Low molecular weight heparin to achieve live birth following unexplained pregnancy loss: a systematic review.

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CRD summary
This review concluded that although there was a trend for increased live births when low molecular weight heparin was used for the prevention of recurrent pregnancy loss, there was insufficient evidence to support its routine use. Given the level of heterogeneity and consequent lack of statistical synthesis, the reliability of this conclusion is unclear. The recommendations for research were appropriate.

Authors' objectives
To assess the benefit of low molecular weight heparin (LMWH) in achieving live birth in women with a history of recurrent or late non-recurrent pregnancy loss who did not have antiphospholipid antibodies.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched without language restrictions up to August 2009. BIOSIS Previews and Conference Papers Index were searched, as were references of a previous review. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared LMWH with placebo or an alternative medication (except anti-coagulants) in women with a viable pregnancy at treatment initiation were eligible for inclusion. Trials were required to enrol women with a history of either at least two early miscarriages or at least one late foetal loss and without evidence of antiphospholipid antibodies or therapeutic indication for anticoagulation treatment. A thorough evaluation for underlying cause of recurrent miscarriage was required (details specified in review). Trials were required to report live birth as an outcome.

Most included studies used enoxaparin at 20mg/day or 40mg/day; one study used dalteparin 5,000 IU plus aspirin 81mg/day. Three studies used aspirin at 100mg/day or 81mg/day; other studies used no intervention or placebo. Where reported, treatment was initiated at the eighth week, between six and 12 weeks of gestation or at ultrasound viability. Inclusion criteria for number or type of previous pregnancy loss experienced varied.

Two reviewers independently assessed the studies for inclusion in the review and resolved differences through consensus. A third reviewer confirmed the exclusion of randomised studies.

Assessment of study quality
The studies were assessed for validity using the five-point Jadad scale of randomisation, blinding and reporting of withdrawals and dropouts.

It appeared that at least two independent reviewers were involved in the assessment process.

Data extraction
Data were extracted to permit the calculation of risk ratios (RR) with 95% confidence intervals (CI).

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis
The authors planned to undertake a random-effects meta-analysis and evaluate statistical heterogeneity using the $X^2$ and $I^2$ statistics. However, the high levels of statistical and clinical heterogeneity observed in the included trials were
Results of the review
Five RCTs (n=757) were included in the review. Sample sizes ranged from 88 to 350. The overall quality of the included studies was considered to be high based on their Jadad scores (four trials scored 3 points and one scored 2 points).

Three RCTs reported no significant difference between LMWH and control (aspirin or no anticoagulant). Two RCTs reported a significant beneficial effect of LMWH compared to aspirin (RR 3.00, 95% CI 2.10 to 4.28) and placebo (RR 1.68, 95% CI 1.22 to 2.30).

Both $X^2$ (p=0.000) and $I^2$ statistics ($I^2=90.4\%$) indicated very substantial levels of statistical heterogeneity between trials. These were not resolved by subgroup analysis of inclusion or exclusion of women with hereditary thrombophilia. Exclusion of the study with the highest risk ratio (n=174) reduced heterogeneity substantially ($I^2=69\%$).

Authors' conclusions
There was a trend for increased live births when LMWH was used for prevention of recurrent pregnancy loss, but there was insufficient evidence to support its routine use and a need for additional studies.

CRD commentary
The review question and inclusion criteria were clear. The authors searched several relevant databases and other sources without language restrictions, which reduced the chances that relevant studies were omitted from the review and that selection biases were introduced. No specific searches for unpublished studies were reported. The authors reported that they used methods designed to reduce reviewer bias and error in study selection and validity assessment, but not in data extraction. Use of the Jadad scale to assess study validity was reasonable, but the description of the overall quality of studies as high based on Jadad scores of 2 or 3 was less so (particularly in the absence of information on criteria met by individual trials) and it is worth noting that the Jadad scale does not consider allocation concealment. The decision not to present the planned meta-analysis was probably correct in view of the levels of both clinical and statistical heterogeneity. Assessment of the influence of different comparators on levels of heterogeneity would have been informative.

The reliability of the authors' conclusions is unclear, given the level of heterogeneity and consequent lack of statistical synthesis. The recommendations for further research were appropriate.

Implications of the review for practice and research
Practice: The authors stated that there was insufficient evidence on the benefit of LMWH for the prevention of recurrent pregnancy loss to support its routine use.

Research: The authors stated that there was a need for additional studies on the use of LMWH in women with a history of unexplained late or recurrent pregnancy loss and that such studies should employ standardised criteria.

Funding
J I Zwicker K23 HL084052.

Bibliographic details

PubMedID
19912516

DOI
10.1111/j.1538-7836.2009.03687.x

Original Paper URL
http://onlinelibrary.wiley.com/journal/122683620/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Abortion, Habitual /blood /prevention & control; Abortion, Spontaneous /blood /prevention & control; Anticoagulants /therapeutic use; Evidence-Based Medicine; Female; Heparin, Low-Molecular-Weight /therapeutic use; Humans; Live Birth; Practice Guidelines as Topic; Pregnancy; Risk Assessment; Risk Factors

AccessionNumber
12010001805

Date bibliographic record published
04/08/2010

Date abstract record published
23/03/2011

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.