The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis

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Authors' objectives
The author's objectives were two-fold:

- to assess the effectiveness of follicle-stimulating hormone (FSH) plus intra-uterine insemination (IUI), compared with FSH plus timed intercourse, in the treatment of persistent unexplained infertility; and

- to determine the independent effects of FSH, IUI, clomiphene citrate, male factor and endometriosis on fecundability in persistent infertility.

Searching
The search strategy was developed by the Cochrane Subfertility Group. MEDLINE was searched using a variety of keywords including 'infertility', 'insemination, homologous', 'insemination, intrauterine', 'ovulation induction' and 'randomized'. Studies were sought on the basis of methodology using the keywords 'comparative study', 'random allocation', 'random' and 'randomized controlled trial'. Forty-three core journals (listed) were handsearched from 1966 onwards, and the bibliographies of potentially relevant studies were examined. In addition, the abstracts from relevant North American and European scientific meetings were handsearched for recent, but as yet unpublished, trials from 1986 to the present (review published in 1997).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
IUI with or without clomiphene citrate and FSH, compared with clomiphene citrate, FSH, IUI or timed intercourse.

Participants included in the review
Couples suffering persistent infertility (unexplained and male factor) were included.

Outcomes assessed in the review
Fecundity was assessed.

How were decisions on the relevance of primary studies made?
The reports were screened for relevance by independent reviewers.

Assessment of study quality
Only RCTs were included in the review; the method of randomisation was noted. The author does not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The data were extracted by independent reviewers.

Methods of synthesis
How were the studies combined?
To assess the effectiveness of FSH plus IUI versus FSH plus timed intercourse in the treatment of persistent
unexplained infertility, common odds ratios (CORs) were generated for each of the eight trials addressing this issue using the Mantel-Haenszel method. An overall COR was also generated with 95% confidence intervals (CIs).

Logistic regression was used to examine the independent effects of FSH, IUI, clomiphene citrate, male factor and endometriosis on fecundability in persistent infertility. The logistic models were constructed with and without scores for quality.

How were differences between studies investigated?
The Breslow-Day statistic was used to examine heterogeneity between the studies (see Other Publications of Related Interest).

Results of the review
Twenty-two RCTs involving more than 1,567 couples were included.

The data from the eight trials comparing FSH plus IUI with FSH plus timed intercourse cycles produced an overall COR for pregnancy per treatment per cycle of 2.37 (95% CI: 1.43, 3.90, p<0.05); this suggested a statistically-significant improvement with IUI following ovulation induction for unexplained infertility. The Breslow-Day test of heterogeneity was not statistically significant. However, low event rates reduced the power of this test, and clinically significant heterogeneity was noted.

A sensitivity analysis excluding two trials of potentially weaker methodology was carried out. The revised COR was found to be 2.56 (95% CI: 1.41, 4.65, p<0.05). Again, no statistically-significant heterogeneity was noted.

Adjusted OR, generated using stepwise logistic regression (22 RCTs, 5,214 cycles) showed the likelihood of pregnancy to be approximately two-fold greater with FSH (OR 2.35, 95% CI: 1.87, 2.94), and nearly three-times greater with IUI (OR 2.82, 95% CI: 2.18, 3.66). This was consistent with the unadjusted data. A diagnosis of male factor infertility or endometriosis reduced treatment effectiveness by approximately 50%; the ORs were 0.48 (95% CI:0.37, 0.61) and 0.45 (95% CI: 0.27, 0.76), respectively.

Authors' conclusions
This summary of published studies of IUI, with or without ovarian stimulation for persistent infertility, indicated that IUI and FSH both significantly improve fecundity.

CRD commentary
This was a well-conducted systematic review, which provided details of a thorough search strategy and clear inclusion criteria. Details of the primary studies included in the review were presented, and the data were combined appropriately. The validity assessment of the primary studies could have been more detailed.

The author provided a thorough discussion on the strengths and weaknesses of the included studies and the review itself.

Implications of the review for practice and research
The author states that further studies of FSH plus IUI versus no treatment are urgently needed. Significant side-effects require careful evaluation. Comparisons of standard high-intensity and reduced-intensity trials are required to assess the appropriate degree of ovarian stimulation for maximum benefit with the least risk and cost.

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