Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies


Authors' objectives
To determine if exposure to benzodiazepines during the first trimester of pregnancy increases the risk of major malformations or cleft lip or palate.

Searching
Searches were conducted of MEDLINE (1966 to December 1997) via Ovid, EMBASE (1980 to December 1997), REPROTOX; references in textbooks on drugs in pregnancy, and references in included studies and review articles. 'Benzodiazepine(s)' (exploded as a subject heading or the various preparations inserted as textwords) was combined with the following words as subject headings or text words: 'fetal diseases', 'infant', 'fetal organ maturity', 'cleft lip', 'cleft palate', 'major malformations' and 'pre-natal exposure'. Unpublished articles were sought by the Toronto-based MotheRisk programme. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Cohort and case-control studies that examined the relationship between human maternal exposure to benzodiazepines in at least the first trimester and major malformations or oral cleft alone were included if they contained an unexposed concurrent control group. Studies with the following characteristics were excluded: case series or reports; editorials; reviews; animal studies; studies that included only stillbirths or abortions; and studies from which data could not be extracted. Reasons were given for the exclusion of identified studies.

Specific interventions included in the review
Exposure to benzodiazepines was studied with exposure being ascertained mainly through interview with the mother. Various benzodiazepines were used or prescribed, including chlordiazepoxide and diazepam.

Participants included in the review
Women exposed to benzodiazepines during the first trimester of pregnancy, including those with epilepsy, were studied.

Outcomes assessed in the review
Major malformations as described by Heinonen et al., and including cleft lip and cleft palate, were assessed (see Other Publications of Related Interest). The term ‘oral cleft’ was used for cleft lip, or palate or both. Cardiac and central nervous system malformations were also assessed. Ascertainment of outcome was through physician examination or records (44% of studies) and malformation registries (30% of studies). The outcomes were assessed separately for patients with and without epilepsy.

How were decisions on the relevance of primary studies made?
The methods sections with study identifiers removed were reviewed independently and in duplicate to determine inclusion. Disagreements were resolved by consensus or a third party.

Assessment of study quality
The following aspects of validity were considered: predefinition of exposure and outcomes; ascertainment of exposure; and equal diagnostic examination between exposed and unexposed groups. Study quality was assessed independently and in duplicate using pre-determined criteria. Discrepancies were resolved by consensus.

Data extraction
The following data were extracted independently and in duplicate using predetermined criteria: author; date of publication; study design; total number in exposed and non-exposed groups; and number malformed and type of malformation in exposed and non-exposed groups. Data were extracted separately for epileptic and non-epileptic women and for case-control and cohort studies. Discrepancies were resolved by consensus.

**Methods of synthesis**

How were the studies combined?
The odds ratio (OR) and 95% confidence intervals (CIs) were calculated using a random-effects model.

How were differences between studies investigated?
Heterogeneity was assessed using a chi-squared test. Sensitivity analysis was conducted for case-control studies to assess the impact of recall bias through the use of normal babies compared to malformed babies as controls. The malformation rate in the exposed groups was regressed on that of the controls using methods described by L’Abbé et al. (see Other Publications of Related Interest). Publication bias was assessed using a funnel plot. Cohort and case-control studies were analysed separately.

**Results of the review**

There were 23 studies, including 7 cohort studies of non-epileptic patients (1,090 exposed and 71,776 unexposed women), 2 cohort studies of epileptic patients (121 exposed and 634 unexposed women), and 4 case-control studies (166 exposed and 5,970 unexposed women). There was some overlap in the above studies.

Studies examining the association of specific malformations with prenatal exposure to benzodiazepine were as follows.

**Oral cleft** was assessed using 3 cohort studies of non-epileptic patients (2,543 exposed providing 1 case, and 135,743 not exposed providing 93 cases), 2 cohort studies of epileptic patients (121 exposed providing 3 cases and 634 not exposed providing 13 cases), and 6 case-control studies (285 exposed providing 105 cases and 14,686 not exposed providing 2,742 cases).

**Cardiac malformations** was assessed using 2 case-control studies (102 exposed providing 59 cases and 8,007 not exposed providing 3,722 cases).

**Malformation of the central nervous system** was assessed using 1 case-control study (750 exposed providing 14 cases and 750 not exposed providing 14 cases).

Twenty (87%) of the 23 included studies predefined exposure, while 22 (96%) predefined the outcome. Equal diagnostic examination occurred in 20 studies. Two studies provided information on duration of maternal exposure. Fourteen studies (61%) reported concurrent use of at least some prescription medicines. A funnel plot showed no obvious publication bias.

**Major malformations.** Cohort studies of non-epileptic patients (7 studies): the OR was 0.90 (95% CI: 0.61, 1.35; heterogeneity, chi-squared 1.74, p=0.62). Cohort studies of epileptic patients (2 studies): individual ORs were not significant. Case-control studies (4 studies): the OR was 3.01 (95% CI: 1.32, 6.84). Two studies reported a significant association and two a non significant association. In terms of heterogeneity, chi-squared was 9.87 (p=0.008).

A regression analysis showed no obvious heterogeneity for either cohort or case-control studies. All case-control studies used normal babies as controls.

**Oral cleft.** Cohort studies of non-epileptic patients (3 studies): the OR was 1.19 (95% CI: 0.34, 4.15; heterogeneity, chi-squared 0.01, p=0.997). Cohort studies of epileptic patients (2 studies): individual ORs were not significant. Case-control studies (6 studies): the OR was 1.79 (95% CI: 1.13, 2.82). Three studies reported significant associations and three reported non significant associations. In terms of heterogeneity, chi-squared was 11.39, (p=0.01). A regression analysis showed no obvious heterogeneity for either cohort or case-control studies. A subgroup analysis of case-control studies with normal babies as controls gave an OR of 1.63 (95% CI: 0.89, 2.96; heterogeneity, chi-squared=3.81, p=0.15). A subgroup analysis of case-control studies with malformed babies as controls gave an OR of 2.03 (95% CI: 0.88, 4.71;
heterogeneity, chi-squared 6.90, p=0.10. A regression analysis showed no obvious heterogeneity for either cohort or case-control studies.

Cardiac malformations (2 case-control studies, 102 exposed, 8,007 not exposed). One study showed a significant association and one did not.

Central nervous system malformations (1 case-control study, 750 exposed, 750 not exposed). The OR was 1.00 (95% CI: 0.47, 2.11).

Authors' conclusions
Pooled data from cohort studies showed no association between foetal exposure to benzodiazepines and the risk of major malformations or oral cleft. On the basis of pooled data from case-control studies, however, there was a significantly increased risk for major malformations or oral cleft. Until more research is reported, level 2 ultrasonography should be used to rule out visible forms of cleft lip.

CRD commentary
The aims and inclusion criteria were clearly stated. Published and unpublished studies in any language were sought. Details were given of methods used to select primary studies and extract data. Certain aspects of validity were assessed. Heterogeneity was evaluated statistically and sensitivity analysis undertaken. The discussion included consideration of some potential causes for difference in results between cohort and case-control studies and possible sources of confounding and bias including concomitant exposure to other medications, relatively small number of reports with results largely derived from 3 large studies; wide-ranging definitions for identification of malformations, and inability to stratify data by cleft type (lip vs palate).

Fuller details of the primary studies would have been welcome including the source of controls for case control studies, specific agents used, and maternal age.

The authors results are supported by the evidence presented. However, the differing results for cohort and case-control studies remains unexplained.

Implications of the review for practice and research
Practice: The authors consider that counselling of all women on the safety of exposure to benzodiazepine is clinically important.

Research: The authors consider that more case-control studies are required to examine the malformations.

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