A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF: a multicenter randomized non-inferiority trial.


Abstract

STUDY QUESTION: In subfertile women with poor ovarian reserve undergoing IVF does a mild ovarian stimulation strategy lead to comparable ongoing pregnancy rates in comparison to a conventional ovarian stimulation strategy?

SUMMARY ANSWER: A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF leads to similar ongoing pregnancy rates as a conventional ovarian stimulation strategy.

WHAT IS KNOWN ALREADY: Women diagnosed with poor ovarian reserve are treated with a conventional ovarian stimulation strategy consisting of high-dose gonadotropins and pituitary downregulation with a long mid-luteal start GnRH-agonist protocol. Previous studies comparing a conventional strategy with a mild ovarian stimulation strategy consisting of low-dose gonadotropins and pituitary downregulation with a GnRH-antagonist have been underpowered and their effectiveness is inconclusive.

STUDY DESIGN, SIZE, DURATION: This open label multicenter randomized trial was designed to compare one cycle of a mild ovarian stimulation strategy consisting of low-dose gonadotropins (150 IU FSH) and pituitary downregulation with a GnRH-antagonist to one cycle of a conventional ovarian stimulation strategy consisting of high-dose gonadotropins (450 IU HMG) and pituitary downregulation with a long mid-luteal GnRH-agonist in women of advanced maternal age and/or women with poor ovarian reserve undergoing IVF between May 2011 and April 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Couples seeking infertility treatment were eligible if they fulfilled the following inclusion criteria: female age ≥35 years, a raised basal FSH level >10 IU/ml irrespective of age, a low antral follicular count of ≤5 follicles or poor ovarian response or cycle cancellation during a previous IVF cycle irrespective of age. The primary outcome was ongoing pregnancy rate per woman randomized. Analyses were on an intention-to-treat basis. We randomly assigned 195 women to the mild ovarian stimulation strategy and 199 women to the conventional ovarian stimulation strategy.

MAIN RESULTS AND THE ROLE OF CHANCE: Ongoing pregnancy rate was 12.8% (25/195) for mild ovarian stimulation versus 13.6% (27/199) for conventional ovarian stimulation leading to a risk ratio of 0.95 (95% CI: 0.57-1.57), representing an absolute difference of -0.7% (95% CI: -7.4 to 5.9). This 95% CI does not extend below the predefined threshold of 10% for inferiority. The duration of ovarian stimulation was significantly lower in the mild ovarian stimulation strategy than in the conventional ovarian stimulation strategy (mean difference -1.2 days, 95% CI: -1.88 to -0.62). Also, a significantly lower amount of gonadotropins was used in the mild stimulation strategy, with a mean difference of 3135 IU (95% CI: -3331 to -2940).
LIMITATIONS, REASONS FOR CAUTION: A limitation of our study was the lack of data concerning the cryopreservation of surplus embryos, so we are not informed on cumulative pregnancy rates. Another limitation is that we were not able to follow up on the ongoing pregnancies in all centers, so we are not informed on live birth rates.

WIDER IMPLICATIONS OF THE FINDINGS: The results are directly applicable in daily clinical practice and may lead to considerable cost savings as high dosages of gonadotropins are not necessary in women with poor ovarian reserve undergoing IVF. A health economic analysis of our data planned to test the hypothesis that mild ovarian stimulation strategy is more cost-effective than the conventional ovarian stimulation strategy is underway.

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