, were more likely to reduce alcohol consumption. Women who had been drinking in the previous 6 months, but not in the 90 days before the intervention, were also more successful in reducing alcohol consumption.<sup>38,62</sup> A detailed assessment, alone, was found to be as effective as an assessment followed by brief intervention in reducing alcohol consumption during pregnancy. However, brief intervention was more effective with the subgroup of heavier drinkers. This benefit, for heavier drinkers, was further augmented when the patient's partner was involved in brief treatment.<sup>63</sup>

Women drinking at light to moderate levels seem to benefit most from brief treatment.<sup>64</sup> Motivational factors, including a patient's belief that they can successfully stop drinking, is strongly associated with successful outcomes. For highly motivated patients, self-help manuals alone have been found to produce significant reductions in alcohol use.<sup>65</sup> Whereas research is limited, brief physician counseling, which may include concerned family members, can increase the likelihood that a patient will enter an intensive substance abuse treatment

**Table 3. Barriers to Providing Screening, Assessment, Brief Intervention, and Referral Services to Prevent Alcohol-exposed Pregnancies**

- Non-therapeutic attitude among family medicine physicians
  - A public health concern, not a clinical problem
  - A concern that questioning about alcohol use will lead to patient resistance, discomfort, and exiting from the practice
  - Other health problems are more urgent or important
  - Denial that drinking is a problem
  - Feeling that treatment isn't effective
- Inadequate knowledge and clinical skills
  - Limited training in medical school and residency
  - Feel ill-prepared to deal with the realities of screening and assessment
  - Lack of provider self-efficacy, feeling you can't make a difference
  - Provider reference material lacks information and consistent recommendation to abstain
- Lack of time
- Inadequate reimbursement
- System barriers
  - Lack of intervention tools
  - Lack of a system strategy or protocol
  - Lack of treatment and referral resources
  - Lack of office staff involvement
- Legal barriers

program,<sup>66,67</sup> although many clinicians would refer a patient who meets criteria for alcohol abuse or dependence to a substance abuse counselor immediately rather than performing a brief intervention first.

#### **Barriers to AEP Prevention in Clinical Practice**

Given the evidence that screening, assessment, education, and brief interventions directed at alcohol use can identify women with alcohol disorders, these practices should be a standard part of a family physician's clinical practice. However, evidence from surveys of family physicians and other health care professionals suggests many barriers to the routine integration of these practices into clinical practice (see Table 3).<sup>14–16,68–75</sup> Studies suggest that few family physicians provide all these services, and fewer patients report receiving them.<sup>75–78</sup>

Unfortunately, simple educational efforts, training and encouraging family physicians to include these services in their clinical practice, will probably not be enough to ensure integration of these skills into clinical practice. Studies that not only teach these skills, but do so from a systems perspec-

**Table 4. Common Myths Regarding Alcohol Use during Pregnancy**

1. Less than 1 drink per day in pregnancy is okay.
2. Drinking late in pregnancy is okay and makes labor easier.
3. Beer and wine are not alcohol, and thus are not a problem.
4. If I drank and have one child without FAS, I can drink and I won't have another child with FAS.
5. If FAS doesn't run in my family, my child won't get FAS.
6. FAS is curable if diagnosed early.

tive, suggest success might be achieved with this new approach.<sup>79–82</sup> Babor and colleagues trained 44 physicians and 41 clinical non-physicians in 10 practices across the country using a 3-hour training module aimed at assisting implementation of alcohol screening and brief intervention services in the primary care setting.<sup>82</sup> The proportion of at-risk drinkers, 3 months after the intervention, in which physicians screened for alcohol use and provided intervention was greater in physicians who received the training than those who did not (47% versus 22%). Actually helping physicians deal with systems barriers in their office and constructing an office support system that facilitated these activities was the key to the success of this educational intervention.

Several patient barriers to preventing AEP also exist, such as patient denial that a problem exists. Surveys have documented lack of knowledge among women, particularly in high-risk groups, regarding the effects of alcohol on the fetus and the importance of abstinence from alcohol during pregnancy.<sup>83–87</sup> Many women believe myths about alcohol use during pregnancy that produce the belief that they are not at risk for an AEP (see Table 4).

Besides accurate knowledge, changing drinking patterns or abstaining from alcohol when pregnant requires behavioral change. Behavioral change requires the patient's time, attention, motivation, and often a helpful, supportive context that facilitates the efforts of the patient to make that change. The patient may not be willing to undergo a behavioral change process due to the time and effort required, confronting resistance from an unsupportive context (such as family and friends who drink freely), or feeling that they will fail (lack of self-efficacy). Further complicating matters are the widespread pro-drinking messages childbearing-aged women receive from the media and the popular culture.<sup>87</sup>

To integrate preventing AEP within their office practice, family physicians can take several steps to

**Table 5. Organizing Your Office to Facilitate Preventing AEP**

Activity	Strategies
Screening	Include alcohol screening questions on initial patient questionnaires or instruct medical assistants to assess alcohol use while assessing vital signs during initial patient intake.
Assessment	Construct a questionnaire or checklist for the nurse to perform the assessment if screening is positive prior to the physician seeing the patient or construct a checklist that the physician can use if initial screening questions are positive while visiting with the patient in the examination room
Education (on alcohol and contraceptive practices)	The clinic nurse can provide alcohol-exposed pregnancy (AEP) prevention education during preconception counseling visits, contraceptive initiation visits, or pregnancy education visits. Posters and brochures on AEP can be placed in waiting rooms and examination rooms.
Brief interventions	Nurses can be trained to conduct brief interventions and follow-up visits can be conducted by telephone. Brief intervention materials can be kept in the examination rooms for physicians to use.

insure that the burden of carrying out AEP prevention activities does not solely fall on themselves. Table 5 describes strategies for organizing an office practice to facilitate AEP prevention, including using already existing office procedures, such as including quantity and frequency questions on an initial new patient office questionnaire, using office personnel to conduct further assessment and brief interventions, and conducting some of the follow-up visits for a brief intervention over the phone. Obviously, AEP prevention activities can also be integrated within existing alcohol screening, assessment, and intervention activities for all patients.

## Conclusion

Current evidence suggests that if family medicine physicians engage in routine screening, assessment, education, and intervention in women of childbearing age regarding their use of alcohol that the risk

of AEP will be decreased (Table 6). Alcohol is a toxin that can result in a range of abnormalities in children; perhaps, the most devastating of which are the neurobehavioral and central nervous system effects. Although profoundly disturbing in their on way, these initial neurobehavioral and cognitive affects result in secondary disabilities in the teenage years that often preclude these individuals from reaching independence as adults.<sup>88</sup> Because these FASD do not occur in the absence of prenatal alcohol exposure and because there is no known cure once they have occurred, preventing an AEP is the most logical intervention strategy for this problem at this time.

Integrating these intervention techniques within family medicine practice will not be easy. Current research suggests that the involvement of the staff and the design of effective office systems could take most of the burden of performing these activities off the family physician and might be the most

**Table 6. Strength of Evidence: Preventing Alcohol-exposed Pregnancies Summary Statement of Evidence**

	Grade
1. Fetal alcohol syndrome (FAS) occurs in 0.3 to 1.5/1000 live births in the United States	B
2. Fetal alcohol effects occur in at least 1/100 live births in the United States	B
3. Approximately one-half of all childbearing-aged women in the United States drink alcohol	C
4. Approximately 10% of all women drink alcohol while pregnant	C
5. Although binge drinking (more than 3 drinks on one occasion) demonstrates the strongest adverse effect on the developing fetus, there is no safe level of alcohol consumption during pregnancy	C
6. With prenatal patients, the T-ACE and TWEAK are more effective screening measures than the CAGE.	C
7. Screening for alcohol use in routine office visits will decrease patients' alcohol consumption.	B
8. Brief physician education and intervention about alcohol use in childbearing-aged women will reduce alcohol use, increase effective contraception or both.	B



effective way of integrating these practices within family practice.

Clearly further translational research is needed to determine the best ways to integrate these practices within the busy family medicine office setting. Practice-based research networks would be an ideal laboratory for carrying out this translational research. Such research should focus on the effectiveness of these practices in the family medicine office setting and determine their impact on reducing alcohol-exposed pregnancy risk and decreasing the prevalence of FASD.

## References

1. Stratton K, Howe C, Battaglia F, editors. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention and Treatment*. Washington (DC): National Academy Press; 1996.
2. Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. *JAMA* 2003;290:2996–9.
3. Wattendorf DJ, Muenke M. Fetal alcohol spectrum disorder. *Am Fam Physician* 2005;72:279–82.
4. Surgeon General's Advisory on Alcohol Use in Pregnancy. News Release. U.S. Department of Health and Human Services, February 21, 2005. Available from: [www.surgeongeneral.gov/pressreleases/sg02222005.html](http://www.surgeongeneral.gov/pressreleases/sg02222005.html) (accessed Aug 18, 2005).
5. Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birth-weight, and preterm delivery. *Ann Epidemiol* 1997;7:498–508.
6. Jacobson JL, Jacobson SW. Prenatal alcohol exposure and neurobehavioral development: where is the threshold? *Alcohol Clin Exp Res* 1994;18:30–6.
7. Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. *J Pediatr* 1999;134:298–303.
8. Sood B, Delaney-Black V, Covington C, et al. Parental alcohol exposure and childhood behavior at 6 to 7 years. I: Dose-response effect. *Pediatrics* 2001;108:E34.
9. Tsai J, Floyd RL. Alcohol consumption among women who are pregnant or who might become pregnant—United States 2002. *MMWR Morb Mortal Wkly Rep* 2004;53:1178–81.
10. U.S. Department of Health and Human Services. *Healthy People 2010*. 2nd Ed. Vol 2. Washington (DC): U.S. Government Printing Office, Nov 2000, p. 16–45.
11. U.S. Preventive Service Task Force. Screening for Alcohol Misuse, April 2004. Available from: [www.ahrq.gov/clinic/uspstf/uspstfdrin.htm](http://www.ahrq.gov/clinic/uspstf/uspstfdrin.htm) (accessed March 1, 2006).
12. 2005 Facts about Family Medicine, Table 27. Number of visits by sex and age of patient to all physicians and selected specialty, United States, 2003. Available from: [www.aafp.org/x782.xml](http://www.aafp.org/x782.xml) (accessed Aug 18, 2005).
13. Cohen D, Guirguis-Blake J, Jack B, et al. The case of the State of Maine: family physicians make a substantial contribution to maternity care *Am Fam Physician* 2003;68:425.
14. Fryor GE, Dovey SM, Green LA. The importance of primary care physicians as the usual source of health in the achievement of preventive goals. *Am Fam Physician* 2000;62:1968.
15. National Center on Addiction and Substance Abuse (CASA). *Missed opportunity: national survey of primary care physicians and patients on substance abuse*. New York: CASA; April 2000. p 5–17.
16. Anderson P. Managing alcohol problems in general practice. *Br Med J* 1985;29:1873–5.
17. Rush BP, Bass M, Stewart M, et al. Detection, prevention and management of patient's alcohol problems by Canadian family physicians. *Can Fam Physician* 1994;40:1557–66.
18. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973;2:999–1001.
19. Centers for Disease Control. National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect. *Fetal alcohol syndrome: guidelines for referral and diagnosis*. Atlanta (GA): U.S. Department of Health and Human Services; 2004.
20. Mattson SN, Riley EP, Gramling L, et al. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome lead to IQ deficits. *J Pediatr* 1997;131:718.
21. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. *Pediatrics* 2005;115:39–47.
22. May PA, Gossage JP, White-Country M, et al. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during and after pregnancy: the risk is relative. *Am J Med Genet* 2004;127C(Vol 1):10–20.
23. May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome. *Alcohol Res Health* 2001;2:159–67.
24. Graham JM Jr., Hanson JW, Darby BL, et al. Independent dysmorphology evaluations at birth and 4 years of age for children exposed to varying amounts of alcohol in utero. *Pediatrics* 1998;81:772.
25. Little BB, Vanbeveren TT. Placental transfer of selected substances of abuse. *Semin Perinatol* 1996;20:147–53.
26. Riley EP, McGee CL, Sowell ER. Teratogenic effects of alcohol: a decade of brain imaging. *Am J Med Genet* 2004;127C:35–41.
27. Mattson SN, Riley EP. Brain anomalies in fetal

- alcohol syndrome. In: Able EL, editor. Fetal alcohol syndrome: from mechanism to prevention. Boca Raton (FL): CRC Press; 1996. p. 51–68.
28. Clarren KS. Neuropathology in fetal alcohol syndrome. In West JR, editor. Alcohol and Brain Development. New York: Oxford University Press; 1986. p. 158–66.
29. Mattson SN, Fennam-Notestine C, Gamst A, et al. Fetal alcohol syndrome: a case report of neuropsychological, MRI and EEG assessment of two children. *Alcohol Clin Exp Res* 1992;16:1001–3.
30. Archibald SL, Fennema-Notestine C, Gamst AC, et al. Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Dev Med Child Neurol* 2001;43:148–54.
31. Project Choices Research Group. Alcohol-exposed pregnancy: characteristics associated with risk. *Am J Prev Med* 2002;23:166–73.
32. Floyd RL, Decoule P, Hungerford DW. Alcohol use prior to pregnancy recognition. *Am J Prev Med* 1999;17:101–107.
33. Maier SE, West JR. Drinking patterns and alcohol-related birth defects. *Alcohol Res Health* 2001;25:168–74.
34. Wechesler H, Davenport A, Dowdell G, Moeykens B, Castillo S. Health and behavior consequences of binge drinking in college: a national survey of students in 140 campuses. *JAMA* 1994;272:1672–7.
35. Bertrand J, Floyd RL, Weber MK, et al. National Task Force on FAS/FAE. Fetal alcohol syndrome: guidelines for referral and diagnosis. Atlanta (GA): Centers for Diseases Control and Prevention; 2004. p. 28.
36. Institute of Medicine. Broadening the base of treatment for alcohol problems. Washington (DC): National Academy Press; 1990.
37. Naimi TS, Lipscomb AL, Brewer RD, Gilbert BC. Binge drinking in the preconception period and the risk of unintended pregnancy: implications for women and their children. *Pediatrics* 2003;111:1136–41.
38. Chang G, Goetz MA, Wilkins-Haug L, Berman S. A brief intervention for prenatal alcohol use: an in-depth look. *J Substance Abuse Treatment* 2000;18:365–9.
39. Autti-Ramo L, Korkman M, Hilakivi-Clark L, Lehtonen M, Halmesmaki E, Granstrom ML. Mental development of 2 year old children exposed to alcohol in utero. *J Pediatr* 1992;120:740–48.
40. Allen J, Litten RZ, Fertig JB, Sillanaukee P. Carbohydrate-deficient transferrin, gamma-glutamyl-transferase, and macrocytic volume as biomarkers of alcohol problems in women. *Alcohol Clin Exp Res* 2000;24:492–6.
41. Substance Abuse and Mental Health Services Administration. A guide to substance abuse services for primary care clinicians. Treatment improvement protocol (TIP) series #24. Washington (DC): US Department of Health and Human Services Government Printing Office; 1997.
42. Bearer CF. Markers to detect drinking during pregnancy. *Alcohol Res Health* 2001;25:210–8.
43. National Institute on Alcohol Abuse and Alcoholism. The physician's guide to helping patients with alcohol problems. National Institutes of Health Publication No. 95-3769. Rockville (MD): Department of Health and Human Services; 1995.
44. Chang G. Alcohol-screening instruments for pregnant women. *Alcohol Res Health* 2001;25:204–9.
45. Ernhart CB, Morrow-Tlucak M, Sokol RJ, Martier S. Underreporting of alcohol use in pregnancy. *Alcohol Clin Exp Res* 1998;12:506–11.
46. Morrow-Tlucak M, Ernhart CB, Sokol RJ, Martier S, Ager J. Underreporting of alcohol use in pregnancy: relationship to alcohol problem history. *Alcohol Clin Exp Res* 1989;13:399–401.
47. Russel M. New assessment tools for risk drinking during pregnancy. *Alcohol Health Res World* 1994;18:55–61.
48. Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol* 1989;160:863–8.
49. Saunders JB, Aasland OG, Babor TF, DeLa Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction* 1993;88:791–804.
50. Thornberry J, Bhaskar B, Krukwitch CJ, et al. Audio computerized self-report interview use in prenatal clinics. *CIN: Computers, Informatics, Nursing* 2002;20:46–62.
51. Svikis DS, Reid-Guinness K. Screening and prevention of alcohol and drug use disorders in women. *Obstet Gynecol Clin N Am* 2003;30:447–68.
52. Russell M, Skinner JB. Early measures of maternal alcohol misuse as predictors of adverse pregnancy outcomes. *Alcohol Clin Exp Res* 1988;12:824–30.
53. Fleming MF, Barry KL, Manwell LB, Johnson K, London R. Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. *JAMA* 1997;277:1039–45.
54. Whitlock EP, Polen MR, Green C, Orleans CT, Klein J. Behavioral counseling interventions in primary care to reduce risky, harmful alcohol use by adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004;140:558–69.
55. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcohol Clin Exp Res* 1998;22:1300–11.
56. Chang G, Wilkins-Haug L, Berman S, Goetz MA,

- Behr H, Hiley A. Alcohol use: improving identification. *Obstet Gynecol* 1998;91:892–8.
57. Waterson EJ, Murray-Lyon IA. Preventing fetal alcohol effects: a trial of three methods of giving information in the antenatal clinic. *Health Educ Res* 1990;5:53–61.
58. Floyd L. Presentation at the National Task Force on FAS/FAE. June 15, 2005. Atlanta (GA): U.S. Public Health Service.
59. Handmaker NS, Wilbourne P. Motivational interventions in prenatal clinics. *Alcohol Res Health* 2001;25:219–29.
60. Manwell LG, Fleming MF, Mundt MP. Treatment of problem alcohol use in women of childbearing age: results of a brief intervention trial. *Alcohol Clin Exp Res* 2000;24:1519–24.
61. The Project Choices Intervention Research Group. Reducing the risk of alcohol-exposed pregnancies: a study of a motivational intervention in community settings. *Pediatrics* 2003;111:1131–5.
62. Chang G, Wilkins-Haug L, Berman S, Goetz M. A brief intervention for alcohol use in pregnancy: A randomized trial. *Addiction* 1999;94:1499–508.
63. Chang G, McNamara TK, Orav J, Kolby D, Lavigne A, Wilkins-Huang L. Brief intervention for prenatal alcohol use: a randomized trial. *Obstet Gynecol* 2005;105:991–8.
64. Hankin JR. Fetal alcohol syndrome prevention research. *Alcohol Res Health* 2002;26:58–65.
65. Spivak K, Sanchez-Craig M, Davila R. Assisting problem drinkers to change on their own: effect of specific and nonspecific advice. *Addiction* 1994;89:1135–42.
66. Chafetz ME, Blane HT, Abram HS, et al. Establishing treatment relations with alcoholics. *J Nerv Ment Dis* 1962;134:395–409.
67. Edwards ME, Steinglass P. Family therapy treatment outcomes for alcoholism. *J Marital Fam Ther* 1995;21:475–510.
68. Bradley K, Curry S, Koepsell T, et al. Primary and secondary prevention of alcohol problems: U.S. internist attitudes and practices. *J Gen Intern Med* 1995;10:67–72.
69. Brown RL. Evaluation of a continuing medical education program for primary care physicians on the management of alcoholism. *J Med Ed* 1988;63:482–4.
70. Fleming MF, Manwell LB, Kraus M, et al. Who teaches residents about the prevention and treatment of substance use disorders? A national survey. *J Fam Pract* 1999;48:726–9.
71. Haack M, Adger H, editors. Strategic plan for interdisciplinary faculty development: arming the nation's health professional workforce for a new approach to substance use disorders. *Substance Abuse* 2002;23(Suppl):1–345.
72. Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? *Am J Publ Health* 2003;93:635–41.
73. Aira M, Kauhanen J, Larivaara P, Rautio P. Factors influencing inquiry about patients' alcohol consumption by primary healthcare physicians: qualitative semi-structured interview study. *Fam Pract* 2003;20:270–5.
74. Rush BR, Powell LY, Crowe TG, et al. Early intervention for alcohol use: family physician's motivations and perceived barriers. *Can Med Assoc J* 1995;152:863–9.
75. Barry KL, Blow FC, Willenbring M, et al. Use of alcohol screening and brief interventions in primary care settings: implementation and barriers. *Substance Abuse* 2004;25:27–36.
76. Friedmann PD, McCullough D, Chin MH, et al. Screening and intervention for alcohol problems: a national survey of primary care physicians and psychiatrists. *J Gen Intern Med* 2000;15:84–91.
77. Arndt S, Schultz SK, Turrey C, et al. Screening for alcoholism in the primary care setting: are we talking to the right people? *J Fam Pract* 2002;51:41–6.
78. Weisner C, Matzger H. Missed opportunities in addressing drinking behavior in medical and mental health services. *Alcohol Clin Exp Res* 2003;27:1132–41.
79. Ockene J, Adams A, Hurley T, Wheeler E, Hebert J. Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers. *Arch Intern Med* 1999;159:2198–205.
80. Adams A, Ockene J, Wheeler E, Hurley T. Alcohol counseling: physicians will do it. *J Gen Intern Med* 1998;13:692–8.
81. Saitz R, Horton NJ, Sullivan LM, et al. Addressing alcohol problems in primary care: a clustered randomized, controlled trial of a system intervention. *Ann Intern Med* 2003;138:372–82.
82. Babor TF, Higgins-Biddle JC, Higgins PS, et al. Training medical providers to conduct alcohol screening and brief interventions. *Substance Abuse* 2004;25:17–26.
83. Testa M, Reifman A. Individual differences in perceived riskiness of drinking in pregnancy: antecedents and consequences. *J Stud Alcohol* 1996;57:360–7.
84. Kesmodel U, Schioler-Kesmodel P. Drinking during pregnancy: attitudes and knowledge among pregnant Danish women, 1998. *Alcohol Clin Exp Res* 2002;26:1553–60.
85. Cornelius MD, Lebow HA, Day NL. Attitudes and knowledge about drinking: relationships with drinking behavior among pregnant teenagers. *J Drug Educ* 1997;27:231–43.
86. Kaskutas LA. Understanding drinking during pregnancy among urban American Indians and African Americans: health messages, risk beliefs, and how we measure consumption. *Alcohol Clin Exp Res* 2000;24:1241–50.

87. The Center on Alcohol Marketing and Youth. Exposure of African-American youth to alcohol advertising. Washington (DC): Georgetown University; 2003. Available from: <http://camy.org/research/afam0603/>.
88. Streissguth AP, Barr HM, Kogan J, et al. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Atlanta (GA): CDC, 1996.
89. Sidhu JS, Floyd, RL. Alcohol use among women of childbearing age—United States 1991–1999. *MMWR Morb Mortal Wkly Rep* 2002;51:273–6.
90. Abel EL. An update on incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol* 1995;17:437–43.
91. Chang G, Behn H, Goetz MA, Hiley A, Bigby J. Women and alcohol abuse in primary care: identification and intervention. *Am J Addict* 1997;6:183–92.
92. Day NL, Cottreau CM, Richardson GA. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. *Clin Obstet Gynecol* 1993;36:232–45.
93. Godel JC, Pabst JF, Hodges PE, Johnson KE, Froese GJ, Joffres MR. Smoking and caffeine and alcohol intake during pregnancy in northern populations: effect of fetal growth. *Can Med Assoc J* 1992;147:181–8.
94. Habbick BF, Nanson JL, Snyder RE, Casey RE, Schulman AL. Foetal alcohol syndrome in Saskatchewan: unchanged incidence in a 20-year period. *Can J Public Health* 1996;87:204–7.
95. May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Soc Biol* 1983;30:374–87.
96. Serdula M, Williamson DF, Kendrick JS, Anda RF, Byers T. Trends in alcohol consumption by pregnant women: 1985–1988. *JAMA* 1991;265:876–9.
97. Sokel RJ, Ager J, Martier S, et al. Significant determinants of susceptibility to alcohol teratogenicity. *Ann N Y Acad Sci* 1986;477:87–102.
98. Wilsnack SC, Klassen AD, Shur BE, Wilsnack RW. Predicting onset and chronicity of women's problem drinking: a five-year longitudinal analysis. *Am J Public Health* 1991;81:305–18.
99. Streissguth AP, Clarren SK, Jones KL. Natural history of the fetal alcohol syndrome: a 10-year follow-up of eleven patients. *Lancet* 1985;2:85–91.
100. Abel EL. Fetal alcohol syndrome in families. *Neurotoxicol Teratol* 1998;10:85–91.
101. Smith IE, Coles CD. Multilevel intervention for prevention of fetal alcohol syndrome and effects of prenatal alcohol exposure. *Recent Dev Alcohol* 1991;9:165–80.
102. Smith IE, Lancaster JS, Moss-Wells S, Coles CD, Falek A. Identifying high risk pregnant drinkers: biological and behavioral correlates of continuous heavy drinking during pregnancy. *J Stud Alcohol* 1987;48:304–9.
103. Haynes G, Dunnagan T, Chistopher S. Determinants of alcohol use in pregnant women at risk for alcohol consumption. *Neurotoxicol Teratol* 2003;25:659–66.
104. Greenfield TK, Rehm J, Rogers JD. Effects of depression and social integration on the relationship between alcohol consumption and all-cause mortality. *Addiction* 2002;97:29–38.
105. Leonardson GR, Loudenburg R. Risk factors for alcohol use during pregnancy in a multistate area. *Neurotoxicol Teratol* 2003;25:651–8.