Prenatal Alcohol Exposure and Risk of Birth Defects

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KEY WORDS

prenatal alcohol exposure, fetal alcohol spectrum disorder, fetal alcohol syndrome, alcohol-related disorders, congenital abnormalities, drug-induced abnormalities, cohort studies

ABBREVIATIONS

aOR—adjusted odds ratio
ARBD—alcohol-related birth defect
ASD—atrial septal defect
FAS—fetal alcohol syndrome
IOM—Institute of Medicine
OR—odds ratio
CI—confidence interval
PAE—prenatal alcohol exposure
RASCALS—Randomly Ascertained Sample of Children born in Australia's Largest State
VSD—ventricular septal defect
WABDR—Western Australia Birth Defects Registry
WA—Western Australia

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WHAT'S KNOWN ON THIS SUBJECT: The evidence supporting the IOM classification of alcohol-related birth defects (ARBDs) comes from studies of high-risk groups and animal studies. There is a lack of population-based evidence for the association between PAE and birth defects.

WHAT THIS STUDY ADDS: Many of the birth defects classified by the IOM as ARBDs either were not present in this cohort or were not related to PAE. These findings raise questions about the clinical validity of labeling specific birth defects as ARBDs.

abstract

OBJECTIVE: The goal was to examine the associations between dose, pattern, and timing of prenatal alcohol exposure (PAE) and birth defects.

METHODS: Data from a randomly selected, population-based cohort of nonindigenous women who gave birth to a live infant in Western Australia (WA) between 1995 and 1997 ($N = 4714$) were linked to WA Midwives Notification System and WA Birth Defects Registry data. We assessed the associations of PAE before pregnancy, in the first trimester, and in late pregnancy with any birth defect and with birth defects classified as alcohol-related birth defects (ARBDs) by the Institute of Medicine (IOM), by using logistic regression.

RESULTS: The prevalence of birth defects classified as ARBDs by the IOM was low. Compared with abstinence, heavy PAE in the first trimester was associated with increased odds of birth defects classified as ARBDs (adjusted odds ratio: 4.6 [95% confidence interval: 1.5–14.3]), with similar findings after validation through bootstrap analysis. There was no association between low or moderate PAE and birth defects.

CONCLUSIONS: A fourfold increased risk of birth defects classified as ARBDs was observed after heavy PAE in the first trimester. Many individual birth defects included in the IOM classification for ARBDs either were not present in this cohort or were not associated with PAE. Large, population-based studies are needed to strengthen the evidence base for ARBDs. *Pediatrics* 2010;126:e843–e850

Prenatal alcohol exposure (PAE) is reported to increase the risk of a range of birth defects, neurodevelopmental disorders, and fetal alcohol syndrome (FAS),[1] which are all included under the umbrella term of fetal alcohol spectrum disorders.[2] The Institute of Medicine (IOM) diagnostic guidelines include a wide range of birth defects within the term alcohol-related birth defects (ARBDs), with the evidence supporting their inclusion being derived from research on high-risk populations or animal studies.[1,3]

Many of the birth defects associated with PAE are not unique to PAE and have other potential causes.[4] Therefore, in the absence of facial dysmorphologic features, attributing a specific birth defect to PAE can be difficult. Several of the birth defects included by the IOM as ARBDs occur rarely, and it is generally accepted that the extent of the birth prevalence of disorders associated with PAE is not known.[5] Other factors limiting our ability to find evidence of the association between PAE and birth defects at a population level include the absence of a marker of alcohol exposure, the lack of routine screening for alcohol use during pregnancy,[6] inadequate documentation of maternal alcohol use in medical records,[7] and a lack of health care professionals' knowledge and awareness of the fetal effects associated with alcohol use in pregnancy.[6] In addition, recent research evidence indicated the importance of examining the effects of dose, pattern, and timing of exposure on fetal outcomes.[8] We used a large, well-defined, well-described, population-based cohort of nonindigenous women who delivered a live infant in Western Australia (WA) to examine the association between dose, pattern, and timing of PAE before pregnancy, in the first trimester, and in late pregnancy for (1) any birth defect and (2) birth defects included in the IOM classifications for ARBDs.

METHODS

Sample Selection

The details of this study were described previously.[8] Between 1995 and 1997, a 10% random sample of all nonindigenous women who gave birth to a live infant in WA were invited by letter at 3 months after birth to participate in the Randomly Ascertained Sample of Children born in Australia's Largest State (RASCALS) study. The RASCALS study was designed to survey health-related behaviors and events before and during pregnancy and early infancy. Children given up for adoption ($n = 5$) were excluded. Information for each individual completing the questionnaire ($N = 4860$; response rate: 81%) was linked to the corresponding birth information recorded in the WA Midwives' Notification System, a statutory, population-based, surveillance system of all births in WA. The prevalences of low birth weight infants and teen mothers were slightly lower than those of the whole population in WA.[9] The analyses reported here were restricted to women with singleton births (multiple births excluded [$n = 66$]) and nonindigenous children (indigenous fathers excluded [$n = 75$]), which yielded a sample size of 4714.

Maternal Alcohol Consumption

Information about maternal alcohol consumption was collected retrospectively at 3 months after birth for the 3-month period before pregnancy and for each trimester separately. Survey questions and coding of PAE with a composite method of classification were reported previously.[8] The composite method categorizes the level of alcohol consumption into 4 mutually exclusive groups, that is, none (abstinent throughout pregnancy), low drinking, moderate drinking (including binge drinking less than weekly), and heavy drinking (including binge drinking weekly or more frequently) (Table 1). One standard drink in Australia is equal to 10 g of alcohol. The low category was defined in line with the 2001 recommendation to women who are pregnant or might soon become pregnant set out by the Australian National Health and Medical Research Council in alcohol guideline 11, which recommended, "If women choose to drink, over a week, they should have less than 7 standard drinks, AND, on any one day, no more than 2 standard drinks."[10] The moderate group included women who drank ≤70 g of alcohol per week, with the majority consuming 21 to 49 g per occasion; therefore, the quantity consumed per occasion discriminated moderate exposure from low exposure. Women who engaged in binge drinking of ≥50 g per occasion less than weekly were included in the moderate group. This amount is equivalent to 5 standard drinks in Australia, 4 standard drinks in the United States, and 6 standard units in the United Kingdom, where standard drinks/units are equal to 10, 12, and 8 g of alcohol, respectively. The heavy group included women who engaged in binge drinking 1 or 2 times per week or more than twice per week and heavy drinkers who consumed <5 standard drinks per occasion (the majority consumed >20 g of alcohol per occasion) but >70 g per week. To present more detail about the distribution of exposure and outcomes, the heavy group was divided into 4 subgroups, that is, binge drinking 1 or 2 times per week, binge drinking more than twice per week, consumption of 70.1 to 140 g per week, and consumption of ≥140.1 g per week with <5 standard drinks consumed per occasion (Table 1).

TABLE 1 Patterns of Maternal Alcohol Consumption Before and During Pregnancy and Prevalence of Birth Defects

	n (%)							
	Abstinent[a]	Low	Moderate		Heavy			
			Moderate	Binge Less Than Weekly	Binge 1 or 2 Times per wk	Binge >2 Times per wk	Heavy (70.1–140.0 g/wk)[c]	Very Heavy (≥140.1 g/wk)[c]
Before pregnancy ($N = 4714$)								
Total	919 (19.5)	1555 (33.0)	1289 (27.2)	236 (5.0)	276 (5.9)	134 (2.8)	209 (4.4)	105 (2.2)
Any birth defect	60 (6.5)	106 (6.8)	75 (5.9)	8 (3.4)	17 (6.2)	13 (9.7)	22 (10.5)	5 (4.8)
ARBD	10 (1.1)	16 (1.0)	11 (0.9)	2 (0.8)	2 (0.7)	5 (3.7)	4 (1.9)	1 (1.0)
First trimester ($N = 3931$)[b]								
Total	1922 (40.8)	1324 (28.1)	446 (9.5)	64 (1.4)	67 (1.4)	31 (0.7)	49 (1.0)	28 (0.6)
Any birth defect	129 (6.7)	77 (5.8)	26 (5.8)	3 (4.7)	5 (7.5)	3 (9.7)	4 (8.2)	2 (7.1)
ARBD	17 (0.9)	12 (0.9)	2 (0.4)	0 (0)	2 (3.0)	1 (3.2)	2 (4.1)	0 (0)
Late pregnancy ($N = 4334$)[b]								
Total	1922 (40.8)	1797 (38.1)	472 (10.0)	38 (0.8)	25 (0.5)	15 (0.3)	49 (1.0)	16 (0.3)
Any birth defect	129 (6.7)	111 (6.2)	33 (7.0)	2 (5.3)	1 (4.0)	1 (6.7)	4 (8.2)	2 (12.5)
ARBD	17 (0.9)	18 (1.0)	8 (1.7)	1 (2.6)	1 (4.0)	0 (0)	1 (2.0)	0 (0)

[a] Abstinent throughout pregnancy.

[b] Numbers do not add to the number for the total cohort ($N = 4714$) because 16.6% of women were abstinent in the first trimester but drank in late pregnancy and 8.1% drank in the first trimester and abstained in late pregnancy.

[c] Women who consume <50 g of alcohol per occasion (no binge drinking).

Birth Defects

The WA Birth Defects Registry (WABDR) collects information for the WA population on birth defects diagnosed for stillbirths, terminated pregnancies, and live births (up to 6 years of age), using multiple sources of ascertainment.[11,12] Strengths of the WABDR data include the use of consistent definitions over time, case review, classification of severity, and inclusion of both major and minor congenital anomalies diagnosed in WA children up to 6 years of age. All birth defects in the cohort were identified, and then the descriptive text for each case was reviewed by 1 of the authors (Dr Bower), who was blinded to PAE. Only birth defects that could not be attributed to another syndrome or a genetic or congenital condition were classified as ARBDs by using the IOM definitions. Birth defects were grouped into 2 categories, irrespective of facial dysmorphologic features, intellectual development, and growth.[3] The categories were (1) any birth defect and (2) ARBDs according to IOM criteria[1,3] (Table 2). Children were included in a category if they had ≥1 birth defect in the category. We were unable to examine the relationship between each individual birth defect and PAE because of the small numbers of some birth defects and the potential for identification of individuals. Data on 4 defects included in the IOM guidelines (strabismus, refractive errors, railroad track ears, and hockey stick palmar creases) are not collected by the WABDR, and those defects were not included in this study.[3]

TABLE 2 Prevalence of Birth Defects Classified by the IOM as ARBDs

Birth Defect Classification	*n* (%)
Any birth defect	306 (6.5)
ARBDs	
Cardiac	
VSDs	32 (0.7)
ASDs	7 (0.2)
Conotruncal heart defects	4 (0.1)
Renal defects	
Horseshoe kidney	1 (0.0)
Ureteral duplications	2 (0.0)
Kidney aplasia/dysplasia/hypoplasia	3 (0.0)
Eyes: ptosis	2 (0.0)
Ears: congenital deafness	1 (0.0)
Skeletal abnormalities: vertebral segmentation defects	2 (0.0)
Minor anomalies: hypoplastic nails	1 (0.0)
Total children	51 (1.1)

Categories are not mutually exclusive because some children had multiple diagnoses. There were no cases of scoliosis, radioulnar synostosis, large joint contractures, retinal vascular anomalies, optic nerve hypoplasia, pectus excavatum, pectus carinatum, short fifth digits, clinodactyly, or camptodactyly.

Data Linkage

Data from the RASCALS cohort were linked by the WA Data Linkage Branch, through probabilistic matching,[13] to 2 data sets, namely, the WA Midwives Notification System, which provided information on maternal characteristics, pregnancy and delivery, and infant outcomes, and the WABDR for cases ascertained up to the end of 2006.[14] After the linkage process, deidentified data files were extracted by the data custodians, merged with the survey data from the RASCALS cohort, and provided to the researchers.

Data Analyses

The effects of PAE in specific periods of pregnancy were examined by investigating the numbers and proportions of birth defects in the offspring of women who drank in the prepregnancy period, in the first trimester, and in late pregnancy (defined as the maximal consumption in the second and/or third trimester). Small numbers prevented examination of each category separately; therefore, binge drinking once per week or more frequently and heavy alcohol consumption of ≥70.1 g per week were combined for the anal-

yses. Occasional binge drinking was combined with the moderate group because the mean, median, and maximal intakes for this group were similar to those for the moderate group.[8]

Multivariate logistic regression analyses were used to assess the association between PAE in each of these time periods and the 4 categories of birth defects described above. The comparison group for the prepregnancy analysis was defined as women who abstained during the prepregnancy period and that for analysis during pregnancy was defined as women who abstained throughout pregnancy. All of the analyses were adjusted for prenatal factors, including maternal age, marital status, parity, income, smoking during pregnancy, and use of drugs (including tranquilizers) during pregnancy. Data analyses were conducted by using SPSS 15.0 (SPSS Inc, Chicago, IL), and results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). To examine the robustness of the estimates, we calculated bootstrap 95% CIs by using Stata 10.1 (Stata, College Station, TX). We also calculated the excess risk, that is, the rate (cases per 1000 births) of the outcome (birth defect or group of birth defects) in the exposed population minus the rate in the unexposed population.[15]

Ethics

Approval for the conduct of this study was granted by the Princess Margaret Hospital Research Ethics Committee and the WA Confidentiality of Health Information Committee.

RESULTS

The frequency of maternal alcohol consumption in the 3 months before and during pregnancy is shown in Table 1. The drinking patterns classified as moderate and heavy for the analyses are shown divided into subgroups. Fewer than one-half (40.8%) of women abstained throughout pregnancy; 8.1% of women who drank in the first trimester abstained in late pregnancy, and 16.6% who abstained in the first trimester drank in late pregnancy. There was a reduction in the proportion of women who drank from the prepregnancy period to the first trimester, with the greatest reduction (75%) for women who reported drinking at heavy levels. Further decreases were observed for all patterns of drinking in late pregnancy, with the exception of women who drank 70 to 140 g per week without binge drinking. Conversely, the proportion of women drinking at low levels increased from 28.1% in the first trimester to 38.1% in late pregnancy. The distribution of any birth defects in the offspring of women who engaged in binge drinking less frequently than weekly was slightly lower than that observed for the moderate group, and there were no ARBDs after less-than-weekly binge drinking in the first trimester. The proportion of ARBDs after binge drinking weekly or more frequently in the first trimester (3%) was similar to the 4% observed after heavy drinking with <5 standard drinks per occasion and 70 to 140 g per week. No ARBDs were observed in the very heavy exposure group.

Any type of birth defect was diagnosed for 306 children (6.5%). With the use of the IOM guidelines to define our categories, 51 (1.1%) had birth defects within the ARBD category, of whom 47 (92%) had 1 birth defect and 4 (8%) had 2 birth defects (Table 2). The most commonly diagnosed birth defects were ventricular septal defects (VSDs) (n = 32 [10.5%]) and atrial septal defects (ASDs) (n = 7 [2.3%]). Almost two-thirds (62.7%) of the birth defects classified as ARBDs were VSDs, and 15.7% were ASDs.

The distribution and risk of any birth defect and those in the various IOM classification categories are presented according to dose, pattern, and timing of PAE in Tables 3 and 4. Compared with the abstinent group, there was no association between low or moderate PAE before or during pregnancy and the occurrence of any birth defect (Table 3) or birth defects within the category of ARBDs (Table 4).

TABLE 3 Prevalence and ORs of Any Birth Defects According to PAE

	Abstinent	Low	Moderate[a]	Heavy
Before pregnancy				
Total, *n* (%)	919 (19.5)	1555 (33.0)	1289 (32.2)	724 (15.4)
No birth defect, *n* (%)	859 (93.5)	1450 (93.2)	1433 (94.5)	667 (92.1)
Any birth defect, *n* (%)[b]	60 (6.5)	106 (6.8)	83 (5.5)	57 (7.9)
Unadjusted OR (95% CI)	1.0	1.05 (0.76–1.45)	0.83 (0.59–1.17)	1.22 (0.84–1.78)
aOR (95% CI)[c]	1.0	1.00 (0.72–1.40)	0.81 (0.57–1.14)	1.21 (0.82–1.80)
First trimester				
Total, *n* (%)	1922 (40.8)	1324 (28.1)	510 (10.8)	175 (3.7)
No birth defect, *n* (%)	1793 (93.3)	1247 (94.2)	481 (94.3)	161 (92.0)
Any birth defect, *n* (%)[b]	129 (6.7)	77 (5.8)	29 (5.7)	14 (8.0)
Unadjusted OR (95% CI)	1.0	0.86 (0.64–1.15)	0.84 (0.55–1.27)	1.21 (0.68–2.15)
aOR (95% CI)[c]	1.0	0.84 (0.62–1.13)	0.85 (0.55–1.29)	1.28 (0.69–2.38)
Late pregnancy				
Total, *n* (%)	1922 (40.8)	1797 (38.1)	510 (10.8)	105 (2.2)
No birth defect, *n* (%)	1793 (93.3)	1686 (93.8)	475 (93.1)	97 (92.4)
Any birth defect, *n* (%)[b]	129 (6.7)	111 (6.2)	35 (6.90)	8 (7.6)
Unadjusted OR (95% CI)	1.0	0.92 (0.70–1.19)	1.02 (0.70–1.51)	1.15 (0.55–2.41)
aOR (95% CI)[c]	1.0	0.87 (0.67–1.14)	1.05 (0.70–1.56)	1.27 (0.59–2.72)

[a] Includes binge drinking less frequently than weekly.
[b] Any birth defect, N = 306 (6.5%).
[c] Adjusted for maternal age, marital status, parity, income, smoking during pregnancy, and drug use during pregnancy.

TABLE 4 Prevalence and ORs of ARBDs According to PAE

	Abstinent	Low	Moderate[a]	Heavy
Before pregnancy				
Total, *n* (%)	919 (19.5)	1555 (33.0)	1289 (32.2)	724 (15.4)
No birth defect, *n* (%)	859 (93.5)	1450 (93.2)	1433 (94.5)	667 (92.1)
ARBD, *n* (%)[b]	10 (1.1)	16 (1.0)	13 (0.9)	12 (1.7)
Unadjusted OR (95% CI)	1.0	0.95 (0.43–2.09)	0.78 (0.34–1.80)	1.53 (0.66–3.57)
aOR (95% CI)[c]	1.0	0.97 (0.44–2.17)	0.80 (0.34–1.85)	1.54 (0.63–3.75)
First trimester				
Total, *n* (%)	1922 (40.8)	1324 (28.1)	510 (10.8)	175 (3.7)
No birth defect, *n* (%)	1793 (93.3)	1247 (94.2)	481 (94.3)	161 (92.0)
ARBD, *n* (%)[d]	17 (0.9)	12 (0.9)	2 (0.4)	5 (2.9)
Unadjusted OR (95% CI)	1.0	1.02 (0.49–2.15)		3.30 (1.20–9.04)
aOR (95% CI)[c]	1.0	1.11 (0.52–2.39)		4.57 (1.46–14.26)
Late pregnancy				
Total, *n* (%)	1922 (40.8)	1797 (38.1)	510 (10.8)	105 (2.2)
No birth defect, *n* (%)	1793 (93.3)	1686 (93.8)	475 (93.1)	97 (92.4)
ARBD, *n* (%)[e]	17 (0.9)	18 (1.0)	9 (1.8)	2 (1.9)
Unadjusted OR (95% CI)	1.0	1.13 (0.58–2.21)	2.01 (0.89–4.54)	
aOR (95% CI)[c]	1.0	1.25 (0.63–2.48)	2.28 (0.98–5.30)	

[a] Includes binge drinking less frequently than weekly.
[b] $N = 51$ (1.1%).
[c] Adjusted for maternal age, marital status, parity, income, smoking during pregnancy, and drug use during pregnancy.
[d] $N = 36$ (0.8%).
[e] $N = 46$ (1.0%).

Compared with the abstinent group, increased odds of having a birth defect classified as an ARBD were found after heavy PAE in the first trimester (adjusted OR [aOR]: 4.57 [95% CI: 1.46–14.26]) (Table 4), and this association was similar after bootstrap analysis with 50 bootstrap samples (aOR: 4.56 [95% CI: 1.60–13.06]). Of the children who had birth defects classified as ARBDs and who experienced heavy PAE in the first trimester, 80% had cardiac septal defects. In this group, the odds of having a VSD or ASD were increased almost threefold (aOR: 2.67 [95% CI: 0.79–9.00]) but the estimate was imprecise because of small numbers. The excess risk after heavy PAE in the first trimester was 1.7 cases per 1000 for a birth defect classified as an ARBD by the IOM.

Although numbers of cases were too small to allow analysis of the group with moderate PAE in the first trimester, there was a doubling of the odds of ARBDs after moderate PAE in late pregnancy (aOR: 2.28 [95% CI: 0.98–5.30]) (Table 3). However, 2 of the 5 children who had birth defects classified as ARBDs and who had moderate PAE in late pregnancy (data not shown) also had heavy PAE during the first trimester.

DISCUSSION

To our knowledge, this is the first study using population data to examine the association between the dose, pattern, and timing of PAE and birth defects. Heavy PAE in the first trimester was associated with a more than fourfold increased risk of ARBDs, as defined by the IOM, and a nonsignificant 2.6-fold increased risk of cardiac septal defects. Not surprisingly, the association was specific to PAE in the first trimester and, although there were only small numbers of cases, the results were supported by the bootstrap analysis. The finding of twofold increased odds of ARBDs after moderate levels of PAE during late pregnancy is likely because many women also had heavy first trimester exposure and reduced their alcohol intake as pregnancy progressed. Our findings are consistent with the fact that the first trimester is a period of rapid fetal development and the most vulnerable time for the occurrence of structural birth defects.[16]

Our results support previous studies that found PAE to be associated with VSDs and ASDs[17–19] and a recent review that found limited evidence of an association between PAE and renal defects.[20] In our study, the most frequently occurring birth defects in the ARBD category were VSDs and ASDs, and there were clear effects of dose and timing on the expression of those defects. The evidence for inclusion of many of the ARBDs in the IOM criteria is from animal studies or high-risk populations,[1] but the strength of the evidence relating PAE and many of the individual defects is not reported. For example, a recent systematic review of the literature found little evidence of an association between PAE and renal birth defects.[20] Although the findings of this study support that review, the evidence would be strengthened by population-based studies with larger numbers of subjects with heavy exposure levels.

Although 59% of the women in our cohort drank alcohol at some stage during pregnancy, many at heavy levels, the prevalence of the individual birth defects within the category of ARBDs was low. Only 40% of the birth defects classified as ARBDs by the IOM were present in the cohort. Birth defects defined as ARBDs occurred in each PAE group, with almost one-half (47%) occurring in infants born to women who had abstained from alcohol during the first trimester. This indicates the difficulty of reliably attributing these birth defects to alcohol in clinical settings, particularly because the dose, pattern, and timing of PAE are not recorded routinely, which suggests that this information is not sought routinely.

It was suggested recently that adding facial anomalies characteristic of FAS, normal growth, and normal intelligence to the diagnostic criteria for

ARBDs would make the diagnostic criteria more practical for clinical and research settings.[3] The recommended changes to the IOM guidelines represent an attempt to enhance their utility in clinical settings, but additional population-based evidence is required to demonstrate their suitability for monitoring ARBDs in the general population. We agree with the authors of the IOM guidelines[1] that clinicians must exclude other possible diagnoses before attributing a birth defect to PAE, as we did in this study, but the new requirements may be counterproductive and need to be validated before they are introduced into practice.

Alcohol consumption[21] and risky drinking[22] are highly prevalent in women of childbearing age, and almost one-half (47%) of the pregnancies in our cohort were reported to be unplanned.[23] This indicates that a substantial proportion of pregnancies are exposed to alcohol, many at heavy levels, before the awareness of pregnancy and at a critical period of development, which places the fetus at risk of a birth defect consistent with a fetal alcohol spectrum disorder. With the assumption that our results indicate a causal association, heavy PAE in the first trimester is a significant contributor to ARBD-classified birth defects, with an excess risk comparable in magnitude to that of neural tube defects in Australia (1.1–1.6 cases per 1000).[14] A range of strategies are in place to prevent neural tube defects in Australia.[24] In contrast, apart from national guidelines on alcohol use for women who are pregnant or planning pregnancy, national or even statewide prevention strategies addressing maternal alcohol consumption during pregnancy have not yet been realized. Interventions to reduce the prevalence of ARBDs will need to target not only pregnant women but also risky drinking and unplanned pregnancies among all women of childbearing age.[25]

It should be recognized that, although we did not find any association between moderate levels of PAE and birth defects, there is evidence supporting an increased risk of child behavioral problems after this level of exposure.[26] The safest choice for women who are pregnant or planning a pregnancy is to abstain from alcohol.

Strengths of this study include the linkage of the cohort data with the WABDR data to ascertain information on birth defects, which overcomes reporting biases and loss to follow-up. Information on outcomes is reliable and valid, because birth defects are ascertained independently by the WABDR and information regarding birth defect diagnoses was linked with pregnancy information through record linkage. Also, the classification of birth defects for this study was undertaken by a birth defects specialist (Dr Bower) who, with blinding to exposure status, reviewed the descriptive categories for each child with a birth defect. Although children who migrated out of WA were not included, $<1\%$ of the population departed permanently or for long periods in 1995,[27] and there were likely few departures within the first year after birth, when $>87.9\%$ of birth defects are detected.[28] Furthermore, we have no reason to suppose that migration out of WA would be related to maternal alcohol consumption. The data on maternal alcohol consumption were collected at 3 months after birth, and we cannot rule out the possibility of recall bias, because some of the birth defects already would have been recognized. However, because we found only an association between heavy PAE and birth defects, this seems unlikely.

Given that many of the birth defects defined as ARBDs in the IOM guidelines are rare, our limited sample size and stratification across PAE levels restricted the opportunity to observe many individual birth defects. The prevalence of birth defects in this cohort (6.5%) reflects the prevalence for the whole of WA (6.8%) during 1995–1997, and the prevalence of most of the individual birth defects in our cohort mirrored the reported state prevalence.[14] However, the prevalence of microcephaly in this study was 0.2 cases per 1000, lower than the WABDR prevalence of 0.53 cases per 1000. Although the prevalence is similar to the 0.23 cases per 1000 in the Eurocat registries[29] and is not substantially lower than the prevalence of 0.37 cases per 1000 reported for Utah in 2006,[30] this discrepancy may be attributable to sample size. Therefore, it is important that the study be repeated with a larger population sample to confirm the findings and to provide more-detailed information on the effects of PAE on specific birth defects.

CONCLUSIONS

Although a large proportion of women in this cohort consumed alcohol during pregnancy, the prevalence of any of the birth defects classified as ARBDs by the IOM was low (2.3%). A significant fourfold increase in birth defects followed heavy PAE during the first trimester, predominantly attributable to VSDs and ASDs. Screening and documentation of alcohol use by women of childbearing age and pregnant women would enhance surveillance efforts and inform prevention.

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