

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

Gibreel A, Maheshwari A, Bhattacharya S. Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008528. DOI: 10.1002/14651858.CD008528.pub2.

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.

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What's a Targeted Update?

Targeted Updates are two to three-page documents that use the Cochrane Review as their foundation, but focus on updating only one or two important comparisons, and the seven most relevant outcomes. They include an updated Summary of Findings table and Abstract, and use Cochrane methodology. The full search results, risk of bias assessments, analyses, and references do not form part of the Targeted Update, but are available as supplementary information. Targeted Updates are intended for use by policy makers.

What's the context for this Targeted Update?

The topic for this Targeted update was identified by the Cochrane Gynaecology and Fertility Group editorial base as being in need of an update.

What's new

This Targeted update identified an additional six studies with 3405 participants. Adding these studies led to a change in conclusions: clomiphene citrate was associated with a small reduction in live birth in this version, compared with no evidence of difference in the previous version.

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 antagonist) is more effective than gonadotropins with gonadotropin-releasing hormone (GnRH) agonists for controlled ovarian stimulation 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

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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	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Gonadotropins	Clomiphene citrate		
Live birth rate (better indicated by higher numbers)	Clomiphene citrate may slightly reduce (worsen) the number of live births per woman.	268 per 1000	224 per 1000	OR 0.79 (0.66 to 0.95) Based on data from 2928 patients in 11 studies	⊕⊕⊕⊕ LOW ^{1,2}
		Difference 44 fewer per 1000 patients (95% CI: 10 to 73 fewer per 1000 patients)			
Ovarian hyperstimulation syndrome (better indicated by lower numbers)	Clomiphene citrate may reduce (improve) ovarian hyperstimulation syndrome.	41 per 1000	6 per 1000	OR 0.15 (0.07 to 0.33) Based on data from 2123 patients in 6 studies	⊕⊕⊕⊕ LOW ^{1,3}
		Difference 35 fewer per 1000 patients (95% CI: 27 to 38 fewer per 1000 patients)			
Clinical pregnancy rate (better indicated by higher numbers)	Clomiphene citrate probably makes little or no difference to clinical pregnancy rate.	195 per 1000	197 per 1000	OR 1.01 (0.83 to 1.22) Based on data from 2840 patients in 12 studies	⊕⊕⊕⊕ MODERATE ¹
		Difference 2 more per 1000 patients (95% CI: 28 fewer to 33 more per 1000 patients)			
Cycle cancellation rate (better indicated by lower numbers)	Clomiphene citrate may increase (worsen) the cycle cancellation rate.	96 per 1000	171 per 1000	OR 1.95 (1.54 to 2.47) Based on data from 2936 patients in 13 studies	⊕⊕⊕⊕ LOW ^{1,4}
		Difference 75 more per 1000 patients (95% CI: 44 to 112 more per 1000 patients)			
Multiple pregnancy rate (better indicated by lower numbers)	Clomiphene citrate may reduce (improve) the number of multiple pregnancies per woman.	295 per 1000	137 per 1000	OR 0.38 (0.25 to 0.57) Based on data from 633 patients in 7 studies	⊕⊕⊕⊕ LOW ^{1,4}
		Difference 158 fewer per 1000 patients (95% CI: 102 to 200 fewer per 1000 patients)			
Mean number of gonadotropin ampoules used (better indicated by lower values)	Clomiphene citrate probably reduces (improves) the mean number of gonadotropin ampoules used.	Mean: 27.6	Mean: 11.41	MD -16.19 (-16.77 to -15.61) Based on data from 1413 patients in 8 studies	⊕⊕⊕⊕ MODERATE ^{1,5}
		Difference 16.19 lower (95% CI: 16.77 to 15.61 lower)			
Mean number of oocytes retrieved (better indicated by higher values)	Clomiphene citrate may reduce (worsen) the mean number of oocytes retrieved.	Mean: 8.5	Mean: 5.68	MD -2.82 (-3.06 to -2.58) Based on data from 3064 patients in 12 studies	⊕⊕⊕⊕ LOW ^{1,4}
		Difference 2.82 lower (95% CI 3.06 to 2.58 lower)			

CI= confidence interval; ICSI=intracellular sperm injection; IVF= in vitro fertilisation; MD=Mean difference; OR=Odds ratio

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 ($I^2 > 50\%$, $P < 0.05$). ⁵Inconsistency (0): Although heterogeneity was considerable, this referred to the magnitude of difference rather than to the direction of evidence.