CRD summary
This review concluded that there is very little information about the safety and risks of using disease-modifying antirheumatic drugs during pregnancy and conception. However, limited evidence suggests that hydroxychloroquine and azathioprine are safe and methotrexate is associated with a high rate of pregnancy losses. The review had limitations but the authors’ cautious conclusions are likely to be reliable.

Authors' objectives
To assess the safety of disease-modifying antirheumatic drugs (DMARDs) in pregnancy.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched for original studies published in English between 1990 and 2004; the search terms were reported. Reference lists of relevant articles, books, guidelines and prescribing information were searched for additional studies.

Study selection
Study designs of evaluations included in the review
The authors did not state any inclusion criteria for study design; it appears that any study design was eligible for inclusion.

Specific interventions included in the review
Studies assessing any DMARD monotherapy for rheumatic diseases were eligible for inclusion; DMARDs prescribed for other conditions were excluded. The DMARDs included in the review were hydroxychloroquine, chloroquine, methotrexate, sulfasalazine and azathioprine. Some studies compared women exposed to DMARDs with unexposed women.

Participants included in the review
Studies of pregnant women undergoing treatment for rheumatic diseases (e.g. rheumatoid arthritis and systemic lupus erythematosus) were eligible for inclusion in the review. Very few details about the study populations were provided.

Outcomes assessed in the review
Studies reporting any pregnancy outcome were eligible for inclusion in the review. The outcomes included number of live births, birth defects, and the number of miscarriages or abortions.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors do not appear to have performed a validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The use of co-medications, follow-up time after pregnancy, and the duration of exposure or drug treatment were reported.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative summary, according to DMARD intervention.
How were differences between studies investigated?
Each drug was discussed individually, according to study design and outcomes of interest.

Results of the review
Thirty studies were included in the review. There were 13 small cohorts (between 4 and 515 (exposed) women in each cohort), 13 case reports (ranging between 1 and 14 cases), one randomised controlled trial (RCT; n=20), one large cohort study (n=19,429) and 2 large case-control studies.

Hydroxychloroquine and chloroquine (8 studies).
One RCT (n=20) comparing hydroxychloroquine with placebo, 2 controlled cohorts (165 exposed and 114 control) exposed to hydroxychloroquine, 3 cohorts (52 pregnancies in total) exposed to hydroxychloroquine, and 2 cohorts (48 pregnancies) exposed to hydroxychloroquine or chloroquine, failed to find an increased risk of congenital malformations.

Methotrexate (13 studies).
Two cohorts (n=38) and 24 case reports of pregnancies exposed to methotrexate reported 12 incidences of minor and major abnormalities. In total, there were 10 terminated pregnancies (of which three had abnormalities) and 12 spontaneous abortions.

Sulfasalazine (3 studies).
One case-control study (22,865 malformations and 38,151 health controls) and a birth registry (n=576,873) reported no significant association between sulfasalazine and malformations. One case report of a neonate with holoprosencephaly born to a woman undergoing continuous treatment with sulfasalazine before and during pregnancy was also identified.

Azathioprine and mercaptopurine (6 studies).
cohort (n=19,429) of which 13 pregnancies were exposed to azathioprine or mercaptopurine, one cohort (n=39) exposed to mercaptopurine, and one case report of azathioprine reported 8 minor or major malformations including 1 death. There were 4 terminations, 9 miscarriages, 1 neonatal death and 2 foetal deaths/losses reported amongst women exposed to azathioprine or mercaptopurine.

Other DMARDs.
There were no significant data on the use of other DMARDs for antirheumatic treatment in pregnancy.

Authors' conclusions
There is very little information about the safety and risks of using DMARDs during pregnancy and conception. From the limited evidence available, most studies concluded that hydroxychloroquine and azathioprine are safe. In contrast, evidence regarding the safety of methotrexate is conflicting, with a high rate of pregnancy losses suggestive of risk to the foetus. No major teratogenic effects have been observed for sulfasalazine, and there is very limited information on the use of other DMARDs.

CRD commentary
This review used broad inclusion criteria in an attempt to summarise all potentially relevant data; this appears appropriate given the review's focus on the assessment of safety and adverse events. A number of electronic databases were searched and reference lists checked; however, as only studies published in English were included, the review findings might be affected by publication and language biases. Similarly, the authors failed to describe the methods used to select the studies and extract the data, so it is unclear whether errors and bias could have been introduced during these stages of the review process. Study quality does not appear to have been assessed, although the authors did acknowledge the limitations of certain study types. The narrative approach appears justified given the wide
variation in study designs. Despite the apparent limitations in the review methodology and the limited and poor-quality data presented, the authors' cautious conclusions appear reasonable.

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

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

Research: The authors stated that further research on the safety and risks of DMARDs in pregnancy is required; they suggested that a good monitoring system reporting all pregnancies irrespective of pregnancy outcome would be beneficial. In particular, the authors stated that research is needed to determine the delay between the cessation of methotrexate treatment and safe conception.

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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.