

# Fetal alcohol-spectrum disorders: identifying at-risk mothers

Annika C Montag

Department of Pediatrics, Division of Dysmorphology and Teratology, University of California San Diego, San Diego, CA, USA

**Abstract:** Fetal alcohol-spectrum disorders (FASDs) are a collection of physical and neuro-behavioral disabilities caused by prenatal exposure to alcohol. To prevent or mitigate the costly effects of FASD, we must identify mothers at risk for having a child with FASD, so that we may reach them with interventions. Identifying mothers at risk is beneficial at all time points, whether prior to pregnancy, during pregnancy, or following the birth of the child. In this review, three approaches to identifying mothers at risk are explored: using characteristics of the mother and her pregnancy, using laboratory biomarkers, and using self-report assessment of alcohol-consumption risk. At present, all approaches have serious limitations. Research is needed to improve the sensitivity and specificity of biomarkers and screening instruments, and to link them to outcomes as opposed to exposure. Universal self-report screening of all women of childbearing potential should ideally be incorporated into routine obstetric and gynecologic care, followed by brief interventions, including education and personalized feedback for all who consume alcohol, and referral to treatment as indicated. Effective biomarkers or combinations of biomarkers may be used during pregnancy and at birth to determine maternal and fetal alcohol exposure. The combination of self-report and biomarker screening may help identify a greater proportion of women at risk for having a child with FASD, allowing them to access information and treatment, and empowering them to make decisions that benefit their children.

**Keywords:** fetal alcohol-spectrum disorder (FASD), alcohol, pregnancy, screening, biomarkers, SBIRT

## Introduction

Fetal alcohol-spectrum disorders (FASDs) are a collection of diverse disorders all caused by prenatal alcohol exposure (PAE). FASD is the leading known cause of developmental disabilities, and represents a serious international public health problem. Over the past four decades, research has established specific patterns of physical effects and an array of neurobehavioral harms resulting from PAE.<sup>1-5</sup>

As our ability to diagnose FASD improves, and more active case-ascertainment research studies are performed, more realistic prevalence estimates from more populations are becoming available. While there are no reliable global estimates of FASD prevalence, studies from the US, European and Scandinavian countries, Australia, and South Africa have estimated that as many as 5% of the general population may be affected.<sup>6-11</sup> Higher FASD-prevalence rates may occur among specific subgroups, eg, people who are in foster care, adopted, or incarcerated.<sup>12-14</sup> Estimates vary, due to cultural differences in patterns of alcohol consumption and contraceptive use, as well as methods of FASD ascertainment and differential occurrence of modifying factors.<sup>7</sup>

Despite increasing awareness of FASD, PAE remains a problem. Recently published data from the 2011–2013 National Survey of Family Growth estimated that 7.3% of

Correspondence: Annika C Montag  
Department of Pediatrics, Division of  
Dysmorphology and Teratology,  
University of California San Diego,  
9500 Gilman Drive – MC 0828, La Jolla,  
San Diego, CA 92093, USA  
Tel +1 619 890 0285  
Fax +1 858 246 1793  
Email amontag@ucsd.edu

women of childbearing age in the US (3.3 million women) were at risk of an alcohol-exposed pregnancy.<sup>15</sup> Women were considered “at risk” if they were non-pregnant and nonsterile, consumed alcohol, and had sex with a nonsterile male. Similar or higher risk estimates have been reported elsewhere.<sup>16–21</sup> The national 10-year objectives designed to improve the health of Americans – Healthy People 2020 – emphasized the importance of FASD prevention with three separate goals: “Increase abstinence from alcohol among pregnant women” (maternal, infant, and child health [MICH]-11.1); “Increase the proportion of women delivering a live birth who did not drink alcohol prior to pregnancy” (MICH-16.4); and “Reduce the occurrence of fetal alcohol syndrome” (MICH-25).<sup>22</sup> Are risk factors for alcohol-exposed pregnancy identical to risk factors for giving birth to a child with FASD? Clearly, they are not. For example, in the National Survey of Family Growth study, older age and having completed fewer years of education were not associated with greater risk of PAE, whereas in most studies they are risk factors for having a child with FASD. Part of the answer as to why risk factors for alcohol-exposed pregnancy and giving birth to a child with FASD are different lies with modifiers of risk that are unevenly distributed among population groups. Another part of the answer lies in our ability to detect alcohol effects. Finally, not all women who are at risk of having an alcohol-exposed pregnancy will give birth.

Investigations into identification of women at risk of giving birth to a child affected by FASD are complicated by challenges in diagnosing FASD. There are many reasons that children are not diagnosed with FASD or misdiagnosed.<sup>23–27</sup> The cardinal facial dysmorphologies of fetal alcohol syndrome, the most complete manifestation under the umbrella diagnosis of FASD, are typically seen in a small subset of affected persons, leaving the majority of those affected without the more visible physical features.<sup>7</sup> The timing, pattern, and magnitude of exposure contribute to differing outcomes. The wide variety of disabilities caused by PAE can have similar characteristics to conditions with different etiologies, such as nutritional deficiencies, genetic factors, or environmental exposure, leading to underdiagnoses or misdiagnosis.<sup>28</sup> There may be limited knowledge regarding FASD and differential diagnoses among parents and health care professionals.<sup>26</sup> Modifiers of risk, such as nutrition, maternal education, and maternal mental health, to name a few, confound diagnosis by concealing the damage due to alcohol among more privileged groups. The diagnostic process requires a multidisciplinary team assessment and is supported by a documented history of PAE, which is

frequently unavailable.<sup>26</sup> Even when the biological mother can be queried, reliance upon maternal self-report to establish a history of PAE is a considerable limitation, due to varying amounts of suspected underreporting.<sup>29</sup> Neurodevelopmental deficits in the children may not manifest until school age, adolescence, or adulthood, and may be obscured by co-occurring mental health disorders.<sup>30</sup> In addition, there has been reluctance among some medical professionals to provide this diagnosis for fear they may stigmatize the child or their family.<sup>31</sup> Recently adopted diagnostic guidelines for neurodevelopmental disorder with PAE may facilitate diagnosis in people without evident physical effects.<sup>32</sup> Better detection of children affected by FASD will lead to improved understanding of maternal risk factors.

This paper addresses ways in which mothers at risk of having a child with FASD may be identified. It is important to identify mothers at risk of having a child with FASD because it allows us to reach them with prevention and risk-reduction interventions. Prior to pregnancy, interventions may focus on contraception, pregnancy planning, and awareness of FASD. During pregnancy, there is benefit to the cessation and/or reduction of alcohol exposure and the implementation of potential “rescue” interventions, such as nutritional supplements (or future pharmacological therapy). Early postnatal interventions are crucial to limiting secondary disabilities. Identifying mothers at risk will also facilitate diagnosis of the child. Early diagnosis with FASD has a protective effect; children not diagnosed experience higher rates of secondary disabilities, including disrupted education, delinquency, institutional confinement, inappropriate sexual behaviors, and alcohol/drug problems,<sup>33,34</sup> as well as mental health issues.<sup>35</sup> Identification of mothers at risk may also benefit future children. Without intervention, alcohol exposure is likely to be repeated in later pregnancies,<sup>36,37</sup> with younger children more severely affected than older children.<sup>38,39</sup> The studies cited in Tables 1 and 2 were chosen based on relevance and rigor of study design.

There are currently three major approaches to identifying specific women at risk of having a child with FASD: 1) using characteristics that may help to “profile” a woman at risk, 2) using laboratory biomarkers of alcohol exposure, and 3) asking the mother herself about her drinking habits and pregnancy history. Of these approaches, the least effective and most likely to limit ascertainment is the first. This method will exclude a huge swath of women who may give birth to affected children whose disabilities are less likely to be diagnosed. All women should be given the opportunity to have a pregnancy free of risks due to alcohol, and all children should have the opportunity to achieve their full potential.

**Table 1** Maternal or pregnancy characteristics commonly associated with having a child with fetal alcohol-spectrum disorder

Risk factor	References
<b>Demographics and lifestyle factors</b>	
Age (higher)	37, 50, 158–162, 181
SES, educational attainment (lower)	50, 59, 73, 131, 159, 161, 163–165
Marital status (unmarried)	50, 131, 162, 166
Employment status (unemployed)	50, 164, 166
Body size/BMI (smaller size, lower BMI)	131, 159, 164
Nutritional status (suboptimal)	47, 131
Religion/spirituality (less)	59, 163
Contraception (less effective)	59
<b>Mental health/psychological factors</b>	
Mental health problems/mental illness	37, 50, 59
Depression	37, 59, 73
Stress	163
Cognitive impairment	59
Trauma or injuries	37, 162
Sexual abuse	37, 59, 162
<b>Alcohol-consumption patterns/factors</b>	
Binge	37, 50, 131, 158, 159, 162
Greater consumption prior to pregnancy	159, 160, 162
Greater quantity/frequency of consumption	37, 50, 73, 131, 158–160, 162, 164, 167
Family history of alcohol problems	158, 163
Alcohol-related medical/life problems	37
<b>Other drug use</b>	
Tobacco use/smoking	50, 159, 160, 162, 164
Illegal drug use	50, 59, 73
<b>Pregnancy</b>	
Parity (higher)	50, 131, 158–160, 162
Gravidity (higher)	37, 131, 158, 159, 162
Prenatal care (late)	73, 160, 161, 166, 168
Prenatal care (less)	37, 50, 160, 161, 168
Already having an affected child	50
<b>Paternal</b>	
Perceived support (lower)	59
Alcohol consumption (higher)	84, 162, 165, 169, 170
Father's age (higher)	161

**Abbreviations:** SES, socioeconomic status; BMI, body mass index.

Using laboratory markers and screening for risk, in combination with pre-pregnancy education and counseling, may identify a greater proportion of women at risk and empower them to make decisions that benefit their children.

## Maternal characteristics

The maternal characteristics most commonly found to be associated with having a child with FASD are illustrated in Table 1. The only critical risk factor is consumption of alcohol in pregnancy. Women who do not consume alcohol during pregnancy do not give birth to children with FASD.

**Table 2** Biomarkers

Marker	Matrix, type of consumption detected, and detection time	References
<b>Indirect</b>		
MCV	<ul style="list-style-type: none"> <li>• Detects chronic and heavy consumption</li> <li>• Insufficiently sensitive or specific for moderate-to-low consumption</li> </ul>	89
GGT		90
CDT		91, 92
<b>Direct</b>		
EtOH	<ul style="list-style-type: none"> <li>• Breath, blood, and urine <ul style="list-style-type: none"> <li>◦ recent consumption (hours)</li> </ul> </li> </ul>	190, 191
FAEEs	<ul style="list-style-type: none"> <li>• Blood <ul style="list-style-type: none"> <li>◦ recent consumption (1–2 days)</li> </ul> </li> <li>• Plasma <ul style="list-style-type: none"> <li>◦ recent consumption (~2 hours)</li> </ul> </li> <li>• Maternal hair <ul style="list-style-type: none"> <li>◦ heavy chronic consumption (months)</li> </ul> </li> <li>• Newborn hair <ul style="list-style-type: none"> <li>◦ heavy consumption over the last 16 weeks of pregnancy (months)</li> </ul> </li> <li>• Meconium <ul style="list-style-type: none"> <li>◦ heavy consumption from ~20th week (months)</li> </ul> </li> </ul>	94, 97, 171–173
EtG (EtS)	<ul style="list-style-type: none"> <li>• Urine <ul style="list-style-type: none"> <li>◦ recent consumption (75–80 hours)</li> </ul> </li> <li>• Blood <ul style="list-style-type: none"> <li>◦ recent consumption (18 hours)</li> </ul> </li> <li>• Plasma <ul style="list-style-type: none"> <li>◦ recent consumption (8 hours)</li> </ul> </li> <li>• Maternal hair <ul style="list-style-type: none"> <li>◦ heavy chronic consumption</li> </ul> </li> <li>• Meconium <ul style="list-style-type: none"> <li>◦ heavy consumption from ~20th week</li> </ul> </li> </ul>	107, 174, 175
PEth	<ul style="list-style-type: none"> <li>• Blood <ul style="list-style-type: none"> <li>◦ low-to-moderate consumption (4–6 weeks)</li> </ul> </li> <li>• DBSs <ul style="list-style-type: none"> <li>◦ prenatal exposure; possibly low-to-moderate consumption (2–3 weeks)</li> </ul> </li> </ul>	118, 176

**Note:** Heavy consumption = three or more drinks/occasion.

**Abbreviations:** MCV, mean corpuscular volume (of erythrocytes); GGT,  $\gamma$ -glutamyltransferase; CDT, carbohydrate-deficient transferrin; EtOH, ethanol; FAEEs, fatty acid ethyl esters; EtG, ethyl glucuronide; EtS, ethyl sulfate; PEth, phosphatidylethanol; DBSs, dried blood spots.

Greater quantities and frequencies of alcohol consumption increase risk.<sup>40,41</sup> The highest risk is associated with heavy episodic or “binge” drinking, as this results in the highest blood-alcohol levels.<sup>42</sup> While the proximal risk factor may be alcohol consumption, the relationship between magnitude of exposure and outcome is not consistent among population groups or individuals. The remaining factors in Table 1 serve to modify the effect of alcohol consumption on outcome.

Common to many studies is the finding that older maternal age at the birth of the child, along with higher

parity and gravidity, are associated with increased risk of giving birth to an affected child, as well as increased risk of having a child who is more severely affected. Perhaps older women, like those women who drink daily, find it more difficult to decrease drinking in pregnancy, because drinking has become an entrenched habit.<sup>43</sup> The nutritional demands of each pregnancy may deplete maternal reserves, effectively limiting availability to future pregnancies, and alcohol consumption may interfere with the absorption of nutrients. Nutritional inadequacies are similarly linked to both increased risk and increased severity of outcome. They may potentiate the effect of alcohol by means of eliminating fail-safe mechanisms.<sup>44–46</sup> Fetal alcohol syndrome appears to be more prevalent in areas where there is undernutrition. Suboptimal status on selected micronutrients or dietary intake has been identified among vulnerable populations in parts of the world where some of the highest rates of FASD are found, eg, South Africa,<sup>47</sup> Russia, and Ukraine.<sup>48</sup> At least one study exploring nutrient supplementation in high-risk pregnancies has documented improved cognitive outcomes in prenatally exposed infants.<sup>44,49</sup> Nutrition may be one of the reasons that having a child affected by FASD is a strong risk factor for having subsequent affected children.<sup>50</sup>

Data regarding maternal body size and the risk of prenatal alcohol vary geographically. In much of the world, lower body mass index and smaller body size are associated with increased risk of having a child with FASD. This association is less evident in the US. For a given amount of alcohol consumed by the mother, smaller body size may lead to greater blood-alcohol levels reaching the fetus, due to less dilution and less first-pass metabolism. It may also be indicative of longer-term or life-long suboptimal nutrition and possibly generational effects of PAE.

When it comes to fetal alcohol syndrome, the most vulnerable in society bear the greatest burden of risk. This may be partly because fetal and child outcomes are affected by both fetal environment and postnatal environment. The severity of FASD effects is modulated by the stability and nurturing of the postnatal environment, which is associated with socioeconomic status and maternal education, as well as marital and employment status.

The contribution of genetic susceptibility to FASD is not fully understood, but may be substantial. Monozygotic (identical) twins are more often similarly affected by PAE than dizygotic (fraternal) twins,<sup>51,52</sup> and children with an affected sibling are at higher risk themselves.<sup>39</sup> Genetic differences in how alcohol is metabolized may influence outcome, as may genetic variations leading to increased risk

of addiction.<sup>53,54</sup> Complexity increases when considering the interaction of maternal, fetal, and paternal genetics and epigenetics.<sup>55–58</sup> The ability to identify epigenetic (including intergenerational) changes may in the future assist in identifying women at risk of having a child with FASD. At present, potential markers of epigenetic modulation by alcohol are being explored.

Having a plan to become pregnant is generally viewed as a protective factor, since most women will reduce risky behaviors when preparing for a pregnancy. However, if contraception is discontinued and alcohol consumption is not, risk is increased. With or without the intention to become pregnant, there are groups of women who are vulnerable as a result of ineffective contraception. They may have limited access to contraception, lack partner support for use of contraception,<sup>59</sup> or be unable to control their own fertility due to FASD effects of their own.

Mental health disorders co-occur with alcohol problems.<sup>59,60</sup> Depression in particular is associated with harmful alcohol consumption (including binge drinking) in women.<sup>61–63</sup> Depression and alcohol consumption also appear to be associated in pregnancy.<sup>64–67</sup> Depressed pregnant women are more likely to drink alcohol, binge-drink, and smoke than nondepressed pregnant women, and less likely to receive prenatal care.<sup>64,66,68–70</sup> Additionally, prenatal depression is associated with poor obstetric and fetal outcomes.<sup>71,72</sup> It is perhaps not surprising that mental health problems, including depression, are more prevalent among women who have given birth to a child with FASD than women who have not.<sup>37,50,59,73</sup> Screening for depression may be a way to identify women at risk of having a child with FASD. Importantly, as depressed women may respond differently to interventions, screening may aid in allocation to specific types of interventions.<sup>74,75</sup>

The role of paternal factors in FASD, including genetic/epigenetic and environmental factors, is emerging, but mechanisms responsible are not yet understood.<sup>76–78</sup> Paternal alcohol consumption has been negatively linked to child cognitive ability, birth weight, and likelihood of live birth.<sup>79–81</sup> Prenatal alcohol consumption is associated with the woman's partner's drinking.<sup>82–84</sup> In one Australian study, 75% of women who drank in pregnancy usually drank with their partner, and that drinking was often partner-initiated. Social and cultural determinants of why women drink in pregnancy include factors that are influenced by partners, such as exposure to intimate partner violence, high life stress, and drug use in the home.<sup>85,86</sup> In one study of 80 birth mothers, 95% had been sexually and/or physically abused at some time in their

lives and more than half suffered from posttraumatic stress and major depressive episode.<sup>59</sup> Interestingly, the benefit of brief intervention increased when a partner participated.<sup>87</sup> Women may be more likely to reduce drinking when their partner does the same.<sup>88</sup> Paternal factors may be of greater interest in prevention of FASD and in elucidating the mechanisms of developmental disruption than in identifying women at risk.

The maternal and environmental factors mentioned may not be as predictive as we would like in identifying women at risk of having a child with FASD. This may be because of differing social norms and differing interactions of modifying effects among populations, and issues associated with diagnosis. Many reflect the benefits to child development provided by a stable, stimulating, and nurturing environment. The one factor that is truly predictive is alcohol consumption during pregnancy. Modifying factors are useful in identifying risk and protective factors for interventions. When used in conjunction with other methods, such as biomarkers, the efficacy of these factors in identifying women at risk will increase.

## Biomarkers

Biomarkers may currently be used to identify alcohol-exposed pregnancies, but not FASD. This does not mean that they are without benefit in identifying women at risk. Women can be identified at various time points, including prior to pregnancy, early in pregnancy, throughout the pregnancy, and at the birth of the child. At each of these stages, opportunities exist to intervene on behalf of the mother, the index child, and future children to prevent or ameliorate negative effects. Considerations in choosing a marker include whether one wants to identify short-term vs long-term alcohol use, the magnitude and timing of use to be identified, and the desired sensitivity and specificity of the marker. A further consideration is the availability and acceptability of the marker. For example, urine samples are noninvasively and routinely collected at prenatal care visits, whereas neonatal hair samples may not be available.

Clinically used indirect markers of chronic alcohol use, such as mean corpuscular volume,  $\gamma$ -glutamyltransferase, and carbohydrate-deficient transferrin (CDT) are particularly useful when part of a panel of biomarkers.<sup>89–91</sup> These markers identify chronic alcohol abuse, but lack the sensitivity and specificity to estimate accurately moderate-to-low levels of alcohol consumption and intermittent or recent exposure. Comorbidities and exposures other than alcohol will affect levels of these markers. Some are also less valid in pregnancy as a result of

normal physiological changes in pregnancy (eg, mean corpuscular volume and CDT increase in later pregnancy).<sup>92</sup>

Direct markers, including alcohol and metabolites of alcohol, are more sensitive and specific, and are able to detect recent alcohol exposure.<sup>93</sup> Timing and magnitude of exposure detected depend upon the maternal and neonatal matrices sampled: biological fluids, nails, or hair. Alcohol, including low levels of exposure, may be detected in breath, blood, and urine. The time after exposure that alcohol may be determined varies by amount consumed, body size, and genetics, but is limited to hours. Alcohol metabolites, including ethyl glucuronide (EtG), ethyl sulfate (EtS), fatty acid ethyl esters (FAEEs), and phosphatidylethanol (PEth) are highly specific and have a wider time window of detection than alcohol itself (see Table 2).

FAEEs can be determined from blood/plasma/serum, hair, or meconium. In blood, FAEEs show alcohol exposure within 1 or 2 days, depending upon magnitude of exposure. Hair and nail samples are used to measure cumulative exposures over time. While low baseline levels are detected in nondrinkers, accepted cutoff values distinguish between light-to-moderate (0.2–0.5 ng/mg of hair) and heavy ( $\geq 1$  ng/mg) use. FAEEs in meconium are of particular interest, because they are specific to the newborn. More than 20 different compounds are formed in the fetus by esterification of alcohol that has crossed the placenta. PAE from approximately the 20th week of gestation to birth is reflected in meconium levels, with an emphasis on the last 2 months of pregnancy. This has become a well-established method, with one FAEE, ethyl linoleate, identifying alcohol exposure with sensitivity of  $\geq 88\%$  and specificity of 64%.<sup>94</sup> Sensitivity decreases at moderate-to-low levels of exposure.<sup>95</sup> FAEEs have been detected in meconium from infants of women who did not consume alcohol in pregnancy, but at much lower levels than among women who did.<sup>96,97</sup> FAEEs in placental tissue, particularly ethyl stearate with a positive predictive value of 50% and a negative predictive value of 97%, may also be used to identify alcohol-exposed newborns.<sup>98</sup> Placenta and meconium values may differ, due to potential metabolism of FAEEs in placenta and additional synthesis in meconium.<sup>96,99</sup>

EtG and EtS are direct, nonoxidative products of alcohol metabolism that can be measured in blood/plasma/serum, urine, hair, and meconium, and have the considerable advantage of being detectable only if alcohol has been consumed. As opposed to FAEEs, they are water-soluble and stable when stored. EtG is the more reliable of the two in serum, has a longer detection period in urine, is more sensitive in meconium, and is more commonly used.<sup>100</sup> EtG in maternal



hair and nails is a far less sensitive marker of PAE than EtG in meconium.<sup>101,102</sup> However, a combination of EtG in maternal hair and meconium was predictive of PAE in a sample of 80 mother–child dyads, with sensitivity of 86% and specificity of 74%.<sup>103</sup> It is possible that EtG crosses the placenta and that EtG in meconium may reflect both fetal and maternal metabolism.<sup>104,105</sup> EtG is detectable for 75–80 hours in urine and 8–18 hours in blood (the shorter estimates if in plasma). It measures recent alcohol exposure after alcohol has been eliminated from the body. Neither EtG nor EtS measurements are affected by alcohol in hand sanitizers, mouthwash, etc.<sup>106</sup> There may be interference from concurrent cannabis use.<sup>107</sup> To control for urine dilution, EtG levels should be reported relative to creatinine values.

PEth is a unique phospholipid that is only formed by the interaction of alcohol with phosphatidylcholine catalyzed by phospholipase D in red blood-cell membranes.<sup>108</sup> It is detectable for 4–6 weeks in blood following low-to-moderate prenatal alcohol consumption.<sup>109</sup> Kinetics, including half-life and peak concentrations, of PEth vary among alcoholics and social drinkers.<sup>110–112</sup> Sensitivity is close to 100% at levels of consumption from <40 g/day to >200 g/day, and PEth concentrations correlate with reported consumption.<sup>113</sup> However, there are interindividual differences.<sup>113,114</sup> Blood samples should be frozen at –80°C to avoid additional PEth formation.<sup>114,115</sup> PAE screening using PEth analysis in dried blood spots (DBSs) from neonatal heel sticks was explored by Bakhireva et al. DBSs are convenient for collection, shipping, and storage, and are routinely obtained from most newborns throughout the world. They are minimally invasive and require small amounts of blood. This screening was found to be feasible and cost-effective.<sup>116,117</sup> In a study of 60 infants, 28 of whom experienced PAE, PEth from DBSs achieved 100% specificity and 32.1% sensitivity, which was higher than the comparison markers ( $\gamma$ -glutamyltransferase, CDT, EtG, and EtS). When PEth, EtG, and EtS were considered in combination, sensitivity increased to 50%.<sup>118</sup>

A battery of biomarkers for each specific purpose may provide the greatest clinical utility. A combination of markers might increase accuracy, such as the combination of FAEE and EtG.<sup>119</sup> To detect both short-term and long-term alcohol consumption, a combination of CDT and PEth may prove valuable.<sup>120</sup> The cost of some analyses, such as meconium markers, may be perceived as high for routine testing, but are cost-effective when compared to the cost of not identifying a newborn with FASD.<sup>121</sup> Identifying a mother at risk of having a child with FASD provides the greatest benefit to a particular pregnancy if accomplished early in pregnancy or pre-pregnancy but, as documentation of PAE is required for

diagnosis, a biomarker establishing PAE is beneficial at any time point, even postnatally.

Technological advances continue to create and refine laboratory markers to more precisely assess exposure and the relationship of exposure to outcomes. They provide insights into mechanisms of harm and may lead to intervention strategies. There is a need for more sensitive biomarkers to identify low-to-moderate and intermittent drinking, as even low exposure levels may be deleterious.<sup>122–125</sup> Ideally, we would like to have markers of fetal effects, not exposure. To accomplish this, we would need not only insight into teratological mechanisms but also a well-characterized study population and the ability to recognize both the physical and the far more common neurobehavioral effects of alcohol exposure. Future directions may include novel markers, such as circulating microRNAs,<sup>126</sup> epigenetic changes,<sup>57</sup> placental human chorionic gonadotropin and insulin-like growth factor 2 expression,<sup>127</sup> or second-trimester ultrasound.<sup>128</sup> Newer sampling matrices, such as placental tissue and breast milk, may prove useful.

In a clinical setting, biomarkers should always be accompanied by a self-report assessment. While current biomarkers are attractive because they do not rely on maternal report, specificity levels of some tests raise the possibility of undermining the patient–provider relationship with potentially negative consequences if a mother is inappropriately approached about alcohol use. Lack of sufficient sensitivity to determine low alcohol exposure may exclude some women at risk.

## Self-report assessment

The simplest approach to identifying women at risk should be asking them about alcohol consumption if they are pregnant and alcohol consumption and contraceptive use if they are not pregnant but have the potential to become pregnant. Among the approaches to asking women about alcohol consumption is the time-line follow-back method.<sup>129,130</sup> Time-line follow-back has been extensively used by May et al in FASD-related studies.<sup>73,131</sup> It provides “memory anchors” by asking about drinking at specific events, such as birthdays and holidays, to aid recall. Self-report in this context may be more accurate than without “memory anchors” but is still vulnerable to bias, due to memory and cognition issues and social desirability. Efforts to reduce the stigma associated with prenatal alcohol consumption may improve the accuracy of self-reported drinking. In some circumstances, asking about pre-pregnancy drinking may be more predictive of exposure than asking about pregnancy drinking.<sup>132,133</sup>

Risky drinking may be identified in pregnant women using validated instruments that have varying sensitivity

**Table 3** Brief alcohol-screening tools for use with women of childbearing age and in pregnancy

Screening tool	Sensitivity/specificity for risky drinking at indicated cut point <sup>#</sup>	Comments	References
T-ACE (T-ACER3)	$\geq 1^*$ : 76%–92%/38%–85% $\geq 2^*$ : 69%–95%/40%–89% $\geq 3^*$ : 38%–79%/81%–97%	<ul style="list-style-type: none"> <li>• Developed for pregnant women</li> <li>• Validated in pregnant women</li> <li>• Sensitive among minority populations</li> <li>• Better than medical records</li> <li>• Focused on heavy drinking</li> <li>• Increasing cut point in T-ACER3 improved specificity while maintaining high sensitivity, thereby improving PPV</li> </ul>	134–139, 177–180, 182
TWEAK	$\geq 1^*$ : 87%–92%/67%–72% $\geq 2^*$ : 79%–100%/36%–83%	<ul style="list-style-type: none"> <li>• Developed for pregnant women</li> <li>• Validated in pregnant women</li> <li>• Less sensitive among minority populations</li> <li>• Focused on heavy drinking</li> </ul>	136, 137, 182–185
AUDIT-C	$\geq 3^*$ : 67%–95%/85%	<ul style="list-style-type: none"> <li>• Developed for pregnant women, but may be unreliable in some obstetric settings</li> <li>• Effective among a variety of populations</li> <li>• Focus on very heavy alcohol exposure</li> </ul>	185, 186–188
CAGE	$\geq 1^*$ : 59%–68%/82% $\geq 2^*$ : 38%–49%/92%–93%	<ul style="list-style-type: none"> <li>• Not developed for or recommended for pregnant women</li> <li>• Less effective in women than men</li> <li>• Less sensitive in non-Caucasian women than Caucasian and minority or disadvantaged compared to T-ACE or TWEAK</li> <li>• Designed to identify lifetime drinking and heavy exposure</li> </ul>	136–138, 180, 182, 189

**Notes:** \*These values indicate the score at which someone is identified as a risky drinker. <sup>#</sup>Data presented as sensitivity (probability that a risky drinker is identified as a risky drinker by the screen – ie, screens positive) and specificity (probability that a nonrisky drinker is negative on the screen).

**Abbreviations:** T-ACE, tolerance, annoyed, cut down, eye-opener; T-ACER3, T-ACE with cut point increased to 3 points; TWEAK, tolerance, worry, eye-opener, amnesia, “kut” down; AUDIT-C, alcohol use disorders identification test – consumption; CAGE, cut down, annoy, guilty, eye-opener; PPV, positive predictive value.

and specificity depending upon the population screened. Examples of such instruments are the T-ACE (tolerance, annoy, cut down, eye-opener) measure,<sup>134,135</sup> the TWEAK (tolerance, worry, eye-opener, amnesia, “kut” down) measure,<sup>136,137</sup> the CAGE (cut down, annoy, guilt, eye-opener) measure,<sup>138</sup> and more recently the T-ACER3<sup>135,139</sup> version of the T-ACE, which increases the score or cut point at which the person is identified as a “risky drinker” to 3 (Table 3). The instruments are easy and quick to use; most are four or five questions long. They may be delivered by in-person interview, paper-based questionnaire, or computer. Additional refinement is necessary to improve sensitivity for any alcohol exposure; a pervasive issue is the inability to detect low levels of alcohol exposure.

SBIRT (screening, brief intervention, and referral to treatment) is a prevention and early intervention approach that uses universal screening, education, feedback specifically tailored to the participant, and referral for professional treatment for those screening positive for alcohol-abuse problems.<sup>140,141</sup> Screening may be accomplished with one of the validated instruments described earlier, and requires minimal time investment. While it is recommended that medical care personnel screen all women of childbearing age for risky drinking,<sup>142,143</sup> many feel uncomfortable discussing alcohol with patients, inadequately trained to

do so, or feel that not all patients need to be screened.<sup>144–147</sup>

In our experience and others’, just asking women about their drinking habits has a beneficial effect in reducing risky alcohol consumption.<sup>74</sup> The brief-intervention component provides personalized feedback and education, which may be delivered by health care personnel using an empathetic, nonjudgmental approach, possibly incorporating motivational interviewing, or by computer. While the framework of SBIRT may be universally applied, the brief-intervention and treatment portions must be tailored to make them relevant and understandable where they are used. Motivational interviewing is an adaptable technique that has been incorporated into a variety of effective programs to reduce risky drinking.<sup>148–150</sup> Timely treatment or counseling supportive of the woman’s unique circumstances should be available upon referral. A combination of SBIRT with feedback regarding biomarker results decreased alcohol consumption in pregnant women.<sup>151</sup>

## Conclusion

To best identify women at risk of having a child with an FASD, both screening and use of effective biomarkers should be incorporated into routine obstetric and gynecologic care. While self-report is a practical method for ascertaining risk, used alone it is likely to miss identifying

some women at risk.<sup>29,152–156</sup> The trust between a woman and her health care providers is crucial. For screening to be effective, women must feel confident that they will not be stigmatized or lose custody of their children, and that treatment will be available should they need it. Referral to treatment is necessary to maintain trust and because brief interventions alone may not be sufficiently effective.<sup>157</sup> At present, there are no diagnostic biomarkers. Limitations of using biomarkers with less than 100% specificity include the potential risk to the patient–health care professional relationship when there are false positives, particularly when combined with self-report. Providers need to be supported with appropriate training and tools to know how to speak to patients about screening results, how to conduct brief interventions, and how to refer to the next level of resources. One beneficial outcome of adopting this screening will be that providers will be encouraged to discuss alcohol use with their pregnant patients.

Universal screening is not only prudent but more in line with bioethical principles, as there are ethical implications to limiting testing to subsets of women. Screening may be done in a manner similar to either HIV or  $\alpha$ -fetoprotein testing. A sound approach would include routine self-report screening of all women of childbearing age, brief interventions for all who consume alcohol and have the potential to become pregnant, and referral to treatment as necessary. Starting at the first prenatal health care appointment and continuing throughout pregnancy, self-report screening should optimally be supplemented with effective biomarker assessment of alcohol consumption. Choice of specific biomarkers will be better informed as technological advances increase sensitivity and specificity of biomarkers or combinations of biomarkers. At birth, meconium, placental, or DBS analyses should ideally be used to determine fetal alcohol exposure, facilitate early diagnosis and treatment, and identify women at risk for future alcohol-exposed pregnancies.

While the resources are not yet in place to support this approach of comprehensive screening of women and infants, the potential for prevention of this common disorder warrants action. The cost of routine screening with SBIRT interventions and biomarkers is justified by avoidance of the substantial cost of a child with FASD.

## Disclosure

The author reports no conflicts of interest in this work.

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