

## Cochrane Review Series (Volume - 6)

**Cochrane review series: Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. Cochrane Database Syst Rev. 2017; 11(11):CD008528.**

**Question: Are ovarian stimulation protocols combining oral medications like Clomiphene citrate or Letrozole with gonadotropins effective and safe compared to gonadotropins alone in women undergoing In-vitro fertilization (IVF)?**

### Focus

Regimens using oral ovulogens and gonadotropins versus gonadotropins alone for women undergoing IVF.

### Population Of Interest

Unselected IVF population of subfertile women undergoing controlled ovarian stimulation for IVF and 'poor' responders

### Intervention Under Investigation

Clomiphene citrate (CC) or Letrozole (Ltz) with gonadotropins for controlled ovarian hyperstimulation (COH).

### What Was The Comparison?

Gonadotropins alone for COH

### What Were The Main Outcomes?

Live birth rate (LBR), ovarian hyperstimulation syndrome (OHSS) rate and cycle cancellation rate.

### Results In Short

- ◆ **Twenty-two trials** including 3599 women undergoing IVF.
- ◆ **Live birth rate: No difference in live birth rate following ovarian stimulation with CC or Ltz with gonadotropins** versus gonadotropins alone (Risk Ratio (RR) 0.92, 95% confidence interval (CI) 0.66 to 1.27; 4 RCTs, 493 women, low-quality evidence) in the general IVF population<sup>1</sup>.  
**No difference in live birth rate following ovarian stimulation with CC or Ltz and gonadotropins** versus gonadotropins alone (RR 1.16, 95% CI 0.49 to 2.79, 2 RCTs, 357 women, low-quality evidence) among poor responders.
- ◆ **OHSS rate: Significantly lower incidence of OHSS following stimulation protocols using CC or Ltz with gonadotropins** versus gonadotropins alone (Peto OR 0.21, 95% CI 0.11 to 0.41, 5 RCTs, 1067 women, low-quality evidence) in the general IVF population.
- ◆ **Cycle cancellation rate: Significantly higher cycle cancellation rate with CC or Ltz and gonadotropins** versus gonadotropins alone (RR 1.87, 95% CI 1.43 to 2.45, 9 RCTs, 1784 women, low-quality evidence) in the general IVF population.
- ◆ **Number of gonadotropin ampoules and number of oocytes retrieved: Decrease in number of gonadotropin ampoules used and mean number of oocytes collected when CC or Ltz with gonadotropins was used** compared with gonadotropin-only regimens (moderate quality evidence) in the general IVF population and poor responders.

### Limitation

- ◆ Only six among 22 included studies reported live birth rates as primary outcome, necessitating cautious interpretation of overall results.
- ◆ Studies included only fresh stimulated IVF cycles. None of the trials addressed surplus frozen embryos available for subsequent transfer; thereby data for cumulative live birth was not available. Currently, cumulative live birth rate is a more preferred outcome to evaluate effectiveness of IVF treatment.
- ◆ Studies that assessed poor responders used varied criteria for inclusion thereby introducing clinical heterogeneity.
- ◆ Lack of blinding in most included trials, poor reporting of methodology, differences in protocol and cycle cancellation policy impacted the overall quality of evidence.

### Evidence Based Practice Points

- ◆ **Current weight of evidence suggests comparable live birth rates between CC or Ltz and gonadotropins versus gonadotropins alone, in both the routine IVF population and among poor responders. It is a viable alternative protocol in certain clinical scenarios like poor responders.**
- ◆ **Addition of CC or Ltz reduces gonadotrophin requirement and incidence of ovarian hyperstimulation syndrome. Reduced gonadotrophin requirement could reduce initial treatment cost.**
- ◆ **Higher cancellation rates and lower oocyte yield following use of CC or Ltz with gonadotrophin is a drawback. Cancellation of cycles can be psychologically distressing for the couples.**
- ◆ **There has been a shift of contemporary practice towards maximizing oocyte yield in single retrieval cycle and "freeze all policy" due to higher cumulative live birth rate<sup>2</sup>. In light of these developments, studies evaluating cumulative live birth following milder stimulation protocols using CC or Ltz with gonadotrophins are needed along with cost effectiveness in order to establish their role in current IVF practice.**

### Reference

1. Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation. Cochrane Database Syst Rev. 2017;11(11):CD008528.
2. Drakopoulos P, Blockeel C, Stoop D, Camus M, De Vos M, Tournaye H, Polyzos NP. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize?



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