Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis

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CRD summary
This review concluded that prenatal exposure to misoprostol is associated with an increased risk of Mobius sequence and terminal transverse limb defects. This appears to be a well-conducted review and the authors' conclusions appear to be supported by the findings. However, the poor quality of the limited number of included studies suggests that the findings should be interpreted with caution.

Authors' objectives
To estimate the risk of congenital defects and other adverse events among children exposed to misoprostol in utero.

Searching
MEDLINE (1966 to June 2005), EMBASE (1974 to June 2005), LILACS (1982 to June 2005), TOXLINE and DART (Developmental and Reproductive Toxicology) were searched; key search terms were reported. The bibliographies of identified studies were reviewed. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Case-control studies were eligible for inclusion.

Specific interventions included in the review
Studies of prenatal exposure to misoprostol were eligible for inclusion. No restriction was applied to the period of gestation at which the exposure occurred. Exposure to misoprostol varied in all of the included studies and was assessed through interviews with the mother; doses (where stated) ranged from 200 to 1,600 micrograms administered orally and/or vaginally.

Participants included in the review
Studies of children under 2 years of age were eligible for inclusion. All of the included studies were carried out in Brazil. Data on the age and gender of the participants were provided for only 1 study, which involved both boys and girls aged from 7 days to 78 months.

Outcomes assessed in the review
Studies investigating congenital abnormalities, foetal death, low birth weight and prematurity were eligible for inclusion. All of the included studies reported congenital abnormalities.

How were decisions on the relevance of primary studies made?
Two authors independently assessed the relevance of the studies. A third author resolved any disagreements.

Assessment of study quality
Two authors independently assessed validity using the Newcastle-Ottawa quality assessment scale. A star was awarded for each criterion met, with studies scoring a maximum total score of nine stars. A third author resolved any disagreements.

Data extraction
Two authors independently extracted the data from the primary studies using a standardised form. A third authors
resolved any disagreements or discrepancies that arose. Odds ratios (ORs) and 95% confidence intervals (CIs) for each study were calculated.

**Methods of synthesis**

How were the studies combined?
The studies were combined using a random-effects model.

How were differences between studies investigated?
A chi-squared test for homogeneity and the I-squared statistic were used to investigate differences between the studies. The analyses were also repeated using a fixed-effect model to assess consistency. Sensitivity analyses were conducted to investigate the effect of excluding studies with poorer methodological quality, and those with the greatest sample size.

**Results of the review**

Four studies (4,899 cases, 5,742 controls) were included in the review.

Out of a maximum of nine stars, the studies received three (1 study), four (2 studies) and five stars (1 study) on the quality scale. One of the nine quality criteria was considered not applicable in any of the studies.

All defects (3 studies, 4,803 cases, 5,646 controls). There was an increased risk of all defects combined associated with misoprostol use (OR 3.56, 95% CI: 0.98, 12.98) from the random-effects model. There was significant heterogeneity between the studies (p<0.001, I-squared 89.7%), which persisted following the exclusion of the study with the poorest quality and the study with the largest sample size. Mobius sequence (2 studies, 125 cases, 183 controls). There was an increased risk of Mobius sequence associated with misoprostol use (OR 25.31, 95% CI: 11.11, 57.56) from the random-effects model, with no evidence of heterogeneity (p=0.71, I-squared 0%).

Terminal transverse limb defects (2 studies, 61 cases, 4,720 controls).

There was an increased risk of terminal transverse limb defects associated with misoprostol use (OR 11.86, 95% CI: 4.86, 28.90, p<0.001) from the random-effects model, with no evidence of heterogeneity (p=0.62, I-squared 0%).

**Authors' conclusions**
Prenatal exposure to misoprostol is associated with an increased risk of Mobius sequence and terminal transverse limb defects.

**CRD commentary**
The review questions and study criteria were well described. The authors carried out a reasonable search for published studies, although there was little evidence of specific attempts to locate unpublished data; there might therefore be a risk of publication bias. The study selection, quality assessment and data extraction appear to have been carried out using methods to minimise the likelihood of errors and/or bias. The meta-analysis was appropriate, although there was little investigation of possible reasons for the heterogeneity seen between study data for ‘all defects’. The quality of the data was considered within the analysis, although only a small number of quite poor-quality studies were included. The study data largely relied on mothers' self-reported exposure to misoprostol and, therefore, may be subject to recall bias. In addition, it is unclear how generalisable the data is to other populations as all of the studies focused on Brazilian populations. Overall, this appears to be a reasonably well-conducted review and the authors' conclusions appear to be supported by the findings. However, the poor quality of the studies suggests that the findings should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are needed to investigate whether misoprostol is associated with other
congenital defects of vascular origin, such as arthrogryposis.

**Bibliographic details**

**PubMedID**
16750609

**DOI**
10.1016/j.reprotox.2006.03.015

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Ulcer Agents /administration & dosage /adverse effects; Case-Control Studies; Congenital Abnormalities /etiology; Dose-Response Relationship, Drug; Female; Humans; Limb Deformities, Congenital /etiology; Misoprostol /administration & dosage /adverse effects; Mobius Syndrome /embryology /etiology; Pregnancy

**AccessionNumber**
12006007633

**Date bibliographic record published**
31/01/2008

**Date abstract record published**
31/01/2008

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.