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Critical Review

Alcohol Use in Pregnancy and Miscarriage: A Systematic Review and Meta-Analysis

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To systematically review and critically evaluate studies reporting alcohol exposure during pregnancy and miscarriage. We searched PubMed, EMBASE, PsycINFO, and ProQuest Theses for publications from January 1970 to January 2019. We identified studies about alcohol exposure during pregnancy and miscarriage. Information about study population, alcohol exposure assessment, outcome definition, covariates, and measures of association was collected. We assessed study quality using an adapted Newcastle-Ottawa Scale. Data were abstracted by 2 investigators independently. We conducted a random-effects meta-analysis to calculate the association between alcohol exposure and miscarriage risk and performed subgroup analyses to determine robustness of results to study differences. For studies reporting dose-specific effects, a pooled dose–response association was estimated using generalized least squares regression with and without restricted cubic spline terms for number of drinks consumed per week. Of 2,164 articles identified, 24 were eligible for inclusion. Meta-analysis of data from 231,808 pregnant women finds those exposed to alcohol during pregnancy have a greater risk of miscarriage compared to those who abstained (odds ratio [OR] 1.19, 95% confidence intervals [CI] 1.12, 1.28). Estimates did not vary by study design, study country, or method of alcohol ascertainment. For alcohol use of 5 or fewer drinks per week, each additional drink per week was associated with a 6% increase in miscarriage risk (OR 1.06, 95% CI 1.01, 1.10). Common study limitations reflect challenges inherent to this research, including difficulty recruiting participants early enough in pregnancy to observe miscarriage and collecting and quantifying information about alcohol consumption during pregnancy that accurately reflects use. This review provides evidence that alcohol consumption during pregnancy is associated with a dose-mediated increase in miscarriage risk. Future studies evaluating change in alcohol use in pregnancy are needed to provide insight into how alcohol consumption prior to pregnancy recognition impacts risk.

Key Words: Alcohol, Drinking, Miscarriage, Pregnancy, Spontaneous Abortion.

MISCARRIAGE OCCURS IN up to 1 in 6 recognized pregnancies (Avalos et al., 2012; Goldhaber and Fireman, 1991; Wilcox et al., 1988), is costly to the healthcare system, and can be emotionally devastating regardless of whether pregnancy was planned (Lok and Neugebauer, 2007; Nikcevic et al., 1998). Though miscarriage is common, few modifiable determinants of pregnancy loss are known. In the United States, 10% of pregnant women and more than 50% of nonpregnant women endorse using alcohol within the past 30 days (Tan et al., 2015). Similarly, studies in other developed countries indicate alcohol use occurs in approximately half of women at pregnancy onset and is prevalent to a lesser extent after recognition (O'Keeffe et al., 2015; Tough et al., 2006). The large number of women exposed to alcohol in pregnancy makes it imperative that we understand the relationship between alcohol use and miscarriage.

While alcohol exposure in pregnancy has been repeatedly linked to adverse outcomes, estimates of alcohol's effect on miscarriage range from protective to increasing risk 3.8-fold. A previous systematic review provides a qualitative summary of the literature about low-to-moderate alcohol consumption in pregnancy and finds 5 of 8 studies suggest alcohol use increases miscarriage risk (Henderson et al., 2007). Our review extends previous work by incorporating all studies of alcohol use in pregnancy and providing a meta-analysis of the association.

In this review, we aimed to systematically review the literature and calculate a summary estimate for the association between alcohol exposure during pregnancy and miscarriage. Research about alcohol use and miscarriage faces

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methodologic challenges including recruiting participants early enough in pregnancy to observe loss, accurately measuring alcohol consumption, and quantifying exposure in a way that is reflective of use (Bailey and Sokol, 2011). Therefore, our secondary objective was to assess the quality of past studies and identify opportunities for future research.

MATERIALS AND METHODS

The literature search, study selection, coding plan, and meta-analysis adhere to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses statement and the MOOSE guidelines for reporting systematic reviews and meta-analysis of observational studies (Liberati et al., 2009; Stroup et al., 2000).

Search Strategy and Study Selection

Studies were identified through searches of electronic databases (PubMed, EMBASE, PsycINFO, ProQuest, and ClinicalTrials.gov) in January 2019 using the following terms: "spontaneous abortion" or "miscarriage" or "pregnancy loss" or "abortion" and "alcohol" or "ethanol" (See Appendix S1 for full search strategy). To ensure capture of all relevant studies, investigators conducted backward and forward citation searches of included studies. Only studies published after January 1, 1970, and available in English were included.

Original studies evaluating the association between alcohol exposure during pregnancy and miscarriage risk were eligible. Exposure was defined as alcohol use during pregnancy, and outcome was miscarriage. Studies that only evaluated preconception alcohol use were excluded. Studies of induced abortions were excluded. Because gestational age threshold for miscarriage varied between studies, we did not exclude based on miscarriage definition, but instead performed sensitivity analyses conditioned on definition.

Titles and abstracts were screened by A.C.S. and one other author (C.L.Y., L.L, or S.Z.). If a study was not excluded by both reviewers at the abstract screening stage, we conducted a full-text review. A full-text review and eligibility decision were made independently by both A.C.S. and S.Z. Discrepancies were adjudicated by S.H.J., who was masked to prior decisions.

Data Extraction

A.C.S. and S.Z. conducted data extraction using standardized forms in REDCap hosted at Vanderbilt University (Harris et al., 2009). Differences were resolved by S.H.J. Data abstraction elements included study design, study years, country, counts of study participants by exposure status and pregnancy outcome, recruitment setting, exposure window, reference group definition, exposure definition and operationalization, miscarriage definition, outcome comparator, crude and adjusted effect estimates and confidence intervals (CI) for the association, and factors included in adjusted models. If a dose–response analysis was performed, crude and adjusted effect estimates were collected for all dose categories. We contacted study authors for missing values (7 of 11 authors provided additional information).

To assess study quality, we used an adapted Newcastle-Ottawa Scale (Table 1), which scores participant recruitment, exposure assessment, outcome assessment, and statistical modeling (Wells et al., 2013). Two reviewers (A.C.S. and S.Z.) collected information about participant inclusion (comparing methods for recruitment of exposed and unexposed in cohort studies and case and control identification for case–control studies), loss to follow-up/nonparticipation rates, average gestational age at recruitment, timing of alcohol exposure assessment (before or after pregnancy outcome), exposure assessment method (self-administered questionnaire or interviewer-conducted survey), assessment of alcohol consumption change during pregnancy, alcohol exposure operationalization, statistical modeling, and covariates included in the adjusted analysis.

Table 1. Adapted Newcastle-Ottawa Scale Quality Domains

Recruitment
Equitable recruitment of exposed and unexposed (cohort studies)
Equitable recruitment of cases and controls (case–control studies)
Recruitment allows for selection of participants representative of general population
Minimal loss to follow-up (<20% loss or <5% nonparticipation rate)
More than 80% of participants recruited prior to 10 weeks' gestation
Outcome ascertainment
Appropriate comparator group (pregnancies surviving past 20 weeks' gestation)
Exposure Ascertainment
Exposure assessed prior to pregnancy outcome to minimize risk of bias (cohort studies)
Exposure assessed through self-administered questionnaires to minimize reporting bias
Study queried change in consumption during pregnancy
Statistical modeling
Alcohol modeled as a time-varying exposure
Adjusted for maternal age ± other confounders
Use of time-to-event analysis

Data Synthesis

We quantified the association between alcohol exposure and miscarriage risk using random-effects meta-analysis. We evaluated alcohol use as both a dichotomous (exposed vs. unexposed) and a continuous variable (number of drinks per week). Random-effects models were used to account for dispersion of true effect across study contexts. Analyses included adjusted data when available. When effect estimates were not reported, odds ratios (OR) were calculated using counts provided in the text. Heterogeneity was assessed using the I^2 statistics, which estimates the proportion of heterogeneity attributable to true between-study differences. We evaluated publication bias using a funnel plot and Egger's regression.

For studies reporting dose-specific effects, we used random-effects meta-analysis to estimate the association between amount of alcohol consumed and miscarriage. We converted alcohol exposure categories to average number of drinks per week. We used the midpoint of each study-specific exposure category, and, for open-ended categories, we divided the interval of the next highest category by 2 and added that value to the lower boundary of the highest category (e.g., if categories were 0, 1 to 4, 5 to 8, and ≥9, doses used in the model would be 0, 2.5, 6.5, and 10.5). We used generalized least squares regression models to perform a random-effects meta-analysis estimating a log-linear trend between alcohol dose and miscarriage risk. This method accounts for nonindependence between effect estimates using the same reference category (i.e., effect estimates for multiple doses in a single study; Greenland and Longnecker, 1992). We evaluated the possibility of a nonlinear relationship between alcohol dose and miscarriage risk using restricted cubic splines (Orsini et al., 2006). We used 3 knots since the inclusion of 4 or more did not improve model fit by the likelihood ratio test and knot placement was determined by Harrell's recommended percentiles (Harrell, 2001). We analyzed studies reporting dose effects in terms of hazard ratios (HR) separately as to not combine estimates that incorporate survival data with those that do not.

For both methods of operationalizing alcohol exposure, we performed a series of subgroup analyses to investigate robustness of

findings to study differences. We evaluated whether findings varied when we restricted the analysis to cohort studies, case–control studies, studies that only included first-trimester miscarriages, studies that included all miscarriages (i.e., excluding the studies that only included first-trimester miscarriages), studies presenting adjusted results, studies that recruited 80% or more of the cohort prior to 10 weeks' gestation, studies with equitable recruitment between study groups (cases and controls for case–control studies and exposed vs. nonexposed for cohort studies), or studies that assessed alcohol use prior to pregnancy outcome.

Analyses were performed in Stata (version 14.2, StataCorp, College Station, TX). We used the "metan" package to estimate aggregate ORs and 95% CIs and the "glst" package to estimate the dose–response effect.

RESULTS

Study Selection and Study Characteristics

We identified 2,136 unique articles. Twenty-four studies were eligible for analysis including 231,808 pregnant women (Fig. 1; Armstrong et al., 1992; Avalos et al., 2014; Borges et al., 1997; Boyles et al., 2000; Buck Louis et al., 2016; Cavallo et al., 1995; Chiodo et al., 2012; Conde-Ferraez et al., 2013; Davis et al., 1982; Dlugosz et al., 1996; Feodor Nilsson et al., 2014; Halmesmaki et al., 1989; Han et al., 2012; Harlap and Shiono, 1980; Kesmodel et al., 2002; Kline et al., 1980; Long et al., 1994; Maconochie et al., 2007; Parazzini et al., 1994; Paszkowski et al., 2016; Rasch, 2003; Windham et al., 1992, 1997; Xu et al., 2014). If data from the same study sample were present in multiple reports (Andersen et al., 2012; Avalos et al., 2009; Kline et al., 1981; Strandberg-Larsen et al., 2008; Zhang and Bracken, 1996), the report with the most complete information was used. Fourteen were cohort studies, and 10 were case–control studies (Table 2). The United States contributed the largest proportion of studies (38%), followed by Denmark (13%) and the United Kingdom (13%). Included studies were published between 1980 and 2016, and sample size ranged from 161 to 89,339 participants.

Twelve of the 20 studies reporting an effect estimate found some level of alcohol exposure was associated with an increased risk of miscarriage (Table S1). Studies varied in methods for assessing alcohol use in pregnancy and measuring risk. Participants in 13 studies were asked to report the average number of drinks they consumed in a typical week or day, while 6 studies classified alcohol as a dichotomous exposure. Other studies collected more granular information about alcohol use whether that be daily use reported in a self-administered questionnaire (Buck Louis et al., 2016), daily use in the past 2 weeks reported at each prenatal visit (Chiodo et al., 2012), or total number and type of drinks consumed since last menstrual period (Avalos et al., 2014).

Risk of Bias

Included studies scored between 2 and 8 of 9 on the Newcastle-Ottawa Scale (higher scores reflecting better study

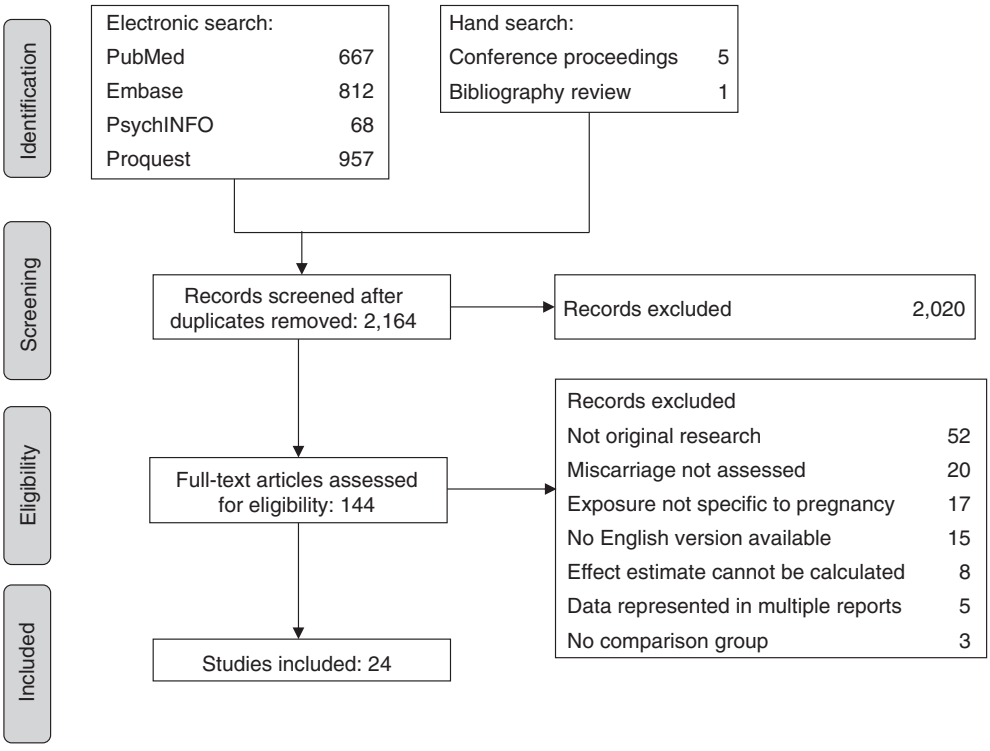

Fig. 1. Flow diagram of studies identified for the systematic review.

Table 2. Characteristics of Studies in Systematic Review

Author, year	Study design	Country	Study years	n (SAB/no SAB)	Recruited population	Exposure ascertainment	Miscarriage definition[a]	Comparator
Armstrong, 1992	Cohort	Canada	1982 to 1984	47,146 (10,191/36,955)	Women delivering or receiving care for SAB across 11 hospitals	In-person interview for first-trimester exposure in index and prior pregnancies	<28	Births
Avalos, 2014	Cohort	United States	1996 to 1998	1,061 (172/889)	KPNC members with record of a positive pregnancy test prior to 10 weeks' gestation	In-person interview prior to 15 weeks' gestation	≤20	Pregnancies surviving past 20 weeks
Borges, 1997	Cohort	Mexico	1988	4,634 (197/4,437)	Women with a prior pregnancy randomly surveyed in urban areas of Mexico	In-person interview for alcohol consumption in most recent pregnancy	–	Pregnancies not ending in SAB
Boyles, 2000	Case–Control	United States	1995 to 1997	970 (400/570)	Women presenting to the emergency department before 22 weeks' gestation	In-person interview during emergency department visit	≤22	Pregnancies surviving past 22 weeks
Buck Louis, 2016	Cohort	United States	2005 to 2009	344 (98/246)	Couples discontinuing contraception with the intention of becoming pregnant	Daily lifestyle journals preconception through 7 weeks postconception	≤22	Pregnancies surviving past 22 weeks
Cavallo, 1995	Cohort	Italy	–	527 (55/472)	Women at first blood test during pregnancy	In-person interview during hospital visit	–	Live births
Chiodo, 2012	Cohort	United States	1999 to 2001	302 (23/279)	Women initiating prenatal care before 28 weeks' gestation at urban clinics	In-person interview repeated at each prenatal visit	≤20	Pregnancies surviving past 20 weeks
Conde-Ferraez, 2013	Case–Control	Mexico	2008 to 2009	281 (143/138)	Women receiving curettage for SAB (cases) or delivering at term (controls)	In-person interview during hospitalization	≤20	Live, term births
Davis, 1982	Cohort	UK	1980	973 (22/951)	Women at booking prenatal visit at study hospital	Self-administered questionnaire at booking visit	–	Stillbirths and live births
Dlugosz, 1996	Cohort	United States	1988 to 1992	2,839 (135/2,704)	Women initiating prenatal care before 16 weeks' gestation	At-home interview before 17 weeks' gestation about exposure in first month	<28	Live births
Feodor Nilsson, 2014	Cohort	Denmark	1996 to 2002	89,339 (3,018/86,321)	DNBC women initiating prenatal care before 22 weeks' gestation	CATI targeted for 12 weeks' gestation	≤22	Pregnancies surviving past 22 weeks
Halmesmaki, 1989	Case–Control	Finland	–	161 (80/81)	Women presenting to hospital for SAB (cases) or prenatal ultrasound (controls, gestational age-matched)	In-person interview at hospitalization	–	Live, term births
Han, 2012	Cohort	South Korea	–	3,507 (254/3,253)	Women participating in the Korean Motherisk Program	Self-administered questionnaire repeated at each prenatal visit	–	Pregnancies surviving past SAB cutoff
Harlap, 1980	Cohort	United States	1974 to 1977	32,019 (1,503/30,516)	KPNC members initiating prenatal care before 28 weeks' gestation	Self-administered questionnaire during prenatal care	<28	Pregnancies surviving past 28 weeks

Continued.

Table 2. (Continued)

Author, year	Study design	Country	Study years	n (SAB/no SAB)	Recruited population	Exposure ascertainment	Miscarriage definition[a]	Comparator
Kesmodel, 2002	Cohort	Denmark	1989 to 1996	24,663 (321/24,342)	Women initiating prenatal care before 8 weeks' gestation at participating hospital	Self-administered mailed questionnaire (median GA 14.7 weeks)	≤28	Pregnancies surviving past 28 weeks
Kline, 1980	Case–Control	United States	1974 to 1978	1,248 (616/632)	Women presenting to hospital for SAB (cases) or for non-SAB pregnancy outcome (controls, age-, and hospital-matched)	Interview at pregnancy outcome	–	Pregnancies surviving past 28 weeks
Long, 1994	Case–Control	UK	–	3,443 (95/3,348)	Consecutive women presenting with SAB or singleton live births past 28 weeks' gestation (controls)	Interview at admission for SAB (cases) or at first prenatal clinic visit (controls)	<13	Live births occurring past 28 weeks
Maconochie, 2007	Case–Control	UK	1980 to 2001	6,458 (569/5,889)	Women responding to a postal survey indicating their most recent pregnancy ended in first-trimester SAB (cases) or survived past 13 weeks (controls)	Self-administered postal survey in 2001 (pregnancies since 1980 included)	<13	Pregnancies surviving past 13 weeks
Parazzini, 1994	Case–Control	Italy	1990 to 1993	1,276 (462/814)	Women presenting to hospital for SAB (cases) or delivery (controls, hospital-matched)	In-person interview during hospitalization for pregnancy outcome	<13	Live, term births (normal weight and Apgar score)
Paszkowski, 2016	Cohort	Poland	2001 to 2004	242 (105/137)	Women hospitalized for threatened abortion	Self-administered questionnaire	–	Live, term births
Rasch, 2003	Case–Control	Denmark	1994 to 1996	1,454 (320/1,134)	Women hospitalized for a D&C for SAB (cases) or women initiating prenatal care and between 6 and 16 weeks of gestation (controls)	Self-administered questionnaire during hospitalization (cases) or during first prenatal visit (controls)	6 to 16	Pregnancies surviving past 16 weeks
Windham, 1992	Case–Control	United States	1986 to 1987	1,919 (623/1,296)	Women presenting to hospital for SAB (cases) or delivery (controls, hospital-, and LMP-matched)	CATI after pregnancy outcome	<20	Live births
Windham, 1997	Cohort	United States	1990 to 1991	5,142 (500/4,642)	KPNC member initiating prenatal care before 12 weeks' gestation	Telephone interviews within 2 weeks of scheduling first prenatal visit	≤20	Pregnancies surviving past 20 weeks
Xu, 2014	Case–Control	China	2009 to 2012	1,860 (620/1,240)	Women presenting to hospital for SAB (cases) or attending prenatal care past 13 weeks' gestation (controls, age-matched)	In-person interview within week of loss (cases) or during gestation (controls)	<13	Pregnancies surviving to 13 weeks

KPNC, Kaiser Permanente Northern California; DNBC, Danish National Birth Cohort; D&C, dilation and curettage; LMP, last menstrual period; CATI, computer-assisted telephone interview; – represents missing data.

[a]Reported as gestational age used to define miscarriage.

quality; Fig. S1). Some deducted quality domains may have been met, but were not counted if the publication lacked sufficient information for scoring. Twelve of 24 studies assessed alcohol exposure after pregnancy outcome. Fifteen of 24 collected information about alcohol exposure through interviews, while the remainder used self-administered questionnaires. Out of the 14 cohorts, 6 recruited the majority of participants in the first trimester or preconception. In 8 of 10 case–control studies, cases were recruited when receiving emergency care and controls were recruited at birth. Neither visual inspection of the funnel plot nor Egger's regression were suggestive of publication bias (Fig. S2; Egger's regression *p*-value 0.96).

Synthesis of Results

In our meta-analysis of the association between alcohol use and miscarriage, exposed pregnancies were 19% more likely to end in miscarriage (OR 1.19, 95% CI 1.12, 1.28; Fig. 2). There was significantly less between-study heterogeneity among cohort studies compared to case–control studies (I^2: 12.3%, 95% CI 0.0%, 34.7% [low heterogeneity] vs. 69.1%, 95% CI 56.8%, 77.9% [moderately high heterogeneity]). Pooled estimates among cohort and case–control studies were similar (OR 1.22, 95% CI 1.16, 1.28 vs. OR 1.20, 95% CI 1.01, 1.43; Table 3). Only 3 studies reported an adjusted risk estimate for the effect of alcohol operationalized as a dichotomous exposure (exposed/unexposed; Borges et al., 1997; Boyles et al., 2000; Kline et al., 1980).

Seventeen studies reported dose-specific effects of alcohol on miscarriage risk. We pooled studies using survival and nonsurvival estimates separately so only like measures were combined. In the random-effects meta-analysis of the 12 studies using nonsurvival data, there was a dose-dependent relationship between alcohol use and miscarriage (Fig. 3 [spline model], Table S2). For alcohol use in pregnancy of 5

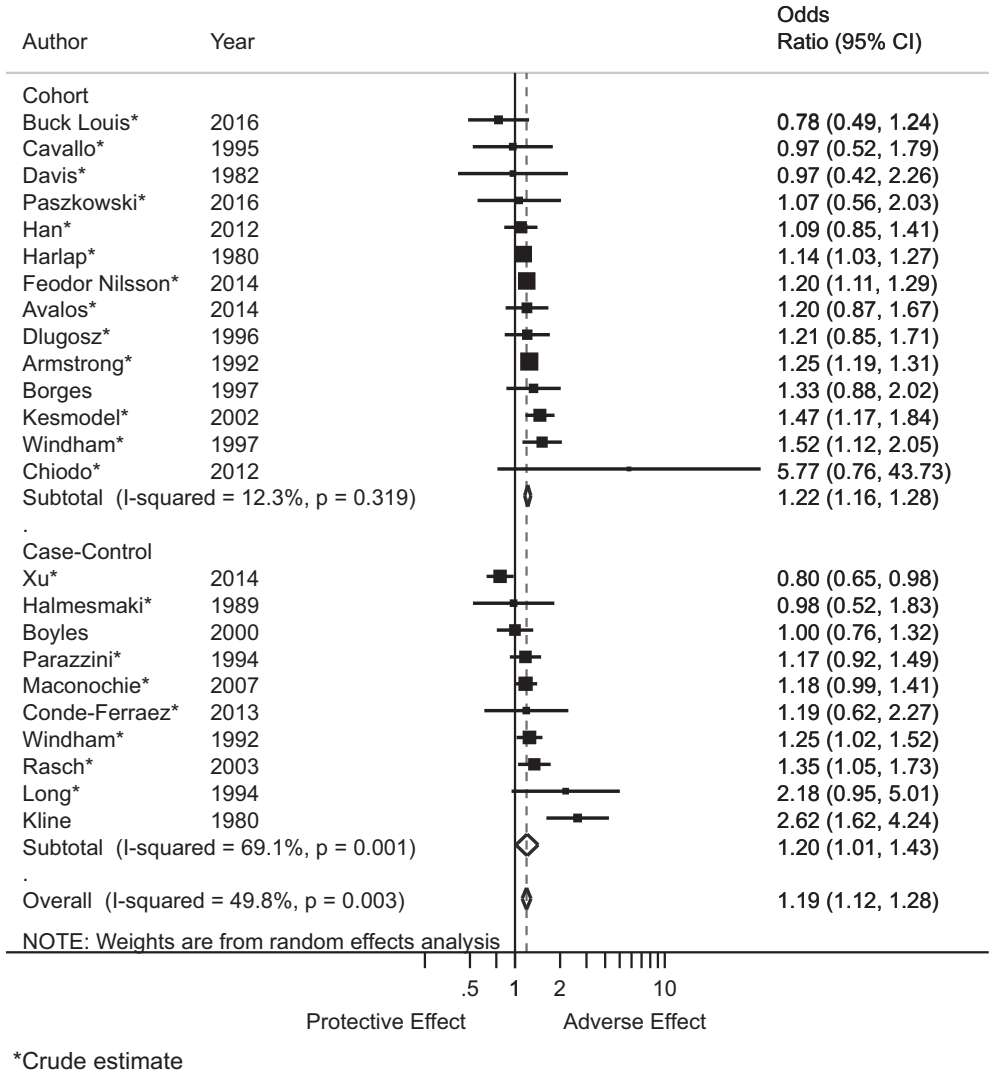

Fig. 2. Forest plot for the association between alcohol exposure during pregnancy and risk of miscarriage with subgroup estimates by study design. Size of point estimate markers indicates weight in meta-analysis. OR, odds ratio; CI, confidence interval.

Table 3. Association Between Alcohol Use During Pregnancy and Miscarriage, Subgroup Analyses

Analysis	Number of Studies	OR	95% CI	τ^2
All eligible studies	24	1.19	1.12, 1.28	0.004
Cohort studies	14	1.22	1.16, 1.28	0.001
Case–control studies	10	1.20	1.01, 1.43	0.045
Studies only including first-trimester miscarriages	5	1.09	0.89, 1.33	0.033
Studies including all miscarriages	18	1.23	1.15, 1.31	<0.001
Studies with adjusted estimates	3	1.48	0.86, 2.53	0.185
Studies with majority of participants recruited in the first trimester	8	1.17	1.03, 1.33	0.009
Studies with equitable recruitment between study groups	14	1.19	1.12, 1.27	0.001
Studies that assess alcohol use before pregnancy outcome	11	1.20	1.11, 1.30	0.004

CI, confidence interval; OR, odds ratio.

Table 4. Risk of Miscarriage for Each Additional Drink Per Week in Pregnancy from Studies not Using Survival Data, Linear Model, Subgroup Analyses

Analysis	Number of studies	OR[b]	95% CI	τ^2
All eligible studies[c]	12	1.06	1.01, 1.10	0.004
Cohort studies	6	1.03	1.02, 1.03	<0.001
Case–control studies	6	1.09	0.96, 1.23	0.023
Studies only including first-trimester miscarriages	4	1.02	1.00, 1.04	<0.001
Studies including all miscarriages	8	1.07	1.02, 1.13	0.005
Studies with adjusted estimates	9	1.05	1.00, 1.11	0.005
Studies with majority of participants recruited in the first trimester	2	1.05	1.01, 1.10	<0.001
Studies with equitable recruitment between study groups	6	1.03	1.01, 1.04	<0.001
Studies that assess alcohol use before pregnancy outcome	5	1.03	1.01, 1.04	<0.001

CI, confidence interval; OR, odds ratio.
[a]Estimates from survival data evaluated separately.
[b]Log-linear estimate valid for alcohol use of 5 or fewer drinks per week.
[c]Armstrong and colleagues (1992), Cavallo and colleagues (1995), Chiodo and colleagues (2012), Davis and colleagues (1982), Dlugosz and colleagues (1996), Harlap and Shiono (1980), Kline and colleagues (1980), Long and colleagues (1994), Maconochie and colleagues (2007), Parazzini and colleagues (1994), Rasch (2003), Windham and colleagues (1992).

or fewer drinks per week, each additional drink per week was associated with a 6% increase in risk (OR 1.06, 95% CI 1.01, 1.10 [log-linear model]). Estimates were similar when comparing results from cohort and case–control studies and when restricting analysis to studies that fulfilled key risk of bias domains (Table 4). The pooled effect was lower among studies restricted to only first-trimester miscarriages when compared to studies that included all miscarriages (OR 1.02, 95% CI 1.00, 1.04 vs. OR 1.07, 95% CI 1.012, 1.13). When aggregating the 5 studies reporting dose-specific effects using survival data, each additional drink per week in pregnancy is associated with a 13% increase in miscarriage hazard (HR 1.13, 95% CI 1.04, 1.22). Subgroup analyses by miscarriage definition could not be carried out for survival data estimates due to the limited number of studies.

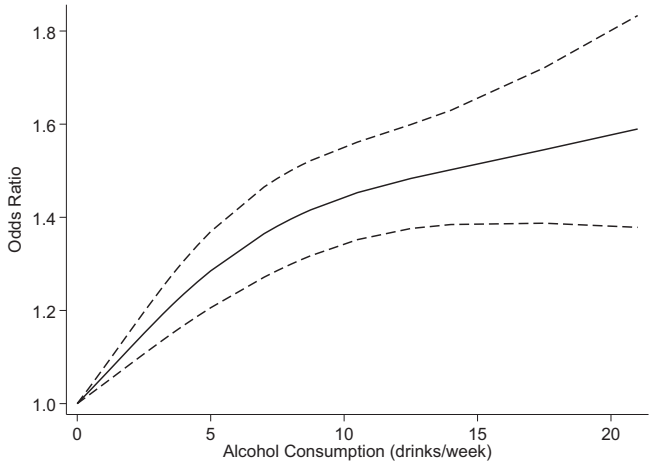

Fig. 3. Dose–response trend for average number of alcoholic drinks per week during pregnancy and miscarriage risk, spline model. Dashed lines represent the 95% confidence interval, and knots selected using Harrell's recommended percentiles located at 0, 3.5, and 14 drinks per week.

DISCUSSION

Main Findings

In this systematic review of alcohol use during pregnancy and miscarriage, we found exposure is associated with a dose-dependent increase in risk. The most common limitations observed in this literature included imperfect capture of pregnancies ending in miscarriage and oversimplified methods for classifying alcohol use during pregnancy. Public health entities recommend complete abstinence for women who are or could become pregnant (Green et al., 2016; U.S. Department of Health and Human Services, 2005), yet 8 to 20% of women drink alcohol during pregnancy and more than half are exposed in early gestation (McCormack et al., 2017; Popova et al., 2017; Substance Abuse and Mental Health Services Administration, 2013; Tan et al., 2015; Tough et al., 2006). Despite the stated limitations, this review of 24 studies affirms previous guidance that no amount of alcohol exposure is known to be safe and provides specific information about incremental risk for each additional drink per week consumed.

We aimed to capture literature with data about the relationship between alcohol and miscarriage in this review. A past systematic review described significantly increased risk among women with low-to-moderate alcohol use in 5 of 8 identified studies (Henderson et al., 2007). The present review includes an additional 16 studies and alcohol use was significantly associated with miscarriage in more than half of the reports, though individual effects varied in magnitude.

The aggregate risk estimate was attenuated compared with a meta-analysis of 3 studies (OR 1.35 vs. 1.19; total N 3,156 vs. 231,808; Makarechian et al., 1998). Unlike this prior meta-analysis, we required included studies to evaluate miscarriage as an outcome independent of stillbirth and we estimated the dose–response risk relationship.

Considerations

Since most miscarriages occur in early pregnancy (Avalos et al., 2012), enrolling women soon after pregnancy detection is critical for capturing a representative sample of miscarriages. Six of the 14 cohort studies in this review either did not recruit most participants within the first trimester or did not report average gestational age at enrollment. This limits the generalizability of findings for very early losses. Recruitment was also limited in case–control studies. Eight of the 10 depended upon hospital-based recruitment of miscarriages, which may lead to selection bias since up to 75% of women opt for expectant management of miscarriage and never receive emergency or inpatient care (Luise et al., 2002). Finally, we are unable to comment on the relationship between alcohol and the estimated 1 in 5 pregnancies to end prior to detection (Wilcox et al., 1988) since the studies in this meta-analysis only included recognized pregnancies.

Exposure to alcohol was collected through maternal self-report in all studies. Alcohol use during pregnancy is stigmatized, and desirability bias, or the tendency to respond in a way viewed favorably by others, may impact reporting (Bailey and Sokol, 2011). Degree of social desirability bias depends on method of data collection and sense of anonymity, with bias being stronger for in-person interviews than self-administered questionnaires (Bowling, 2005; Ernhart et al., 1988). Eight of the included studies assessed alcohol exposure through self-administered questionnaires, while others used in-person or telephone interviews. Data collection regarding alcohol use in early pregnancy is logistically difficult and often takes place after miscarriage occurs even in cohort studies, making recall bias a common vulnerability (Bailey and Sokol, 2011; Feldman et al., 1989). Generally, women who experience an adverse pregnancy outcome are more likely to report exposure (Rockenbauer et al., 2001), but the stigma attached to alcohol use in pregnancy makes the direction of reporting bias difficult to anticipate and may vary from woman to woman (Del Boca and Darkes, 2003). While self-report is currently the best method for measuring alcohol use, it is important to interpret findings in light of these limitations.

Alcohol use is generally classified as number of drinks consumed per week. This convention does not capture number of drinking episodes per week, episodic dose, or binge drinking. A prior review of moderate alcohol use and binge drinking and pregnancy health found few studies reported on miscarriage risk and those that did report inconsistent effects (Meyer-Leu et al., 2011). Further investigation of how these factors influence risk of miscarriage is warranted. Methods for determining amount of alcohol consumed did not uniformly account for alcohol content by liquor type and drink size. Both pregnant women and women in the general population tend to overestimate the size of a standard drink (Kaskutas and Graves, 2001; Kerr et al., 2005). On average, alcohol content of a drink as judged by women in the general population is 43% more than a standard drink (Kerr et al., 2005). As a result, dose categories used in the dose–response analysis likely approximate true exposure to varying degrees. Imprecision in alcohol dose assignment would diminish the ability to precisely estimate a dose–response relationship. Additionally, 3 of the 17 studies with information about dose-specific effects were not adjusted for potential confounders. Nonetheless, the subgroup analysis of studies with adjusted estimates did not differ from the estimate including all dose-specific effects (OR 1.05 vs. 1.06).

Since only 2 studies reported miscarriage risk by alcohol type, we could not provide a pooled estimate for how this characteristic relates to risk. One study indicated women who drank only spirits during pregnancy had a greater than 2-fold risk of miscarriage compared to abstainers, while drinking only wine, only beer, or a combination of alcohol types was not associated with increased miscarriage risk (Avalos et al., 2014). The other study did not detect an association between number of glasses of wine or total alcoholic beverages per week and miscarriage risk (Parazzini et al., 1994).

Timing of alcohol exposure during pregnancy likely plays a critical role in determining risk of miscarriage (Hertz-Picciotto et al., 1996), but there is no consensus on how to leverage this information when measuring risk. More than half of the women consume alcohol during pregnancy, but most quit or sharply decrease their consumption upon pregnancy recognition (Day et al., 1993; McCormack et al., 2017; Pryor et al., 2017). While half of the studies in this review assessed whether a change from prepregnancy alcohol use occurred, this information was seldom incorporated into measures of association. Most commonly, alcohol use was classified as consumption after pregnancy recognition, while some studies calculated an across-pregnancy average. These approaches are limited since the first neglects the effect of early alcohol exposure and the second disregards that most use occurs in early gestation and then rapidly tapers after pregnancy detection. One study evaluated risk by week of exposure and demonstrated that consuming 3 or more beverages in weeks 8 through 10 of pregnancy conferred the most risk (Windham et al., 1997). Kline and colleagues measured the effect of duration of alcohol use in pregnancy and found that each additional day of exposure increased relative risk of miscarriage by 3% (1981). Five studies included in this review described risk associated with prepregnancy alcohol use in a separate analysis, with discordant results. Two additional studies found that periconceptional use was not associated with miscarriage (Gaskins et al., 2016) or only associated with risk at very high levels of exposure (greater than 10 drinks per week; Henriksen et al., 2004). Since "prepregnancy" alcohol use may persist into early gestation

to varying extents, evaluating these behaviors separately likely fails to tell the whole story. Future studies investigating alcohol use before and after a change in consumption occurs and timing of that change could provide more specific information about the ramifications of timing of pregnancy awareness and alcohol use cessation.

CONCLUSION

This review provides evidence that alcohol use during pregnancy increases risk of miscarriage and the relationship is dose-dependent. These findings align with public health guidance that no amount of alcohol during pregnancy is known to be safe. Our results also suggest incremental decreases in alcohol exposure dose may translate to risk reduction. Information about how pattern of alcohol use in early pregnancy influences risk is scarce. Most women reduce or quit consuming alcohol after pregnancy detection, and risk likely depends on when in gestation alcohol use occurs. Future studies that prioritize recruitment of participants early in gestation and use more sophisticated methods for incorporating information about pattern of exposure into measures of risk would provide needed insight into how timing of alcohol use in pregnancy relates to miscarriage.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Full search strategy.

Table S1. Methods and main findings of studies on alcohol use during pregnancy and miscarriage.

Table S2. Risk of miscarriage by number of alcohol drinks per week in pregnancy, estimates from spline model.

Figure S1. Summary of risk of bias based on adapted Newcastle-Ottawa Scale.

Figure S2. Funnel plot of estimates from included studies with Egger's linear regression.