Effectiveness of assisted reproductive technology (ART)

CRD summary
This review evaluated the safety and effectiveness of assisted reproductive technology, ovulation induction and superovulation. It concluded that there was little high-quality evidence upon which to draw conclusions regarding the choice of specific interventions. This was generally a well-conducted review and the authors' conclusions are likely to reflect the available evidence.

Authors' objectives
To evaluate the safety and effectiveness of assisted reproductive technology, ovulation induction and superovulation.

Searching
MEDLINE was searched from January 2000 to January 2008 for English-language studies; search terms were reported. Reviews published by the Cochrane Menstrual Disorders and Subfertility Review Group were handsearched to identify additional studies.

Study selection
Studies that assessed the effectiveness of assisted reproductive technology, ovulation induction and superovulation in women aged 45 years or younger were eligible for inclusion; non-randomised studies had to recruit at least 50 participants. Included studies had to report: the predictive value of diagnostic tests and prognostic factors; the benefits or risk of superovulatory drugs and metformin; the success rate of laboratory or clinical practices to produce singleton pregnancies and which may lead to multiple births; or adverse events. Inclusion criteria were applied differently across questions. The outcomes of interest were pregnancy, live birth or adverse events. Included interventions comprised: oestrogen inhibitors; insulin sensitisers; gonadotrophins; combination therapies; surgical interventions; pituitary down-regulation; ovarian stimulation; inducing final follicular maturation; oocyte retrieval; embryo transfer; luteal support; medical therapy; prevention of ovarian hyperstimulation syndrome; fertilisation; assisted hatching; and other adjunctive interventions.

Pairs of reviewers independently selected studies for inclusion in the review. Differences were resolved by consensus.

Assessment of study quality
Randomised controlled trials were assessed in terms of randomisation method, adequacy of allocation concealment, blinding and dropout rate. Cohort studies were assessed in terms of population selection and size, reporting of baseline characteristics, use of validated methods for determining exposure and outcomes, follow-up and the analysis used. Case-control studies were assessed in terms of establishment of cases, selection and appropriateness of controls, comparability at baseline and the analysis used.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
For each study the relative risk or odds ratio together with 95% confidence intervals were calculated. One reviewer extracted data for each study question and a second checked for accuracy.

Methods of synthesis
A narrative synthesis was provided, supported by tables. Differences between studies were discussed in the text. Results from Cochrane reviews and other systematic reviews were presented for comparison.

Results of the review
A total of 478 studies were included in the review.
**Induction of ovulation:** Of 36 comparisons of medical therapy, only eight reported statistically significant results. Pregnancy was achieved more frequently with: clomiphene administered within five days compared to after five days; metformin compared to clomiphene (two studies) or placebo; and clomiphene combined with either oral contraceptive pre-treatment, n-acetylcyesteine or dexamethasone compared to clomiphene alone. Ongoing pregnancy was achieved more frequently with: metformin compared to clomiphene (two studies); and clomiphene combined with ketoconazole, phytoestrogen or estradiol compared to clomiphene alone. Of the six comparisons of surgical therapy, only the addition of metformin to laparoscopic ovarian diathermy showed a significant result when compared to placebo (one study).

**Superovulation in ovulating women:** There were 16 comparisons of medical therapy. Only one reported a significant improvement in pregnancy rates: follicle-stimulating hormone (FSH) combined with cetrorelix compared to follicle-stimulating hormone alone (two of three studies). One study reported a higher rate of pregnancy in women who underwent endometrial polypectomy.

**Assisted conception:** Of 72 comparisons of pituitary down-regulation, ovarian stimulation, or induction of final follicular maturation, only 11 reported a statistically significant improvement in the rate of pregnancy or live births. Successful treatments of the female partner included: 1.87mg compared to 3.5mg triptorelin; ganirelix compared to buserelin; oral contraceptive pretreatment plus antide compared to gonadotrophin plus antide; short compared to long protocol buserelin when a poor response was likely; six days urinary follicle-stimulating hormone followed by recombinant follicle-stimulating hormone; individualised follicle-stimulating hormone dose compared to standard step-up; recombinant follicle-stimulating hormone plus gonadotrophin compared to recombinant follicle-stimulating hormone plus leutinising hormone; buserelin with or without human chorionic gonadotropin compared to buserelin alone; and triptorelin compared to human chorionic gonadotropin.

**Adverse events:** Most adverse longer-term outcomes were associated with infertility. Infants that resulted from infertility treatments were considered to be at risk for complications associated with abnormal implantation of placenta, although the degree to which this was due to underlying infertility, the treatment, or both was unclear. Preterm delivery increased two-fold in singleton pregnancies achieved after assisted reproductive technology compared with those conceived spontaneously. An increased risk of breast and ovarian cancer was associated with infertility but no infertility treatment.

Results for oocyte retrieval, embryo transfer, embryo culture, luteal support and other adjunct treatments are presented.

**Authors’ conclusions**

There was little high-quality evidence from which to draw conclusions regarding the choice of specific interventions.

**CRD commentary**

This review was based on a number of broad questions which were appropriately defined in terms of the participants, interventions and outcomes of interest. The literature search was limited to one database and restricted to identifying English-language publications with no specific search for unpublished studies, therefore, publication and language bias could be present and studies may have been missed. Study selection and data extraction were conducted in duplicate, which reduced potential for error and bias. Appropriate criteria were used to assess the quality of the included studies. It was unclear how many reviewers were involved in the process and it seemed likely that this too was undertaken in duplicate. Given the heterogeneity between the studies the decision to employ a narrative synthesis was appropriate. This was generally a well-conducted review, the limitations of which were acknowledged by the authors. The conclusions are likely to reflect the available evidence.

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

**Practice:** The authors stated that clomiphene was an effective first-line therapy for women with polycystic ovary syndrome. Laparoscopic cautery, followed by ovulation induction if necessary, produced comparable pregnancy and live birth rates compared to immediate gonadotropin use in clomiphene-resistant women. Metformin may result in further improvements.

**Research:** The authors stated that research priorities were interventions currently in use and the effectiveness and long-term outcomes in male partners and prevention of preterm birth. Further investigation was required for: potential links between infertility, infertility treatments and pregnancy outcomes associated with implantation and placentaion; long-
term cardiovascular risk in mothers; patient decision making; and methods for valuing the impact of infertility.
Recommendations were made regarding study design, data collection, barriers to high-quality research and areas for prioritising research.

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