Intrauterine insemination: a systematic review on determinants of success

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Authors' objectives
To assess methods used in intra-uterine insemination (IUI), focusing on the following: the success rate of IUI compared with timed intercourse (TI) or with intracervical insemination (ICI); the success rate of IUI cycles for natural cycle versus controlled ovarian hyperstimulation (COH); the timing and frequency of IUI; the identification of male and female factors that predict IUI outcome; a review of the risk factors for multiple pregnancy; and the evaluation of the cost-effectiveness of IUI as a treatment for infertility.

Searching
MEDLINE and the Cochrane Library were searched and the reference lists of identified studies were checked. The search was not restricted to English language publications.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not explicitly defined in terms of the study design. The included studies were parallel-group and crossover randomised controlled trials (RCTs), meta-analyses and retrospective analyses. Studies of any design that examined factors influencing IUI success, or risk factors for multiple pregnancy, were included. Only RCTs were included for the comparisons of IUI with TI and ICI, natural cycle versus COH IUI regimens, and the methods used to time IUI with ovulation.

Specific interventions included in the review
The inclusion criteria were not explicitly defined in terms of the interventions. The clearly stated review objective implied that studies of the following were eligible: comparisons of IUI with timed intercourse or with ICI; comparisons of natural cycle with COH; studies of methods used to time IUI with ovulation; and studies of methods of the IUI process. The included studies used clomiphene citrate (CC) and/or gonadotrophins for COH.

Participants included in the review
The inclusion criteria were not explicitly defined in terms of the participants. The review objective implied that studies of infertile couples (both male and female partners) were eligible. The included studies were of couples with unexplained infertility, male subfertility and infertility due to cervical factor, endometriosis, ovulatory dysfunction, corrected tubal factor, one-sided tubal pathology, combined male and female factors, peritoneal factors, a wide range of male and female factors, pelvic adhesions and uterine factors.

Outcomes assessed in the review
The inclusion criteria were not explicitly defined in terms of the outcomes. The objective implied that studies that assessed the following outcomes were eligible: IUI success rates; male and female factors influencing success rates; and risk factors for multiple pregnancy. The included studies reported the success rates in terms of the conception and pregnancy rates per completed cycle.

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
Validity was assessed on the basis of the method of randomisation, allocation concealment and drop-outs. The authors did not state how the papers were assessed for validity, or how many reviewers performed the 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 tabulated information included study design, the number of couples, the number of completed cycles, interventions and outcomes.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to the interventions examined. Where the data were statistically homogeneous, the pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for each comparison using the fixed-effect (Peto) model.

How were differences between studies investigated?
Statistical heterogeneity was tested using the Breslow-Day statistic.

**Results of the review**

At least 26 RCTs and 11 retrospective studies were included.

IUI versus TI and ICI.

Compared with TI, IUI significantly increased the conception rates in natural cycles (6 RCTs; OR 2.5, 95% CI: 1.6, 3.9), while IUI plus COH significantly increased the pregnancy rates (7 RCTs; OR 2.2, 95% CI: 1.4, 3.6). In couples with unexplained fertility, IUI slightly increased the pregnancy rate in comparison with TI or ICI (2 RCTs, 1,691 cycles; OR 2.7, 95% CI: 1.0, 4.4), while IUI plus COH significantly increased the pregnancy rate in comparison with TI (7 RCTs, 980 cycles; OR 1.8, 95% CI: 1.3, 2.6).

IUI using natural cycle versus COH. In couples with male subfertility, COH with CC did not increase the pregnancy rate (2 RCTs; OR 0.78, 95% CI: 0.14, 4.3), whereas COH with gonadotrophins significantly increased the pregnancy rate in comparison with IUI alone (2 RCTs; OR 2.0, 95% CI: 1.1, 3.8). In couples with unexplained infertility, COH using either CC (1 RCT) or gonadotrophins (1 RCT) increased pregnancy when compared with IUI alone; COH/IUI significantly increased conception when compared with IUI alone (1 RCT; OR 1.7, 95% CI: 1.2, 2.6); and COH/IUI significantly increased the pregnancy rate in comparison with ICI (1 RCT; OR 3.2, 95% CI: 2.0, 5.3).

Timing or induction of ovulation and frequency of insemination.

Double IUI at 12 to 43 hours after gonadotrophins seemed to increase the pregnancy rate in comparison with single IUI (3 RCTs; OR 2.3, 95% CI: 1.4, 3.9). The earliest RCT (49 cycles of COH/IUI) found that double insemination increased cycle conception rates using the husband’s sperm; the second RCT (169 COH/IUI cycles) found no difference. The most recent RCT (449 COH/IUI cycles using CC and gonadotrophins) found that double insemination 12 and 34 hours after gonadotrophin administration increased pregnancy, compared with single and double insemination at 34 and 60 hours after the administration of gonadotrophins. Five retrospective studies found conflicting results on pregnancy outcome for single versus double insemination frequency.

Factors influencing the pregnancy rates.

Factors within couples: 2 studies found different results. One RCT (258 couples, 963 cycles) found no association between the duration of infertility and conception rate, while one retrospective analysis (260 cycles) found that increasing duration of infertility was associated with a decreased conception rate.

Female factors: the factors associated with the success of IUI treatment included an absence of previous pelvic corrective surgery (1 retrospective analysis, 1,728 cycles), unexplained infertility and anovulation (1 retrospective analysis, 2,473 cycles), and age (6 studies). Endometriosis or tubal problems were associated with decreased success (1 retrospective analysis, 485 cycles).

Male factors: there was a lack of standardisation of the semen analysis. Lower sperm motility counts (3 retrospective analyses) and lower post-wash sperm motility (1 retrospective analysis) were associated with a reduced success of IUI.
One meta-analysis found that poor sperm morphology (4% or less) slightly reduced the pregnancy rates in comparison with normal morphology (greater than 4%); the pooled OR (6 studies) was -0.07 (95% CI: -0.11, -0.03).

Sperm processing methods: there was no agreement on the methods used to process sperm for IUI. The pooled data from 2 RCTs (465 cycles, 433 couples) found that density gradient centrifugation led to a borderline increase in the pregnancy rate compared with the wash method; the OR was 1.7 (95% CI: 1.0, 1.9).

Factors associated with multiple pregnancy.

The multiple pregnancy rates for couples undergoing IUI ranged from 14 to 39% (3 studies). The factors associated with multiple pregnancy were peak estradiol level and the number of pre-ovulatory follicles on the day of gonadotrophin (2 studies).

Cost information
The review objective included an evaluation of the cost-effectiveness of IUI.

One study found that one cycle of in vitro fertilisation (IVF) was more expensive than four cycles of COH/IUI. One study found no difference in the cost per delivery between IUI and COH/IUI, and found that both procedures were less expensive than assisted reproductive technologies (IVF, gamete-intra-fallopian transfer, zygote-intra-fallopian transfer). Two RCTs concluded that IUI and COH/IUI were more cost-effective than IVF. One RCT reported mean pregnancy costs of US$38,012 for IVF and US$16,725 for standard infertility treatment; the other reported that the mean cost per pregnancy resulting in at least one live birth was US$5,108 for COH/IUI and US$13,132 for IVF. Neither of these studies considered the costs of antenatal care.

Authors' conclusions
IUI was successful in treating selected infertile couples, but more research is required. The authors further stated that decisions about infertility treatment need to take account of the age of the woman, the cause of the infertility, and the cost-effectiveness of other treatments.

CRD commentary
The review question was clear in terms of the intervention, participants and outcomes, although the inclusion criteria for the review were not explicitly stated.

Only two databases were searched, which may have resulted in the omission of other relevant studies, and the dates searched were not reported. However, the search terms were stated and non-English language publications were eligible. There was no attempt to locate unpublished studies, thus raising the possibility of publication bias.

The methods used to select the studies, assess validity and extract the data were not described. Hence, it was unclear whether attempts were made to reduce bias and errors by carrying out these processes in duplicate. Validity was assessed using defined criteria and, where possible, only evidence from RCTs was included. Some relevant information was tabulated, but the methods used to determine pregnancy and the stage of pregnancy assessed were not reported. The studies were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. The evidence presented appears to support the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that IUI is a valuable and cost-effective treatment for infertility due to certain conditions. IUI is more effective than TI for male subfertility and unexplained infertility.

Research: The authors stated that research is required to determine uterine cavity and fallopian tube characteristics that would optimise IUI success. They further stated that the cost-effectiveness of the treatment options needs to be assessed and that such assessments should evaluate the costs of neonatal intensive care.
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