Folic acid and risk of twinning: a systematic review of the recent literature, July 1994 to July 2006

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CRD summary
The authors concluded that there is evidence of a possible association between periconceptional folic acid and the risk of twinning, but further research is required. The authors’ cautious conclusions appear to reflect the limited data, but the poorly defined review question, inadequate reporting of the review methods and inadequate quality assessment make it difficult to assess the reliability of these conclusions.

Authors' objectives
To examine the association between periconceptional folic acid (FA) supplementation and fortification of foods with FA and the risk of twinning.

Searching
The Cochrane Library (Issue 4, 2005), MEDLINE via PubMed, MEDLINE In-Process and Other Non-Indexed Citations, CINAHL, and EMBASE were searched for studies published between July 1994 and July 2006; the search terms were reported. Studies published before this had been included in a Cochrane review (see Other Publications of Related Interest). In addition, the reference lists of the included studies were screened.

Study selection
Study designs of evaluations included in the review
Experimental and observational studies were eligible for inclusion. The included studies were prospective and retrospective observational studies.

Specific interventions included in the review
Studies that evaluated periconceptional FA supplementation or fortification of foods with FA were eligible for inclusion. Studies evaluating FA supplementation used doses ranging from 0.4 to 9 mg/day and were conducted in the USA, Norway, Hungary, Sweden and China. The assessment of FA intake was based on asking women what they had taken, or from medical records. All but one of the studies evaluating food fortification with FA were conducted in the USA where fortification of enriched grain products has been optional from 1996 and mandatory since 1998; one study was conducted in Chile where fortification of flour became mandatory in 2000. Some studies included cointerventions with multivitamins.

Participants included in the review
Inclusion criteria were not specified in terms of the participants but it was clear that studies of women who had given birth were eligible for inclusion. One study was performed in pregnant women with sickle cell anaemia.

Outcomes assessed in the review
Studies that assessed the incidence of twinning were eligible for inclusion. Most of the included studies confirmed twin deliveries using birth certificates.

How were decisions on the relevance of primary studies made?
Two reviewers independently applied the inclusion criteria and selected the studies.

Assessment of study quality
The authors stated that two reviewers independently assessed study validity and opportunity for bias. However, no formal assessment of validity was reported, although the methodological limitations of the included studies were
discussed with particular reference to potential confounders.

**Data extraction**

Two reviewers independently extracted the outcome data. The authors did not explicitly state what outcome data were extracted.

**Methods of synthesis**

**How were the studies combined?**

Studies of FA supplementation and studies of fortification of foods with FA were discussed separately in a narrative synthesis. The level of evidence for association between FA and twinning was graded using the hierarchy of evidence described by the Food Standards Australia New Zealand framework (accessed 07/03/2008). See Web Address at end of abstract. The review stated that evidence was classified as convincing, probable, possible or insufficient.

**How were differences between studies investigated?**

The influence of maternal age, artificial reproductive techniques (ART) and zygosity of the association between FA and twinning was examined.

**Results of the review**

Twelve studies were included. These comprised 6 observational studies that evaluated the association between risk of twinning and FA supplementation (n=1,491,728, possibly an overestimate since 2 studies reported data from the Swedish Medical Birth Registry and covered overlapping years) and 6 retrospective studies that evaluated the association with FA fortification of food (the maximum possible n was 7,807,364; the review stated there was some overlap among studies).

**FA supplementation.**

Five of the 6 studies either stratified or adjusted for maternal age. Two studies used adequate methods to account for ART. One study reported an underreporting of ART that led to classification bias. Two studies reported whether twins were of the same or different sexes.

Methodological problems included variation in the use of FA among different populations (range: 0.6 to 53%), the use of FA assessed retrospectively with the potential for bias, and small sample size. The reviewers stated that 3 of the 6 studies had major methodological flaws.

The reviewers stated that the 'best risk estimate' of the risk of twinning came from 1 study (n=176,042). It reported that FA supplementation (0.2 or 0.4 mg/day) was associated with no statistically significant increase in the risk of overall twinning (adjusted odds ratio, OR 1.02, 95% confidence interval, CI: 0.85, 1.24). There was no significant association between FA and same sex twins, classified as monozygotic (adjusted OR 0.70, 95% CI: 0.35, 1.40), or unlike-sex twins, classified as dizygotic (adjusted OR 1.26, 95% CI: 0.91, 1.73). The analyses were adjusted for age, parity and underreporting of FA and in vitro fertilisation use.

**Fortification of foods with FA.**

Studies conducted in the USA used different definitions for FA exposure during the optional fortification period (1996 to 1998). There was overlap in the populations among these studies. The reviewers stated that none of the studies was able to ascertain the comparability of FA exposure in women delivering twins compared with women delivering singletons.

One study reported that stratification by maternal age had no effect. In 2 studies, the analysis was adjusted for maternal age. Four studies did not account for ART. The 2 most recent U.S. studies took account of ART and induction of ovulation. Only 1 study accounted for zygosity.

One U.S. study reported no increase in the risk of twins associated with FA (relative risk 1.00, 95% CI: 0.95, 1.04).
Three U.S. studies reported a maximum annual increase in the risk of twinning of between 2.4% and 4.6% across all ages. One U.S. study reported a maximal percentage annual increase in twinning of 2% for women aged over 30 years and no increase for younger women. The other study had methodological flaws.

**Authors' conclusions**
There was evidence of a possible association between periconceptional FA and the risk of twinning, but further research is required.

**CRD commentary**
The review question was poorly defined and had to be deduced from the objective of the review. Several relevant sources were searched but no attempts were made to minimise publication bias. It was not explicitly reported whether any language restrictions had been applied. Two reviewers independently selected the studies, assessed validity and extracted the data, thus reducing the potential for reviewer bias and error; however, it was not stated what data were extracted. The reviewers stated that validity was assessed and they did discuss some methodological limitations of the included studies, but explicit criteria for assessing methodological quality do not appear to have been applied. In view of the differences between studies, a narrative synthesis appears appropriate and study limitations were taken into account when discussing the evidence. The authors' cautious conclusions appear to reflect the limited data, but the poorly-defined review question, the lack of detail of the review methods and the lack of a formal validity assessment means it is difficult to assess the reliability of these conclusions.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there is a need for additional, well-designed, long-term studies in areas where there is FA fortification, to determine the dose response and the influence of fertility treatments. Studies should measure blood FA levels.

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**Other publications of related interest**

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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.