

## MILD OVARIAN HYPERSTIMULATION FOR ART

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The history of IVF has been characterized by profound ovarian hyperstimulation protocols, in an attempt to optimise pregnancy rates per cycle. These approaches aiming at generating as many oocytes as possible were meant to counterbalance shortcomings in in vitro oocyte fertilisation, embryo culture conditions, as well as embryo selection for transfer. Another reason often put forward to justify profound stimulation is the cryostorage of surplus embryos, providing additional pregnancy chances in unstimulated cycles. Over the years ovarian stimulation protocols have become extremely complex and time consuming, associated with much patient discomfort. Moreover, costs of applied medication may outweigh the cost of IVF treatment itself. High doses of exogenous gonadotrophins are usually combined with extended suppression of endogenous pituitary function using GnRH agonist. In many centers, ovarian stimulation is preceded by the suppression of ovarian function using steroid contraceptives, aiming at 'synchronising' follicle development and also for logistic reasons. Consequently, ovarian stimulation usually takes 1 to 2 months, and associated patient discomfort and cost are substantial. Moreover, much time is required in between IVF cycles to allow for the ovary to recover, and patient drop out rates are high. The stimulation of numerous dominant follicles increases chances for the rare but dangerous ovarian hyperstimulation syndrome, oocyte retrieval may be more time consuming and painful, the large oocyte number generated may potentially affect oocyte quality, the high oestrogen concentrations associated with multiple dominant follicle development may give rise to decreased endometrial receptivity (reducing pregnancy chances), and finally the true added value of embryo cryostorage is limited.

The aim of milder forms of ovarian hyperstimulation is to render stimulation less complex, less time consuming and less costly while improving patient acceptability by reducing side effects. This may result in the improvement of the cost effectiveness of IVF and may also result in reduced drop outs rates. These women may be exposed to additional chances to achieve a pregnancy in subsequent IVF cycles. Only in this context can mild ovarian hyperstimulation be appreciated, since no doubt that the overall pregnancy rate for a given IVF cycle will be slightly reduced. Therefore, the concept of mild ovarian hyperstimulation (just like the transfer of a single embryo) can only be developed further in the context of a holistic perspective of IVF, involving healthy children as outcome, in the context of overall patient discomfort, chances for complications and cost per IVF treatment (which may involve multiple IVF cycles) over a given period of time.

The introduction of GnRH antagonists into the clinic (where the period of administration can be restricted to the period indeed at risk for a premature LH rise) allowed for an IVF cycle to commence with a physiological recruitment of a limited number of follicles in the beginning of the cycle, just like under normal conditions. Therefore, the use of GnRH antagonists has facilitated the further development of mild stimulation applying low doses of exogenous FSH during the mid- to late-follicular phase aiming to interfere with single dominant follicle selection. Initial proof of principle studies have further explored this concept. Subsequently, a large effectiveness trial comparing a mild (mild stimulation along with single embryo transfer) with a conventional approach has been performed showing similar cumulative term live birth rates at lower cost, less patient discomfort and a dramatic reduction in multiple pregnancies. Moreover, it has been shown that mild ovarian stimulation is associated with a reduced proportion of aneuploid embryos as assessed by preimplantation genetic screening.