In vitro fertilization for unexplained subfertility

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RHL Summary

Key findings

This updated review compared the effectiveness and safety of IVF with other interventions for the management of unexplained subfertility. Key findings were:

- Live birth rate per woman/couple was significantly higher with IVF than expectant management or unstimulated intrauterine insemination (IUI)
- Among women pretreated with clomiphene citrate (CC), live birth rates were significantly higher with IVF than IUI + gonadotrophins
- Among treatment-naive women, there were no differences in live birth rates between IVF and IUI + gonadotrophins or between IVF and IUI + CC
- Evidence pertaining to adverse events including multiple pregnancy rate and ovarian hyper stimulation syndrome associated with these interventions was limited

Evidence included in this review

1,622 couples were included, from eight randomized trials conducted in high-income countries.

Quality assessment

Quality of included studies ranged from very low to moderate for the primary outcomes, as assessed by the GRADE method.

Clinical implications

Current evidence shows that IVF may be effective, as indicated by higher live birth rates. However, evidence pertaining to adverse events remains limited across all treatment modalities. Clinicians and couples are advised to balance the invasive nature and related costs of IVF against the chances of success with alternative treatment.

Further research

Large RCTs with harmonized definitions and stronger methodology are warranted. Including participants of
Cochrane review


Abstract

One-third of subfertile couples have no identifiable cause for their inability to conceive. In vitro fertilisation (IVF) is a widely accepted treatment for this condition; however, this treatment is invasive and expensive and is associated with risks.

To evaluate the effectiveness and safety of IVF compared with expectant management, unstimulated intrauterine insemination (IUI) or intrauterine insemination along with ovarian stimulation with gonadotropins (IUI + gonadotropins) or clomiphene (IUI + CC) or letrozole (IUI + letrozole) in improving pregnancy outcomes.

This review has drawn on the search strategy developed by the Cochrane Menstrual Disorders and Subfertility Group. We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched May 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, first quarter), MEDLINE (1946 to May 2015), EMBASE (1985 to May 2015), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (May 2015) and reference lists of articles. We searched the following trial registries: clinicaltrials.gov (http://www.clinicaltrials.gov) and the World Health Organization International Trials Registry Platform search portal (http://www.who.int/trialsearch/Default.aspx). We searched the Web of Science (http://wokinfo.com/) as another source of trials and conference abstracts, OpenGrey (http://www.opengrey.eu/) for unpublished literature from Europe and the Latin American Caribbean Health Sciences Literature (LILACS) database (http://regional.bvsalud.org/php/index.php?lang=en). Moreover, we handsearched relevant conference proceedings and contacted study authors to ask about additional publications.

Two review authors independently assessed trial eligibility, extracted data and assessed risk of bias. The primary review outcome was cumulative live birth rate. Multiple pregnancy and other adverse effects were secondary outcomes. We combined data to calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs). We assessed statistical heterogeneity by using the I² statistic. We assessed the overall quality of evidence for the main comparisons using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods.

We included randomised controlled trials (RCTs) in which the effectiveness of IVF in couples with unexplained subfertility was compared with that of other treatments, including expectant management, unstimulated IUI and stimulated IUI using gonadotropins or clomiphene or letrozole.

Live birth rate (LBR) per woman was the primary outcome.

Two review authors independently assessed the eligibility and quality of trials and evaluated the quality of the evidence by using GRADE criteria.

**IVF versus expectant management (two RCTs):**
Live birth rate per woman was higher with IVF than with expectant management (odds ratio (OR) 22.00, 95% confidence interval (CI) 2.56 to 189.37, one RCT, 51 women, very low quality evidence). Multiple pregnancy rates (MPRs), ovarian hyperstimulation syndrome (OHSS) and miscarriage were not reported.

**IVF versus unstimulated IUI (two RCTs):**

Live birth rate was higher with IVF than with unstimulated IUI (OR 2.47, 95% CI 1.19 to 5.12, two RCTs, 156 women, I² = 60%, low quality evidence). There was no evidence of a difference between the groups in multiple pregnancy rates (OR 1.03, 95% CI 0.04 to 27.29, one RCT, 43 women, very low quality evidence).

**IVF versus IUI + ovarian stimulation with gonadotropins (three RCTs) or clomiphene (one RCT) or letrozole (no RCTs):**

Data from these trials could not be pooled because of high statistical heterogeneity (I² = 93.3%). Heterogeneity was eliminated when studies were stratified by pretreatment status.

In trials comparing IVF versus IUI + gonadotropins among treatment-naive women, there was no conclusive evidence of a difference between the groups in live birth rates (OR 1.27, 95% CI 0.94 to 1.73, four RCTs, 745 women, I² = 8.0%, moderate-quality evidence). In women pretreated with IUI + clomiphene, a higher live birth rate was reported among those who underwent IVF than those given IUI + gonadotropins (OR 3.90, 95% CI 2.32 to 6.57, one RCT, 280 women, moderate-quality evidence). There was no conclusive evidence of a difference in live birth rates between IVF and IUI + CC in treatment-naive women (OR 2.51, 95% CI 0.96 to 6.55, one RCT, 103 women, low quality evidence).

In treatment-naive women, there was no evidence of a difference in rates of multiple pregnancy between women who underwent IVF and those who received IUI + gonadotropins (OR 0.79, 95% CI 0.45 to 1.39, four RCTs, 745 women, I² = 0%, moderate quality evidence). There was no evidence of a difference in MPRs between women who underwent IVF compared with those given IUI + CC (OR 1.02, 95% CI 0.20 to 5.31, one RCT, 103 women, low-quality evidence).

There was no evidence of a difference in ovarian hyperstimulation syndrome rate between treatment-naive women who underwent IVF and those given IUI + gonadotropins (OR 1.23, 95% CI 0.36 to 4.14, two RCTs, 221 women, low quality evidence). There was no evidence of a difference in OHSS rates between groups receiving IVF versus those receiving IUI + CC (OR 1.02, 95% CI 0.20 to 5.31, one RCT, 103 women, low-quality evidence).

In treatment naive women, there was no evidence of a difference in miscarriage rates between IVF and IUI + CC (OR 1.16, 95% CI 0.44 to 3.02, one RCT, 103 women, low-quality evidence), nor between women treated with IVF versus those receiving IUI+ gonadotropins (OR 1.16, 95% CI 0.44 to 3.02, one RCT, 103 women).

No studies compared IVF with IUI + letrozole.

The quality of the evidence ranged from very low to moderate. The main limitation was serious imprecision resulting from small study numbers and low event rates.
IVF may be associated with higher live birth rates than expectant management, but there is insufficient evidence to draw firm conclusions. IVF may also be associated with higher live birth rates than unstimulated IUI. In women pretreated with clomiphene + IUI, IVF appears to be associated with higher birth rates than IUI + gonadotropins. However in women who are treatment-naïve there is no conclusive evidence of a difference in live birth rates between IVF and IUI + gonadotropins or between IVF and IUI + clomiphene. Adverse events associated with these interventions could not be adequately assessed owing to lack of evidence.


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