Targeted Update

Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization.

This is a Targeted update of the Cochrane Review


Latest search was performed: 8 February 2015

Results of the search, list of new references, details of updates to methods, study characteristics, risk of bias assessments, and details of data analyses can be found in the Supplementary material.

This Targeted update document was prepared by Hanna Bergman¹ and Rachel Marshall². Data were taken from the previously published full review and from results of the updating process carried out by Hanna Bergman¹, Antonio Grande¹, and Nicola Maayan¹. The abstract was adapted from the previously published full review.

Acknowledgements: Ahmed Gibreel³ provided content expertise.

¹Enhanced Reviews, UK; ²Cochrane Editorial Unit, UK; ³Mansoura

Copyright © 2016 The Cochrane Collaboration.
Sources of Support: Funded by Cochrane as part of a pilot project.
Clomiphene citrate with gonadotropins compared to gonadotropin protocols for controlled ovarian stimulation in women undergoing *in vitro* fertilisation:

- May slightly reduce (worsen) the number of live births per woman;
- May reduce (improve) ovarian hyperstimulation syndrome.

**Background**
Gonadotropins are the most commonly used medication for controlled ovarian stimulation in *in vitro* fertilization (IVF). However, they are expensive, invasive, and are associated with risk of ovarian hyperstimulation syndrome (OHSS). With recent calls for patient-friendly IVF, there has been an interest in the use of clomiphene citrate, a low cost, widely available oral selective estrogen receptor modulator, with gonadotropins, to reduce the burden of injections. However, it is not known whether regimens using clomiphene citrate are at least as effective as gonadotropins alone.

**Objectives**
To determine whether clomiphene citrate with gonadotropins (with or without mid-cycle GnRH antagonist) is more effective than gonadotropin alone in IVF or intracytoplasmic sperm injection (ICSI) treatment.

**Search methods**
Electronic databases, Cochrane Menstrual Disorders and Subfertility Group Trials Register, and ongoing trials registries were searched in February 2015.

**Selection criteria**
Randomised controlled trials (RCTs) were included. Live birth rate (LBR) per woman was the primary outcome.

**Data collection and analysis**
Two review authors independently assessed the eligibility and quality of trials. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous data, and mean differences (MD) with 95% CIs for continuous data. The fixed-effects model was used.

**Main Results**
Twenty studies were included in the review. Six studies were added at this update and 14 studies were in the previous version. In addition, five ongoing studies and one study awaiting assessment were found. Meta-analysis could be performed with the data of 18 included studies, with a total of 5941 participants. Meta-analysis could not be performed with two studies because they were published as abstracts with limited information.

Risk of bias was unclear or high for most included studies as the randomisation process was not adequately described in the reports, participants were excluded from analyses without explanation, or data were analysed per cycle as opposed to per participant. Half of the trials included were published over 10 years ago, and outcomes such as live births, multiple pregnancy, OHSS, and miscarriages have not been reported by many studies.

There was low quality evidence of a small reduction on live birth rate (LBR) with clomiphene citrate with gonadotropins for IVF, with or without mid-cycle GnRH antagonist, when compared with gonadotropins alone in GnRH agonist protocols (11 RCTs, 2928 women; OR 0.79, 95% CI 0.66 to 0.95). For a typical clinic with a LBR of 27% using a GnRH agonist regimen, switching to clomiphene protocols may result in LBRs between 20 and 26%. There was also low quality evidence of: a reduction in OHSS; an increase in cycle cancellation rate; a reduction in multiple pregnancies; and a reduction in the mean number of oocytes retrieved with clomiphene citrate when compared with gonadotropins. There was moderate quality evidence of little or no effect on clinical pregnancy, and a reduction in the mean number of gonadotropin ampoules used with clomiphene citrate.

**Implications and conclusions**
There was some evidence that clomiphene citrate with gonadotropins (with or without GnRH antagonist) may worsen LBR, cycle cancellation rate, and number of oocytes retrieved, but probably has little or no difference on clinical pregnancy rate and may improve OHSS, multiple pregnancy rate, and mean number of ampoules used, when compared with gonadotropins in GnRH agonist protocols. However, for most outcomes the quality of the evidence was low, and further research is very likely to have an important impact on these estimates.
## Summary of Findings: Clomiphene citrate for controlled ovarian stimulation in IVF

**Patients and setting:** Subfertile women undergoing controlled ovarian stimulation for IVF and ICSI cycles. Studies were set in Austria, Canada, Iran, Italy, Japan, the Netherlands, Poland, Taiwan, the UK, and the USA.

**Comparison:** Clomiphene citrate with gonadotropins (with or without mid-cycle antagonist) versus gonadotropins with GnRH agonists protocols.

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plain language summary</th>
<th><strong>Absolute effect</strong></th>
<th><strong>Relative effect (95% CI) Nº of participants &amp; studies</strong></th>
<th><strong>Certainty of the evidence (GRADE)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth rate (better indicated by higher numbers)</td>
<td>Clomiphene citrate may slightly reduce (worsen) the number of live births per woman.</td>
<td>268 per 1000 224 per 1000</td>
<td>OR 0.79 (0.66 to 0.95) Based on data from 2928 patients in 11 studies</td>
<td>🍂🍂 LOW 1,2</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome (better indicated by lower numbers)</td>
<td>Clomiphene citrate may reduce (improve) ovarian hyperstimulation syndrome.</td>
<td>41 per 1000 6 per 1000</td>
<td>OR 0.15 (0.07 to 0.33) Based on data from 2123 patients in 6 studies</td>
<td>🍂🍂 LOW 1,3</td>
</tr>
<tr>
<td>Clinical pregnancy rate (better indicated by higher numbers)</td>
<td>Clomiphene citrate probably makes little or no difference to clinical pregnancy rate.</td>
<td>195 per 1000 197 per 1000</td>
<td>OR 1.01 (0.83 to 1.22) Based on data from 2840 patients in 12 studies</td>
<td>✨ Moderate 1</td>
</tr>
<tr>
<td>Cycle cancellation rate (better indicated by lower numbers)</td>
<td>Clomiphene citrate may increase (worsen) the cycle cancellation rate.</td>
<td>96 per 1000 171 per 1000</td>
<td>OR 1.95 (1.54 to 2.47) Based on data from 2936 patients in 13 studies</td>
<td>🍂🍂 LOW 1,4</td>
</tr>
<tr>
<td>Multiple pregnancy rate (better indicated by lower numbers)</td>
<td>Clomiphene citrate may reduce (improve) the number of multiple pregnancies per woman.</td>
<td>295 per 1000 137 per 1000</td>
<td>OR 0.38 (0.25 to 0.57) Based on data from 633 patients in 7 studies</td>
<td>🍂🍂 LOW 1,4</td>
</tr>
<tr>
<td>Mean number of gonadotropin ampoules used (better indicated by lower values)</td>
<td>Clomiphene citrate probably reduces (improves) the mean number of gonadotropin ampoules used.</td>
<td>Mean: 27.6 Mean: 11.41</td>
<td>MD -16.19 (-16.77 to -15.61) Based on data from 1413 patients in 8 studies</td>
<td>🍂🍂 Moderate 1,5</td>
</tr>
<tr>
<td>Mean number of oocytes retrieved (better indicated by higher values)</td>
<td>Clomiphene citrate may reduce (worsen) the mean number of oocytes retrieved.</td>
<td>Mean: 8.5 Mean: 5.68</td>
<td>MD -2.82 (-3.06 to -2.58) Based on data from 3064 patients in 12 studies</td>
<td>🍂🍂 LOW 1,4</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>CI = confidence interval; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; MD = Mean difference; OR = Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Design (-1): Method of allocation concealment was either not described or not mentioned at all in most included trials. 2Indirectness (-1): Reported as ongoing pregnancy or cumulative live birth rates in half of the included studies. 3Imprecision (-1): Small number of total events. 4Inconsistency (-1): Substantial heterogeneity (I² &gt; 50%, P &lt; 0.05). 5Inconsistency (0): Although heterogeneity was considerable, this referred to the magnitude of difference rather than to the direction of evidence.</td>
</tr>
</tbody>
</table>