ORIGINAL ARTICLE: INFERTILITY

Low dosing of gonadotropins in in vitro fertilization cycles for women with poor ovarian reserve: systematic review and meta-analysis

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Objective: To evaluate the effectiveness of low doses of gonadotropins and gonadotropins combined with oral compounds compared with high doses of gonadotropins in ovarian stimulation regimens in terms of ongoing pregnancy per fresh IVF attempt in women with poor ovarian reserve undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment.
Design: A systematic review and meta-analysis of randomized controlled studies that evaluate the effectiveness of low dosing of gonadotropins alone or combined with oral compounds compared with high doses of gonadotropins in women with poor ovarian reserve undergoing IVF/ICSI treatment.
Setting: Not applicable.
Patient(s): Subfertile women with poor ovarian reserve undergoing IVF/ICSI treatment.
Intervention(s): We searched the PubMed, EMBASE, Web of Science, the Cochrane Library, and the Clinical Trials Registry using medical subject headings and free text terms up to June 2016, without language or year restrictions. We included randomized controlled studies (RCTs) enrolling subfertile women with poor ovarian reserve undergoing IVF/ICSI treatment and comparing low doses of gonadotropins and gonadotropins combined with oral compounds versus high doses of gonadotropins. We assessed the risk of bias using the criteria recommended by the Cochrane Collaboration. We pooled the results by meta-analysis using the fixed and random effects model.
Main Outcomes Measure(s): The primary outcome was ongoing pregnancy rate (PR) per woman randomized.
Result(s): We retrieved 787 records. Fourteen RCTs (N = 2,104 women) were included in the analysis. Five studies (N = 717 women) compared low doses of gonadotropins versus high doses of gonadotropins. There was no evidence of a difference in ongoing PR (2 RCTs: risk rate 0.98, 95% confidence interval 0.62–1.57, $I^2 = 0$). Nine studies (N = 1,387 women) compared ovarian stimulation using gonadotropins combined with the oral compounds letrozole (n = 6) or clomiphene citrate (CC) (n = 3) versus high doses of gonadotropins. There was no evidence of a difference in ongoing PR (3 RCTs: risk rate 0.90, 95% confidence interval 0.63–1.27, $I^2 = 0$).
Conclusion(s): We found no evidence of a difference in pregnancy outcomes between low doses of gonadotropins and gonadotropins combined with oral compounds compared with high doses of gonadotropins in ovarian stimulation regimens. Whether low doses of gonadotropins or gonadotropins combined with oral compounds is to be preferred is unknown, as they have never been compared head to head. A health economic analysis to test the hypothesis that an ovarian stimulation with low dosing is more cost-effective than high doses of gonadotropins is needed.
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The mean age of women giving birth to their first child is still increasing, especially in Western countries (1). As a result, more women face subfertility due to diminished ovarian function who then seek medical help to become pregnant (2).

Older women are increasingly seeking and obtaining IVF and it is estimated that 37% of all IVF cycles are performed in older women (3–5). At present, the ovarian stimulation regimen for women with poor ovarian reserve, regardless of their age, includes high doses of gonadotropins—up to 600 IU/d—combined with various protocols of GnRH analogues in an attempt to achieve high follicular recruitment (6–9) Despite these high doses of gonadotropins, oocyte yield remains poor and cancellation rates are high (10, 11) This is due to a patient factor that is completely unrelated to ovarian stimulation per se (12). At birth, both ovaries contain approximately one to two million primordial follicles, of which only about 300,000 are available for ovulation at puberty. Thereafter, there is a steady loss of follicles, at a rate of about 1,000 per month, and this accelerates beyond 35 years of age with a factor of two (13, 14).

Because there are at present no means for improving ovarian reserve, the question arises as how to obtain the best possible outcome, with the least patient discomfort and lowest costs while maintaining overall success rates in IVF. During the years several low doses of gonadotropins and gonadotropins combined with oral compounds for ovarian stimulation regimens have been suggested as alternatives for women with poor ovarian reserve, aiming at reducing the dose of gonadotropins or shortening the duration of stimulation using oral compounds such as antiestrogens or aromatase inhibitors (15–18). Striving for low doses of gonadotropins in women with poor ovarian reserve is a valid approach for two reasons. First, high doses have been shown not to be beneficial in women with poor ovarian reserve (19). Second, high doses increase the costs of IVF, a consequence that would only be acceptable if paralleled by an improvement in IVF outcome. Oral compounds, such as clomiphene citrate (CC), have been used for decades as an adjunct to increase the pituitary FSH secretion by reducing estrogen (E) negative feedback (20). The alternative adjunct, aromatase inhibitors, inhibits the aromatase activity in granulosa cells (GCs) and thereby increases the intraovarian concentration of androgens by blocking the aromatization to E. The low E then triggers the pituitary gland to an increase in FSH release (21). Both mechanisms lead to a reduced required dose of gonadotropins for stimulation.

There are several clinical trials and reviews that evaluated the treatment options for women with poor ovarian reserve including low dose gonadotropins for ovarian stimulation, The overall conclusion of these is that there is still insufficient evidence whether low doses of gonadotropins are a good alternative to high doses for subfertile women with poor ovarian reserve undergoing IVF (6, 7, 22–25). We therefore designed this systematic review and meta-analysis to evaluate the effectiveness of low doses of gonadotropins in ovarian stimulation regimens in subfertile women with poor ovarian reserve in comparison to high doses of gonadotropins in terms of ongoing pregnancy rate (PR) per fresh IVF attempt.

MATERIALS AND METHODS

Search Strategy for Identification of Studies

We searched the following electronic databases: MEDLINE, EMBASE, Web of Science, Cochrane library, and the Central Register of Controlled Trials (http://clinicaltrials.gov/), covering the period from their inception up to June 2016. The following terms: GnRH antagonist, long GnRH agonist, oral compounds, clomiphene citrate, letrozole, aromatase inhibitors, low dose gonadotropins, mild ovarian stimulation, minimal ovarian stimulation, poor ovarian reserve, poor responders, GnRH analogues, GnRH agonist, natural cycle, gonadotropins, low dose, high dose, pregnancy rate, number of oocytes, cancellation rate "AND" IVF/ICSI/ART "AND" randomized controlled trial(s) "OR" randomised controlled trial(s), were used. We examined the reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (e.g., ESHRE and ASRM), and included studies to identify additional relevant citations. If necessary, additional information was sought from the authors. The search was not restricted by language. The searches were conducted independently by M.A.-F.Y. and U.M.F.

Selection of Studies and Data Extraction

We included all parallel randomized controlled studies (RCTs) that recruited subfertile women, characterized as having poor ovarian reserve, and who had low or high doses of gonadotropins in IVF/intracytoplasmic sperm injection (ICSI) treatment programs, irrespective of the definition of poor ovarian reserve or response, and irrespective of the type of gonadotropins or the type and protocol of GnRH analogues. We considered any comparison between lower doses of gonadotropins or combinations of gonadotropins with oral compounds—to shorten the duration of stimulation and thereby lowering the total dose of gonadotropins—compared with higher doses of gonadotropins in the comparison arm suitable for inclusion in our review.

We selected the studies in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (M.A.-F.Y. and U.M.F.). Complete articles were obtained that were likely to meet the predefined selection criteria. Second, final inclusion

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