Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis

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Authors' objectives
To assess the benefit of intra-uterine insemination (IUI) in combination with superovulation with gonadotrophin, compared with timed intercourse in combination with superovulation with gonadotrophin, in the treatment of couples with unexplained infertility.

Searching
MEDLINE was searched from 1966 to 1997, and the bibliographies of relevant publications and review articles were searched manually.

Study selection
Study designs of evaluations included in the review
The included trials were those reporting prospective studies, where the infertile couples with unexplained infertility were randomly allocated to the following two treatments: superovulation with gonadotrophin combined with IUI with the husband’s sperm, or superovulation with gonadotrophin combined with timed intercourse. Trials with superovulation with hMG or FSH were included, whereas trials using clomiphene citrate alone were excluded.

Trials investigating other categories of infertility along with unexplained fertility were only included if they reported the data for the latter category separately.

Specific interventions included in the review
The superovulation regimes included the following hormonal treatments: follicle-stimulating hormone (FSH) and human menopausal gonadotrophin (hMG); buserelin acetate followed by hMG, with progesterone support for patients having less than 4 follicles; hMG; and clomiphene citrate and hMG with luteal support using human chorionic gonadotrophin (hCG). Single IUI with the husband’s sperm was performed 36 to 42 hours after hCG administration. The sperm were prepared by washing and layering, the Percoll method, sperm washing by self-migration in hyaluronic acid, or sperm swim-up.

Participants included in the review
The participants were couples with unexplained fertility, defined as follows: at least a 2-year history of infertility; spontaneous ovulation had been confirmed; diagnostic laparoscopy had been performed and demonstrated tubal patency; and the male partner had had at least two normal semen analyses. The duration of infertility ranged from 2 to 16 years, and the female partners were aged from 22 to 42 years.

Outcomes assessed in the review
The primary outcome was the clinical pregnancy rate, defined as the detection of foetal cardiac activity by ultrasonography.

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

Assessment of study quality
The quality of the individual studies was assessed using a modified method of Chalmers et al. (see Other Publications of Related Interest no.1). Points were awarded on aspects of study design, analysis and presentation, and then totalled. The maximum score possible was 65 points. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The odds ratios (OR) from the individual studies were combined using the fixed-effect model of Peto (see Other Publications of Related Interest no.2) to give a pooled OR and 95% confidence interval (CI).

How were differences between studies investigated?
Homogeneity was tested using the Breslow-Day test (see Other Publications of Related Interest no.3), and was rejected if the P-value was less than 0.10.

Results of the review
Seven randomised controlled trials were used to compare the pregnancy rates of the treatments (980 cycles).

Two randomised controlled trials were used to compare the rates of multiple pregnancies (334 cycles).

Scores on the quality criteria ranged from 49.23 to 70.77% of the maximum score possible.

Pregnancy rates: the results showed a timed intercourse pregnancy rate of 11.37% (49 pregnancies in 431 cycles), and an IUI pregnancy rate of 20.04% (110 pregnancies in 549 cycles).

The OR favouring IUI was 1.84 (95% CI: 1.30, 2.62), and the Breslow-Day score was 8.97 (d.f.=6, P=0.18).

The ORs in the individual studies ranged from 0.98 to 3.57, with 95% CIs ranging from 0.22 to 43.01.

For multiple pregnancies, the OR was 1.59 (95% CI: 0.39, 6.14).

Cost information
At the authors’ institution, the average total costs of superovulation, including medications and monitoring, was between US$1,400 and US$3,000, and each IUI cost US$253.

Authors’ conclusions
Couples treated for unexplained fertility can benefit from the addition of IUI to superovulation.

The use of IUI in combination with gonadotrophin will help many couples to avoid the stress and cost of more invasive procedures.

CRD commentary
This clearly written and presented review included well-defined inclusion criteria, a defined primary outcome, criteria for quality assessment, an investigation of statistical heterogeneity, and mention of the costs of IUI and superovulation treatment. The discussion referred to the potential problems associated with gonadotrophin treatment and IUI. In addition, it highlighted the fact that the determination of the cost-benefit ratio of adding IUI to superovulation depends on the local costs of the interventions. The potential causes of heterogeneity among studies, such as different patient populations and different approaches to sperm preparation and insemination, were also mentioned. The authors acknowledged the limited power of the studies in assessing outcomes of spontaneous abortion and multiple pregnancy.

Comprehensive details of the literature search would have been helpful, such as the keywords used and any language restrictions applied to the retrieved articles. Details of the methods used to select the studies for inclusion, to score
quality and to extract the data were lacking. The failure to detect statistical heterogeneity among studies may be due to the wide confidence limits in the results from individual studies, arising from the small numbers of pregnancies. Further information on multiple pregnancies and live births may have been available from the original authors. A sensitivity analysis could have been performed by analysing data from better quality studies.

The available evidence appears to support an increased pregnancy rate from the use of IUI in addition to superovulation. However, further investigations of outcomes such as rates of live births, multiple pregnancy and spontaneous abortion, and an evaluation of costs per live birth, are required before this intervention can be strongly supported.

**Implications of the review for practice and research**
The authors consider that since none of the included studies scored highly on quality criteria, an 'ideal' large randomised prospective study would be justified.

**Bibliographic details**

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**Other publications of related interest**

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Subject indexing assigned by NLM

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**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.