Benzodiazepine Use During Pregnancy Alone or in Combination With an Antidepressant and Congenital Malformations:
Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To summarize the effects of antenatal benzodiazepine exposure as monotherapy and in combination with antidepressants on the risk of congenital malformations.

Data Sources: MEDLINE, PsycINFO, CINAHL, Embase, and the Cochrane Library were searched from inception to June 30, 2018, using controlled vocabulary and keywords (eg, *prenatal, benzodiazepines, malformation*).

Study Selection: English-language cohort studies with prospectively collected data on the risk of malformations in benzodiazepine-exposed and -unexposed offspring were evaluated. 23,909 records were screened, 56 studies were assessed for eligibility, and 8 studies were included.

Data Extraction: Quality was assessed by 2 independent reviewers and data extracted. Random-effects models were used for outcomes (≥ 3 studies). Subanalyses examined effect of potential moderators including study quality and timing of exposure, among others.

Results: Prenatal benzodiazepine use was not associated with an increased risk of congenital malformations (odds ratio [OR] = 1.13; 95% CI, 0.99 to 1.30, 8 studies, n = 222/5,195 exposed and 64,335/2,082,467 unexposed), including with first trimester exposure specifically (OR = 1.08; 95% CI, 0.93 to 1.25, *P* = .33; 5 studies, n = 181/4,331 exposed and 64,308/2,081,463 unexposed). There was no significant association with cardiac malformation following exposure (OR = 1.27; 95% CI, 0.98 to 1.65, *P* = .07; 4 studies, n = 61/4,414 exposed and 19,260/2,033,402 unexposed). However, concurrent use of benzodiazepine and antidepressants during pregnancy was associated with a significantly increased risk of congenital malformations (OR = 1.40; 95% CI, 1.09 to 1.80, *P* = .008; 3 studies).

Conclusions: Benzodiazepine exposure during pregnancy does not appear to be associated with congenital malformations or with cardiac malformations specifically. There may be an increased risk of congenital malformations when benzodiazepines are used in conjunction with antidepressants, suggesting that caution with this combination is warranted.

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Clinical Points

- Benzodiazepines have not been found to be teratogenic overall in previous work but have been associated with specific malformations in retrospective studies.
- Our systematic review and meta-analysis replicated previous work concluding that benzodiazepines are not teratogenic. Further, we found that benzodiazepines are not associated with cardiac malformations.
- Benzodiazepines in combination with antidepressants appear to convey an increased risk for major malformations, although the clinical significance appears low.

While anxiety treatment recommendations and prescribing patterns have shifted in recent years away from benzodiazepine therapy to newer antidepressants,[1,2] benzodiazepines continue to be used frequently for anxiety disorders.[3] Importantly, benzodiazepines are often used concurrently with antidepressants at the beginning of treatment with an antidepressant for depression when anxiety is a prominent feature[4] or as augmentation/combination with an antidepressant, for example, when depression is comorbid with anxiety disorders.[5] Anxiety disorders are common in pregnancy, with rates up to 15% being reported,[6] and they are often comorbid with depression, rendering them even more common.[7,8] This leaves women with a treatment conundrum as to the choice of whether to use benzodiazepines during pregnancy, as monotherapy or in combination with an antidepressant. In addition, given the frequent use of medications in women compared to men[9,10] and in reproductive-aged women,[11] women may have

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exposure without awareness during the first trimester, when organogenesis is taking place. Benzodiazepines were found to be the third most frequently used psychotropic drug in pregnancy (following selective serotonin reuptake inhibitors and benzodiazepine-like medications),[12] and a recent large cohort study reported a rate of prenatal benzodiazepine use of 2.5%, with 84% of use occurring in the first trimester.[13] Due to conflicting results across studies, it is unknown if benzodiazepine exposure during pregnancy is associated with an increased risk of congenital malformations. While 2 meta-analyses (one with > 1,000,000 women[14,15]) suggested nonteratogenicity with benzodiazepine use in general, retrospective studies have indicated an increase in congenital malformations[16,17] and in oral clefts specifically, suggesting an almost 2-fold risk (odds ratio [OR] = 1.79)[14,18] in an examination of case-control studies. Moreover, although combination treatment may be used, subsequent risks are unknown. Newer data are now available, including data on the risk of cardiac anomaly and the combined use of benzodiazepines and antidepressants in pregnancy specifically. Up-to-date information about risks constitutes a critical component of the risk-benefit profile that clinicians and patients require to inform their treatment decisions.

The aim of this study was to reevaluate the risk of congenital malformations following exposure to benzodiazepines. To minimize bias,[19] we assessed prospectively collected data from cohort studies comparing malformations in benzodiazepine-exposed and -unexposed pregnancies. We conducted a systematic review and meta-analysis where possible on the risk of antenatal benzodiazepine exposure and congenital malformations in the infant, including cardiac malformations. Potential effect modifiers as sources of heterogeneity were also assessed through subanalyses. The effect of benzodiazepines combined with an antidepressant, which to our knowledge has not been previously summarized, was also evaluated.

METHODS

Search Strategy

This work followed the guidelines of the Meta-Analyses and Systematic Reviews of Observational Studies,[20] using methods previously described.[21] Briefly, as part of a broader study of the impact of prenatal anxiety and prenatal use of anxiety-related medications, 2 psychopharmacology and psychiatry experts in library science independently conducted literature searches. One librarian searched Ovid MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, PsycINFO, CINAHL, Embase, and the Cochrane Library from their start date to June 30, 2018, using keywords that included *antianxiety agents, anxiolytic, benzodiazepine, antenatal, congenital anomaly, congenital malformation,* and *malformation,* among others (full search strategy available from the authors upon request). The second librarian used an iterative process to develop and test their search strategy in consultation with the review team. Strategies utilized a combination of keywords (eg, *prenatal, anxiolytics*) and

Figure 1. Flow Diagram of Study Identification, Selection, and Reasons for Exclusion in Systematic Review
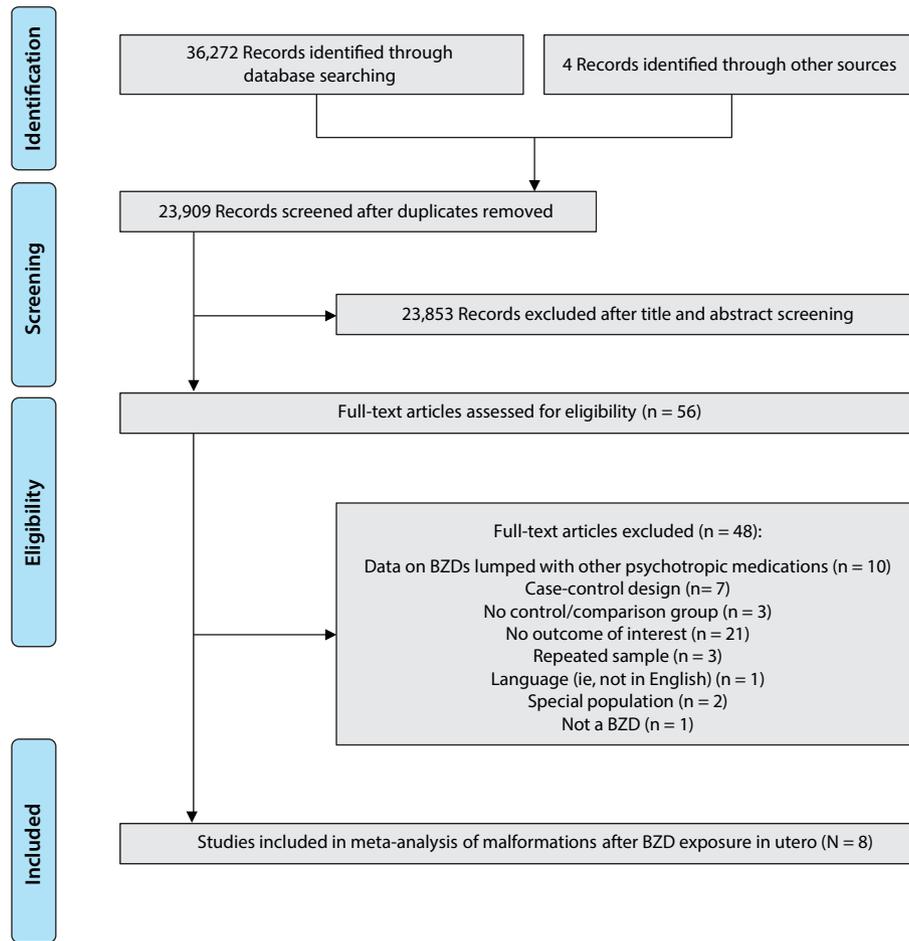
Abbreviation: BZD = benzodiazepine.

controlled vocabulary (eg, "Pregnancy," "Anti-Anxiety Agents"), and vocabulary and syntax were adjusted across databases as needed. Prior to execution, this strategy was reviewed by another senior information specialist using the Peer Review for Electronic Search Strategies checklist.[22] Results were limited to the English language, human studies, and non-opinion pieces. We also searched reference lists from reviews, meta-analyses, and the final selection of included articles. The PRISMA checklist for reporting systematic reviews and meta-analyses was followed[23] and reported in Figure 1.

Inclusion and Exclusion Criteria

Cohort studies that provided original, prospectively collected data on congenital malformations in a benzodiazepine-exposed and -unexposed comparison group were eligible. Acceptable assessment of benzodiazepine exposure included either a prescription for a benzodiazepine or notation of benzodiazepine use in maternal/clinical charts. For cases in which a sample was repeated in more than one publication, the article with the largest sample size was included. Studies presenting only data lumping

benzodiazepines with other psychotropic medication(s) and case-control studies were excluded. Due to the volume of potentially eligible studies, unpublished data, abstracts, and conference proceedings were also excluded. Eligible studies that did not have outcome data comparable from at least 2 other studies were excluded (ie, minimum of 3 studies).

Quality Assessment and Data Extraction

Our team developed methods for quality assessment and data extraction, described in detail elsewhere.[24] Briefly, independent quality assessments used the Systematic Assessment of Quality in Observational Research (SAQOR), which was adapted from the Downs and Black[25] checklist and the Newcastle-Ottawa Scale.[26] Quality categories included (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences/control for confounders. Combined with a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[27] SAQOR assessments provided each article with a quality rating of high, moderate, low, or very low quality. Ratings were then further classified as either "above quality threshold" (high, moderate, and low

Table 1. Characteristics of Studies Included in the Meta-Analysis of Prenatal Benzodiazepine Use and Risk of Congenital Malformations

Article/Country	Data Source	Exposure/Sample Size	Exposure Details	Variables Adjusted	Outcome Definitions	Results
Ban et al, 2014[32], United Kingdom[a]	Inclusion: singleton live births, whose mothers were 15–45 years of age during 1990–2010 in a UK primary care database Exclusion: women with bipolar disorder, schizophrenia (and other psychotic disorders), or epilepsy or prescriptions of antiepileptic drugs during pregnancy; genetic anomalies or from known teratogens	Diazepam in 1st trimester: n = 1,159 Not exposed to diazepam in 1st trimester + no depression or anxiety: n = 351,785 (Also provide data comparing to nonexposed in 1st trimester + diagnosed depression and/or anxiety)	Diazepam, prescribed 4 weeks before estimated onset of LMP up to 12 weeks after (other drugs listed as well) Indications: diagnosed anxiety, depression, insomnia; taken from medical records Mean drug dose unknown, but analysis for high dose provided "Presence or absence of… prescription" (p e100996) Use of AD excluded unless specified in specific analysis	Maternal age, calendar year of birth, maternal smoking, BMI, SES	Any MCA, ICD codes Heart-specific MCA (other MCAs reported as well) (Data extracted from database)	Diazepam and MCA: 31/1,159 in diazepam-exposed vs 9,368/351,785 in unexposed (AR = 267 per 10,000 vs 266 per 10,000); aOR = 1.02 (99% CI, 0.63 to 1.64) MCA for diazepam + AD: aOR = 1.07 (99% CI, 0.53 to 2.17) Diazepam and heart MCA: 12/1,159 vs 2,642/351,785 (AR = 104 per 10,000 vs 75 per 10,000); aOR = 1.34 (99% CI, 0.63 to 2.86) (Provide separate analysis comparing BZD use to unmedicated depression or anxiety in 1st trimester, MCA NS) (Provide sensitivity analyses for high-dose [≥ 15 mg/d] diazepam and for restricting to women with ≥ 2 prescriptions: similar effect noted as in main analysis, with overlapping 99% CIs)
Hartz et al, 1975[33], United States[b]	Inclusion: pregnant women, from 12 university-affiliated hospitals, 1958 to 1966, sampling criteria of the Collaborative Perinatal Project Exclusion: abortions (before end of 5th lunar month); prenatal rubella; multiple pregnancies; nonwhite, black, or Puerto Rican ethnic group; and missing data	Chlordiazepoxide in early pregnancy ("first 4 lunar months"): n = 257 Exposed to chlordiazepoxide in late pregnancy (from the fifth lunar month of pregnancy onward): n = 483 Not exposed to chlordiazepoxide: n = 48,412	Interviewed mothers at entry, report of use in pregnancy and month before the last menses, and interviewed at 4-week intervals throughout pregnancy. "With few exceptions," medication histories confirmed by attending physician/review of hospital/clinic record Indication: "Ostensibly, the indication for… chlordiazepoxide is anxiety" noted (but diagnosis not confirmed) Mean drug dose unknown Pattern of use unknown Use of other psychotropics unknown	Unadjusted data used in analyses Maternal age, child's sex and birth weight, pregnancy duration, single umbilical artery, hypertension during pregnancy/toxemia signs, hemorrhage and placental factors, vena cava syndrome, hydramnios, maternal cardiovascular disease, diabetes mellitus, hyperthyroidism and other endocrine disorders, syphilis, convulsive disorder, pelvic or abdominal x-ray exposure, and family history of congenital defects (first-order relatives)	Congenital malformations (Children examined at birth and yearly until 8th birthday)	Early pregnancy exposure: 11/257 in exposed vs 2,179/48,412 in unexposed: SRR = 0.8 (95% CI, 0.4 to 1.6) Late pregnancy exposure: 30/483 in exposed vs 2,179/48,412 in unexposed: SRR = 1.2 (0.8 to 1.7)
Källén et al, 2013[34], Sweden[a]	Inclusion: Swedish Medical Birth Register data, 1996–2011 Exclusion: none stated	BZD in 1st trimester: n = 1,932 Not exposed to BZD in 1st trimester: n = 1,573,915	At first antenatal visit (weeks 10–12 typically), during midwife interview, patient interviewed regarding drug use since becoming pregnant Indication not stated Mean dose unknown No. of prescriptions unknown Use of other psychotropics possible	Year of birth, maternal age, parity, smoking, and BMI	"Relatively severe" malformations (CMs) (Common conditions and conditions of little clinical importance excluded) Any cardiovascular defect Data from medical birth register + register of birth defects + hospital discharge register; data linked	CM: aOR = 1.11 (95% CI, 0.92 to 1.35), P > .05 CM for BZD + AD: OR = 1.36 (1.01 to 1.83), P < .05 Cardiac: aOR = 1.25 (0.92 to 1.71), P > .05 Also provide CM for BZD and other combinations and for cardiovascular defect

(continued)

Table 1 (continued).

Article/Country	Data Source	Exposure/Sample Size	Exposure Details	Variables Adjusted	Outcome Definitions	Results
Laegreid et al, 1992[35], Sweden[a]	Inclusion: patients at general maternity outpatient unit and at the 2 delivery departments, May 1984 to August 1986. Reference group was randomly selected from 3 maternal welfare centers, with no history of psychiatric disease and negative for metabolites of BZD. Exclusion: maternal report of the use of illicit drugs or alcohol abuse	BZD + psychiatric disease (oxazepam, diazepam, or lorazepam): n=17 (1 twin birth). Healthy (no diagnosed psychiatric disease, BZD or other psychotropic or illicit drugs, alcohol, or nicotine): n=29	Maternal report. All mothers in the BZD group had diagnosis of depression (n=2) or anxiety (n=14). Mean dose unknown (ranges, 15–60 mg oxazepam, 5–30 mg diazepam, 5–15 mg lorazepam). No. of prescriptions unknown, but "regular use" (p 18); "continuously" (p 22). Other psychotropic drugs listed separately	Unadjusted data. Confounders compared	Major malformations (included n=1 with hydronephrosis [BZD group], n=1 with unilateral cleft lip [reference group]). Data obtained from review of obstetric and neonatal records	Major malformations: 1/17 vs 1/29
Milkovich and van den Berg, 1974[36], United States[a]	Women in prenatal care, 1959–1966 (part of child health and development studies). Exclusion: none stated	Chlordiazepoxide at any time during pregnancy (+6 months prior) + anxiety: n=175 (about half after 1st trimester). Not exposed to chlordiazepoxide, meprobamate, or any other drug to treat anxiety + anxiety: n=509	Combined clinic and hospital records. Indications: anxiety, tension, mild depression. Mean dose unknown. Pattern of use unknown. Use of other psychotropics possible	Unadjusted data	Severe congenital anomalies = "hazardous, if not corrected, would impair the child's development or well-being or both". Data from physicians' records (mothers' medical records), 5-year follow-up	CA: 9/175 in exposed any time in pregnancy vs 14/509 in not exposed any time in pregnancy. CA: 5/73 in exposed in 1st trimester vs 7/174 in not exposed in 1st trimester
Oberlander et al, 2008[37], Canada[a]	Inclusion: all live births, April 1997–March 2002. Five administrative databases linked, all prescriptions dispensed by nonhospital pharmacies recorded. Exclusion: neonates with 1st trimester exposure to anticonvulsant medications. Excluded specific minor congenital anomalies	Exposed to BZD in 1st trimester (no SSRI): n=968 (lorazepam [44%], clonazepam [21%], oxazepam [15%], alprazolam, temazepam, diazepam, clobazam, bromazepam, triazolam, chlordiazepoxide, flurazepam, nitrazepam). Not exposed to BZD or SSRI in 1st trimester: n=107,320. BZD + SSRI: n=359	Data dispensing date and day supply. Exposure in 1st trimester ("period...BZD... dispensed...overlapped... the LMP to LMP + 90 days" [LMP from hospital discharge records where gestational age based on last menses]). No information on indication (depression known). BZD dose unknown but analysis for high dose provided. No. of prescriptions unknown. Use of other psychotropics possible	Unadjusted data used (author contacted but data no longer available to calculate aOR). Adjusted for age; prenatal care visits; no. of depression diagnoses, no. of visits to psychiatrist, and no. of visits to a physician in the year before LMP; pregnancy diseases/complications diagnosed >60 days before birth; depression in the 1st trimester; and a dummy variable indicating mother filled a prescription after knowing she was pregnant	Major congenital anomalies: ICD-9 codes 740.0–759.9. Cardiovascular defect, congenital heart disease, or cardiovascular congenital defect: ICD-9 codes 745.0–747.9	MCA: 31/968 vs 3,369/107,320; incidence (95% CI)=3.20 (2.27 to 4.51), RD (95% CI)=0.06 (−0.88 to 1.37), aRD (95% CI)=−0.41 (−1.51 to 0.69). MCA for BZD + SSRI: 20/359 vs 3,369/107,320; incidence=5.57 (3.63 to 8.45), RD=2.43 (0.49 to 5.31), aRD=1.65 (−0.49 to 3.79). Cardiovascular defect: 5/968 vs 512/107,320; incidence=0.52 (0.22 to 1.20), RD=0.04 (−0.26 to 0.73), aRD=−0.13 (−0.55 to 0.29). Converted to z scores and reported "There was no association between increased 1st trimester dose and risk of MCA or congenital heart disease in the simple comparisons or in the regression models; for SRI + BZ... even controlling for length of time of medication use and maternal characteristics" (p 71) (Article provides other data, but only outcomes used in our analyses are listed)

(continued)

ratings) or "below quality threshold" (very low rating) for parsimony and to include enough data to permit meta-analysis.

Procedures for data extraction followed the Strengthening the Reporting of Observational Studies in Epidemiology criteria.[28] Extracted data included authors, year of publication, source country, details of study design, participants (sample, control, demographics, and clinical characteristics), inclusion/exclusion criteria, details of benzodiazepine use (timing and indication of use in pregnancy, benzodiazepine type, and dose), use of other psychotropics in pregnancy, outcomes and their assessment methods and definitions, statistical adjustment for confounders, and loss to follow-up. For studies presenting outcome data following more than one benzodiazepine exposure time point in pregnancy, data from all time points were extracted and the largest sample size was used for the overall analysis, keeping in mind that time was assessed separately. When separate first trimester data were provided and included a smaller sample size, these data were used for the first trimester analysis. Adjusted estimates with their variances were extracted when available; when adjusted estimates were not provided in the published data, we calculated crude odds ratios or mean differences and sample variances. Before calculating the odds ratio for studies that included cells with a 0 count, we added 0.5 to these cells. Data were extracted by one reviewer and checked by another and the primary author (S.G.); disagreements were resolved by the primary author. Outcomes were as defined by the authors of the original publication. We contacted one author to request adjusted estimates and received a reply indicating that these data were not available (T. F. Oberlander, electronic communication; November 16, 2017). As such, raw data from this study were included.

Statistical Analyses

Pooled estimates of the odds ratio following random effects models were calculated using the DerSimonian and Laird method.[29] Between-study

Table 1 (continued).

Article/Country	Data Source	Exposure/Sample Size	Exposure Details	Variables Adjusted	Outcome Definitions	Results
Ornoy et al, 1998[38], Israel[b]	Inclusion: live births, women calling a teratogen information service regarding exposure to BZD prior to or during pregnancy, 1988 to 1996, with follow-up data Exclusion: none stated	BZD before or during pregnancy (68% in 1st trimester only, 30% throughout pregnancy—ie, 98% exposed in 1st trimester); N=355 (alprazolam [32%], lorazepam [24%], diazepam [19%], oxazepam [19%], clonazepam [15%], brotizolam, nitrazepam, other) Calling service regarding non-teratogen exposure: n=382	Drug information from mothers or MD/RN report No information on indication (Alprazolam 0.5–1.0 mg, lorazepam 0.5–2 mg, clonazepam 1–2 mg, diazepam 5–100 mg/d and occasional use in infants with malformations) Pattern of use not known Other psychotropic use noted	No adjustments Confounders compared, and differences in maternal age found Reported no effect of dose	Congenital anomalies/malformations Congenital heart defects Diagnosis from pediatricians or family doctors	Congenital anomalies: 11/355 (3.1%) vs 10/382 (2.6%), P=.51; OR=1.20 (0.50 to 2.80) Congenital heart defects: 4/355 vs 1/382, P=.202
Pastuszak et al, 1996[39], Canada[a]	Inclusion: live births, women calling teratogen information service, counseled about 1st trimester exposure to BZD (Motherisk) Exclusion: none stated	BZD at any time during pregnancy: n=106 live births (93% took in 1st trimester only) (diazepam, lorazepam, alprazolam, triazolam [10%–30%]; remainder used bromazepam, chlordiazepoxide, clonazepam, flurazepam, nitrazepam, oxazepam, temazepam) Non-teratogenic drug exposure: n=115 live births	Drug history via maternal interview Indications: 2 "nervous breakdown," 11 depression, 22 insomnia, 9 panic attacks, 47 anxiety/stress, plus others Mean dose 0.07–202 mg Pattern of use not known but duration described Other psychotropics documented— 9.5% used TCA	Unadjusted Confounders assessed and compared between groups included maternal age, obstetric history (gravidity, parity, previous elective abortion, previous miscarriage), tobacco, ethanol, marital status Controls matched temporally closest to the study case in the computerized database	Major birth defects/major congenital defect Pregnancy outcome from telephone maternal report+confirmation by pediatrician written report	Major birth defects: 1/106 (1%) vs 3/115 (2.6%), P=.69

[a]Above quality threshold. [b]Below quality threshold.
Abbreviations: AD=antidepressant, aOR=adjusted odds ratio, AR=absolute risk, aRD=adjusted risk difference, BMI=body mass index, BZ or BZD=benzodiazepine, CA=congenital anomaly, CI=confidence interval, CM=congenital malformation, LMP=last menstrual period, MCA=major congenital anomaly, MD=medical doctor, NS=nonsignificant, OR=odds ratio, RD=risk difference, RN=registered nurse, SES=socioeconomic status, SRR=standardized risk ratio, SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant.

heterogeneity was assessed with Cochrane Q and quantified with I^2, which represents the percentage of the between-study variance in excess of what is expected due to chance.[30]

As part of the main analysis, we examined potential sources of heterogeneity through subgroup analyses, regardless of the Q statistic. These subgroup/moderator analyses identified between- and within-group differences in pooled effects based on study characteristics including (*a*) study quality (above or below quality threshold), (*b*) sample type (population-based or convenience), (*c*) timing of benzodiazepine exposure (any time, first trimester or late pregnancy), (*d*) statistical adjustments (adjusted or unadjusted estimates), (*e*) exposure to other psychotropic drugs (benzodiazepine monotherapy or use of any other psychotropic medications possible), (*f*) statistical adjustment/control for psychiatric diagnoses, (*g*) benzodiazepines used solely for anxiety, and (*h*) country. Separate analyses were conducted for the risk of malformations following benzodiazepine exposure in the first trimester, the risk of cardiac malformations following prenatal benzodiazepine exposure, and the risk of major congenital malformations following exposure to concurrent use of benzodiazepine and antidepressant in pregnancy.

Publication bias was assessed in analyses with a sufficient number of studies by visual inspection of funnel plots displaying individual study estimates (log odds ratio) by their standard error. The number of unpublished studies was estimated using Duval and Tweedie's trim and fill method,[31] and when one or more unpublished study was estimated, these were imputed around the summary estimate and a new (adjusted) summary OR was generated. All analyses were conducted using Comprehensive Meta-Analysis, Version 3 (Biostat; Englewood, New Jersey).

Patient Involvement

This study was conducted without patient involvement.

RESULTS

Of 23,909 unique records identified and screened, 56 full-text articles were retrieved and assessed for eligibility, and, of these, 8 studies were included in the present analyses (Figure 1).[32–39] Characteristics of included studies are shown in Table 1, along with relevant descriptions. Six of the 8 studies that provided data on congenital malformations were above quality threshold, and 3 of the 4 studies with data on cardiac malformations were above quality threshold. Six of the 8 studies provided data on major malformations (Hartz et al[33] [1975] and Ornoy et al[38] [1998] did not specify).

When pooling the 8 included studies, we found that benzodiazepine exposure in utero was not associated with the risk of congenital malformations (OR = 1.13; 95% CI, 0.99 to 1.30; P = .07, n = 222/5,195 exposed and 64,335/2,082,467 unexposed). The between-study heterogeneity for this analysis was not significant (Q_7 = 4.53, P = .72, I^2 = 0.0%) (Figure 2A). Not surprisingly, moderator analysis did not reveal significant moderators (all P values ≥ .10; Table 2). The subanalysis that

included data that did not control for psychiatric diagnosis was significant (5 studies; OR = 1.18; 1.00 to 1.39, P = .046). Among 5 studies that specifically examined exposure to benzodiazepine in the first trimester, there again was no significant risk of congenital malformation (OR = 1.08; 0.93 to 1.25, P = .33, n = 181/4,331 exposed and 64,308/2,081,463 unexposed; Figure 2B), with no heterogeneity between studies (Q_4 = 1.09, P = .90, I^2 = 0.0%; Table 2).

Four studies investigating prenatal use of benzodiazepine (at any time during pregnancy) and cardiac malformations (OR = 1.27; 0.98 to 1.65, P = .07, n = 61/4,414 exposed and 19,260/2,033,402 unexposed, Figure 2C) were pooled, and a nonsignificant effect was shown. However, concurrent benzodiazepine and antidepressant use in the first trimester was significantly associated with the risk of major congenital malformations (OR = 1.40; 1.09 to 1.80, P = .008; 3 studies), with no significant between-study heterogeneity (Q_2 = 2.30, P = .32; I^2 = 12.9%; Figure 3). As there were only 3 studies, we did not run subgroup analyses.

Publication Bias

Assessment of publication bias was possible only for the main analysis and the analysis of malformations following first trimester benzodiazepine exposure. For the main analysis, publication bias was indicated by asymmetry of the funnel plot. The Duval and Tweedie trim and fill method imputed 1 missing study and provided a revised estimate similar to main results (OR = 1.12; 95% CI, 0.98 to 1.28), and this was still not significant. There was no evidence of publication bias for the analysis of the risk of malformations following first trimester benzodiazepine exposure.

DISCUSSION

In our meta-analysis that included 8 prospective cohort studies, we found no significant risk for congenital malformation following exposure at any time in pregnancy to benzodiazepine or during the first trimester exclusively. We also did not find an increased risk of cardiac malformations following benzodiazepine exposure. Interestingly, we found a significant pooled association between concurrent benzodiazepine and antidepressant use in pregnancy and the risk of major malformations, and to our knowledge this has not been previously reported. Despite the fact that an association would likely occur with a specific malformation if one exists, this study is the first step to help focus future research. Together, these results have significant implications for clinicians to streamline treatment regimen and for reproductive-age and pregnant women and their families. Of note, implications for clinicians extend beyond psychiatrists since the majority of benzodiazepine prescriptions are written by general practitioners[9,40] and obstetricians.[41]
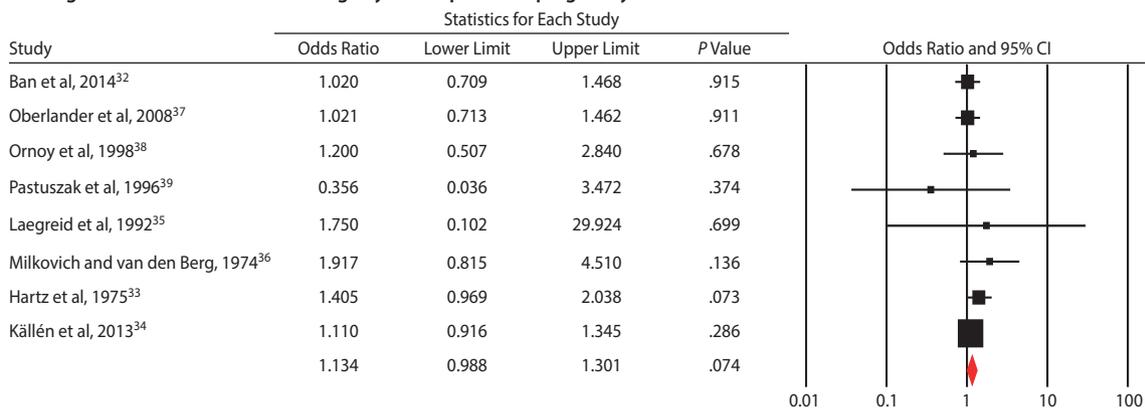
Strengths

This study has several strengths. We applied a rigorous process and conducted a comprehensive review. Our results update the previous meta-analysis by Enato et al (2011)[14] and
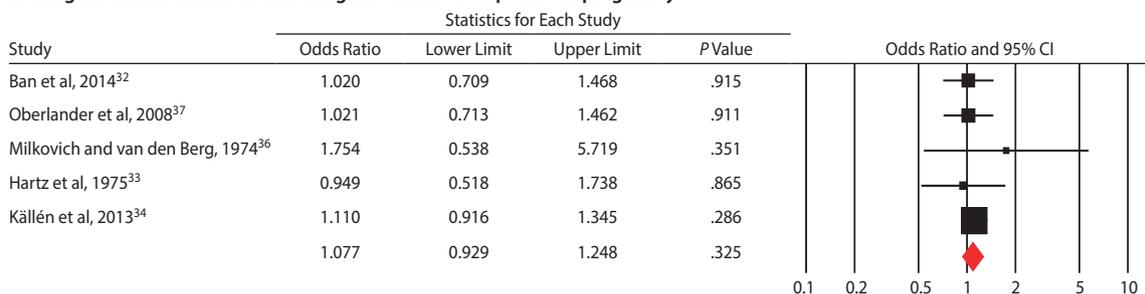
Figure 2. Risk of Malformations Following Benzodiazepine Exposure

A. Congenital malformations following anytime exposure in pregnancy

Study	Odds Ratio	Lower Limit	Upper Limit	P Value	Odds Ratio and 95% CI
		Statistics for Each Study			
Ban et al, 2014[32]	1.020	0.709	1.468	.915	
Oberlander et al, 2008[37]	1.021	0.713	1.462	.911	
Ornoy et al, 1998[38]	1.200	0.507	2.840	.678	
Pastuszak et al, 1996[39]	0.356	0.036	3.472	.374	
Laegreid et al, 1992[35]	1.750	0.102	29.924	.699	
Milkovich and van den Berg, 1974[36]	1.917	0.815	4.510	.136	
Hartz et al, 1975[33]	1.405	0.969	2.038	.073	
Källén et al, 2013[34]	1.110	0.916	1.345	.286	
	1.134	0.988	1.301	.074	

0.01 0.1 1 10 100

B. Congenital malformations following first trimester exposure in pregnancy

Study	Odds Ratio	Lower Limit	Upper Limit	P Value	Odds Ratio and 95% CI
		Statistics for Each Study			
Ban et al, 2014[32]	1.020	0.709	1.468	.915	
Oberlander et al, 2008[37]	1.021	0.713	1.462	.911	
Milkovich and van den Berg, 1974[36]	1.754	0.538	5.719	.351	
Hartz et al, 1975[33]	0.949	0.518	1.738	.865	
Källén et al, 2013[34]	1.110	0.916	1.345	.286	
	1.077	0.929	1.248	.325	

0.1 0.2 0.5 1 2 5 10

C. Cardiac malformations following anytime exposure in pregnancy

Study	Odds Ratio	Lower Limit	Upper Limit	P Value	Odds Ratio and 95% CI
		Statistics for Each Study			
Ban et al, 2014[32]	1.340	0.754	2.383	.319	
Oberlander et al, 2008[37]	1.083	0.448	2.619	.859	
Ornoy et al, 1998[38]	4.342	0.483	39.033	.190	
Källén et al, 2013[34]	1.250	0.917	1.704	.158	
	1.274	0.983	1.651	.067	

0.01 0.1 1 10 100

replicate the conclusion of the critical review by Bellantuono et al (2013)[42] that there appears to be no association between benzodiazepine exposure in the first trimester and increased risk of congenital malformations. With the addition of new data, we were able to pool data on previously unsynthesized outcomes, namely, cardiac malformations and major congenital malformations specifically following concurrent prenatal use of benzodiazepine and antidepressant. By including only cohort studies with prospectively collected data, we have reduced the possibility of certain types of bias, keeping in mind that cohort studies inherently contain other types of design bias and between-study heterogeneity. Additionally, we explored potential sources of heterogeneity between pooled studies, and none of the moderators we identified a priori were significant. This is a very positive outcome as it suggests the data have little variability. The pooled association for studies that did not control for psychiatric diagnosis was significant but not the overall moderator analysis supporting the lack of heterogeneity overall. Interestingly, the "any time" in pregnancy exposure subanalysis was not significant, nor was the "first trimester" exposure. Organogenesis occurs during the first trimester primarily (note that the central nervous system continues to develop), and we would not expect significance in the "any time" exposure analysis. The fact that the "any time" analysis had a much wider confidence interval than the "first trimester" exposure analysis lends more confidence in the results.

Limitations

Results should nevertheless be interpreted with some caution as our analyses do have limitations. Namely, included studies reported on risks of malformations in populations/samples that included only live-born infants, potentially underestimating the risk of malformations following exposure to benzodiazepine antenatally,[19] especially given that prenatal benzodiazepine may be associated with loss (ie, miscarriages and induced abortions), although this

Table 2. Prenatal Benzodiazepine Use on the Risk for Congenital Malformations

Analysis	No. of Studies	Odds Ratio or Mean Difference (95% CI)[a]	P Value	Q_{df} Within	P Value	I^2 (% of variance explained)	Q_{df} Between	P Value
				Heterogeneity			Effect of Moderator	
All studies	8	1.13 (0.99 to 1.30)	.07	4.53_7	.72	0.0		
Study quality							1.42_1	.23
Above quality threshold	6	1.09 (0.94 to 1.27)	.25	3.00_5	.70	0.0		
Below quality threshold	2	1.37 (0.97 to 1.93)	.07	0.11_1	.74	0.0		
Sample type							0.53_1	.47
Population-based	4	1.12 (0.97 to 1.29)	.12	1.95_3	.58	0.0		
Convenience	4	1.39 (0.78 to 2.48)	.26	2.05_3	.56	0.0		
Timing of benzodiazepine exposure							2.21_2	.44
Any time in pregnancy	4	1.39 (0.78 to 2.48)	.26	2.05_3	.56	0.0		
1st trimester	3	1.08 (0.93 to 1.25)	.33	0.27_2	.88	0.0		
Late pregnancy	1	1.41 (0.97 to 2.04)[b]	.07					
Statistical adjustments							0.61_1	.51
Adjusted data	2	1.09 (0.92 to 1.29)	.32	0.16_1	.69	0.0		
Unadjusted data	6	1.22 (0.97 to 1.55)	.09	3.76_5	.59	0.0		
Exposure to other psychotropic							0.32_1	.57
No, exclusion criterion	2	1.03 (0.72 to 1.48)	.88	0.14_1	.71	0.0		
Not specified/assessed	6	1.15 (0.99 to 1.34)	.06	4.07_5	.54	0.0		
Controlled for psychiatric diagnoses							0.85_1	.36
Yes, adjusted or excluded	3	1.03 (0.79 to 1.32)	.85	0.14_2	.93	0.0		
Not specified/assessed	5	1.18 (1.00 to 1.39)	.046	3.54_4	.47	0.0		
Benzodiazepine indication solely for anxiety							0.80_1	.37
Yes	4	1.25 (0.97 to 1.73)	.08	2.59_3	.46	0.0		
No	4	1.09 (0.92 to 1.28)	.99	1.14_3	.77	0.0		
Continent							0.50_2	.78
North America	4	1.23 (0.91 to 1.66)	.17	3.70_3	.30	18.8		
Europe	3	1.09 (0.92 to 1.29)	.31	0.27_2	.87	0.0		
Other	1	1.20 (0.51 to 2.84)[b]	.68					

[a]Pooled effect size estimated using random-effects model.   [b]Pooled effect size estimated using fixed-effects model.

Figure 3. Risk of Major Congenital Malformation Following Concurrent Exposure to Benzodiazepines and Antidepressants During the First Trimester

Study	Odds Ratio	Lower Limit	Upper Limit	P Value	Odds Ratio and 95% CI
		Statistics for Each Study			
Ban et al, 2014[32]	1.070	0.626	1.829	.805	
Oberlander et al, 2008[37]	1.820	1.158	2.861	.009	
Källén et al, 2013[34]	1.360	1.010	1.831	.043	
	1.402	1.094	1.797	.008	

0.1 0.2 0.5 1 2 5 10
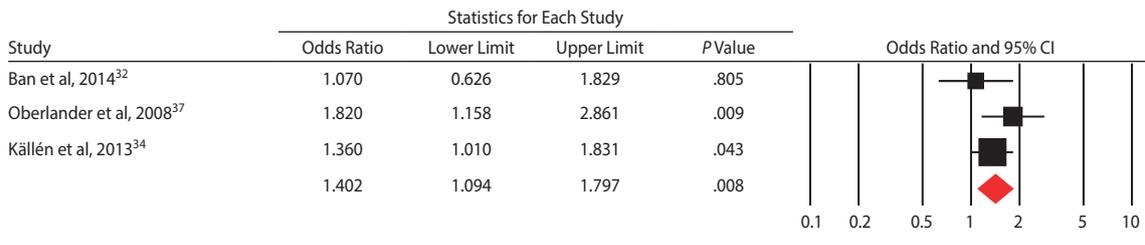
is not clear.[43,44] The major malformations may have been selected out. We were also limited by the drug-specific data provided in the included studies that did not always specify indication and duration of use and, in all but 1 study (Ban et al[32]), did not examine variable effects for different doses of benzodiazepine. Different patterns of benzodiazepine use exist, with some women using these medications on occasion and others chronically; as a result, different patterns of use may have diverse implications for both mother and fetus. Further, large-scale studies that utilized data from prescription databases are limited by unclear "true" usage patterns. The poor adjustment for confounding cannot be totally overcome in the meta-analysis, and the original confounds can still influence the findings. For example, 6 of the studies (see Table 2) had unadjusted data, although it was reassuring that both the adjusted and unadjusted subanalyses were not significant. Finally, there were variable definitions of "major malformations" across studies, and we chose to group these, while providing original definitions (in Table 1). Some malformations therefore may be missed, but this is an issue with all teratogenic studies and points to the need for standardization for comparability across studies. Likewise, grouping all malformations together may mask associations between medication exposure and specific malformations (ie, cleft palate, which has been previously found in early case-control studies).[14,18] We pooled data for specific malformation when available, and it was possible for only 1 outcome (cardiac malformations).

Implications

Benzodiazepines are commonly used in pregnancy, and we now have a sample size of 5,195 exposures compared to 2,082,467 not exposed, increasing our confidence in the absence or lack of an association with malformations

when the drugs are used as monotherapy. Moreover, we are also reassured regarding cardiac malformations. Our analyses examined benzodiazepines as a class as there were insufficient data to analyze the pooled risk of malformations in association with specific drugs. As seen in research on use of other drugs in pregnancy, there may be differing risk profiles for adverse outcomes across different drugs within the same class. Of note, Källén et al (2013)[34] reported that benzodiazepines, as a group, were not associated with a significant risk of severe congenital malformations or of congenital malformations, but significant risk of these outcomes was seen following alprazolam exposure from a small exposure group (total 444 events). The combination of benzodiazepines and antidepressants appears to be associated with major malformations, which is discouraging, as often these medications are used together, especially at the beginning of treatment. The mechanism needs to be determined if an association truly exists; it may be merely a function of increased surveillance for adverse effects given that more than one drug was used or that the women may have been more severely ill or perhaps the combination of medication may cause an interaction that results in increased blood drug levels, which may be associated with increased risk for anomaly.[37] Given, however, that we are not provided with information on the pattern of use of the benzodiazepine with the antidepressant in the original studies, it makes intuitive sense to extrapolate that the occasional use would confer less risk, but this hypothesis also needs to be tested. Regardless, for now, our significant combined analysis of benzodiazepines and antidepressants argues against the use of more than one drug and supports the clinical recommendation of monotherapy that has often been made in past guidelines.[45] Studies have been inconsistent, but some have implicated a potential signal for malformations following antidepressant exposure, although recent work has not found a signal overall.[46,47] Further work is needed to determine if there is a particular combination of antidepressant with benzodiazepine that may be of concern versus the drugs in general. For example, a recent meta-analysis for citalopram specifically[48] did not find an association, while for fluoxetine an effect was found.[49] However, polypharmacy may still be the important factor as large, well-controlled studies of various medications did not find an effect.[46] At least in one study, use of a benzodiazepine with antidepressant was found to aggravate adverse effects seen in the neonate.[50] Fortunately, however, the OR in our analysis is small and, although statistically significant, clinically less likely to be so, especially since it is less than 2 (traditionally used a cutoff for clinical significance by clinical experts). Even the upper limit of the confidence interval was below the threshold of 2.[47] As we are still hypotheses-driven in the area, this suggests that future research *must* look into the effects of polypharmacy and the compounding effects of severe mental illness.

Treatment of mood and anxiety disorders is paramount especially during pregnancy. This study provides more evidence that the risk-benefit ratio must be carefully considered and that it must be individual for every woman and her family. The weight load of the treatment can fluctuate and certainly may depend on symptom severity. Women with severe symptoms may not be able to participate in psychotherapy that has been recommended as first-line treatment, precisely because the symptoms render them unable. Monotherapy, although aspired to, may not be possible especially in the aforementioned cases. Treatment decisions are not easy to make and must take into account the effect of untreated illness on the mother, baby, and family as well as the potential adverse effects of the treatment itself. Although statistically significant, the clinical significance of the findings needs to be thought of carefully, especially in light of the small magnitude. Mothers are motivated to do what is best for their baby, and treatment of their illness must certainly be given heavy consideration. It is important not to lose sight of our role as health care providers, which is to work collaboratively with those we care for and do what is in their best interests within the context of their family.

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POSTTEST

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1. **According to the results of this study, what is the best strategy for prescribing benzodiazepines to women with anxiety disorders when they are pregnant?**

   a. They can be used in severe cases

   b. They should be prescribed to women with mild anxiety

   c. They can be used in women who have used them in the past

   d. Their use depends on the risk-benefit ratio for each woman

2. **This study reported which of the following findings?**

   a. Benzodiazepines were found to be associated with risk of minor congenital malformations when combined with an antidepressant

   b. Benzodiazepines were found to be associated with minor congenital malformations

   c. Benzodiazepines were found to be associated with congenital malformations when used in the first trimester

   d. Benzodiazepines were found to be associated with risk of major congenital malformations when combined with an antidepressant

3. **Ms Gregor is in her first trimester of pregnancy, is having panic attacks daily, worries about her pregnancy, and has been feeling increasingly despondent. At work, she is avoiding her coworkers because she does not want them to see her upset. Her anxiety is also interfering with her ability to stay on task and finish assignments. Ms Gregor has missed several days of work, is isolating herself more and more, and asks you about medication. Which of the following strategies is *least* appropriate, according to the results of this study?**

   a. Tell her that neither selective serotonin reuptake inhibitors (SSRIs) nor benzodiazepines are teratogenic overall, although certain drugs may differ, and suggest starting an SSRI

   b. Tell her that neither SSRIs nor benzodiazepines are teratogenic overall, although certain drugs may differ, and suggest starting both an SSRI and a benzodiazepine

   c. Tell her that neither SSRIs nor benzodiazepines are teratogenic overall, although certain drugs may differ, and suggest starting a benzodiazepine