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## Editorial

# Ovarian stimulation protocols : Milder, Mildest or back to Nature ?

### Introduction

The use of controlled ovarian stimulation to obtain multiple eggs has resulted in a compromise - in terms of the risk of OHSS, expense, multiple pregnancies, wastage of or the need for cryopreservation of surplus embryos. Even some women, with apparently normal menstrual cycles, might become 'poor responders' when administered with follicular stimulants, and we still do not know if the incidence of oocyte aneuploidy is artificially raised after stimulation. Considerable changes are afoot in the practice of assisted human conception, mostly in going back to milder stimulation protocols. Routine IVF (IVF), is being challenged by simpler methodologies. These include natural cycle IVF (nIVF), controlled natural IVF (cnIVF), minimal stimulation IVF (msIVF), and the in-vitro maturation of human oocytes ready for fertilization in vitro (IVM). These four approaches are now practiced in increasing numbers of IVF clinics, and may well replace routine IVF.

The global trend is towards milder stimulation protocols even for IUI and OI. Researchers are investigating new protocols to reduce or substitute gonadotropins with more "physiological" alternatives. Robust evidence is lacking but based on the available results, gonadotropins might be the most effective drugs when IUI is combined with ovarian hyperstimulation<sup>1</sup>. When gonadotropins are applied it might be done on a daily basis<sup>1</sup>. When gonadotropins are used for ovarian stimulation, low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chances to encounter negative effects from ovarian stimulation, such as multiples and OHSS, are limited with low dose gonadotropins<sup>1</sup>. Patients being treated for IUI with FSH and 5.0 mg/day of letrozole required a lower dose of FSH than the group co-treated with 2.5

mg/day of letrozole or with FSH alone<sup>2</sup>. The paper summarized that in terms of cost-effectiveness, 5.0 mg/day of letrozole is more effective than the 2.5 mg/day in co-treatment with no adverse effect on pregnancy rate or outcome<sup>2</sup>.

### Discussion

The first IVF baby was conceived following a natural cycle<sup>3</sup> and indeed natural cycle IVF (nIVF) was the method of choice for the first few years of IVF treatment. In a natural cycle, several follicles are recruited initially but it is only one that attains dominance and goes on to ovulate. Being able to control ovulation was one of the reasons why natural cycles were replaced with ovarian stimulation cycles, because the first oocyte retrievals had to be performed according to the natural LH surge and resulted in collections at any time of the day or night in order to collect the oocyte before ovulation. A Japanese group recently described three successful cases involving patients of advanced age from whom dominant follicles were retrieved during the natural cycle<sup>4</sup>. All patients had failed to bear children through stimulated in vitro fertilization. In case 1, a follicle was retrieved after a gonadotropin-releasing hormone agonist was used to induce luteinizing hormone surge. In cases 2 and 3, pregnancy was achieved via completely natural cycles. One embryo was transferred every 16 cycles. The authors concluded that mature oocyte retrieval followed by natural rather than stimulated in vitro fertilization might be a potential treatment for patients of advanced age when stimulated in vitro fertilization has been repeatedly unsuccessful<sup>4</sup>. Analysis of 500 consecutive natural cycles IVF was done by another group<sup>5</sup>. Oocytes were found in 391 cases (78.1%), and cleaving embryos suitable for transfer were obtained in 285 cycles (57.0%). Pregnancy was observed in 49 cases, with a pregnancy rate of 9.8% per cycle, 17.1% per transfer, and 16.7% per patient.



The authors concluded that in poor responder patients, natural-cycle IVF is an effective treatment, especially in younger women <sup>5</sup>.

Developments of gonadotropin-releasing hormone (GnRH) antagonists allowed once again the possibility of using a controlled natural cycle, by preventing the occurrence of a premature LH surge and thereby allowing better control <sup>6</sup>. More recently, Trokoudes et al published a series of controlled nIVF cycles (cnIVF) in which he showed that cnIVF could be a useful tool in the management of some patients presenting for fertility treatment <sup>7</sup>. A total of 134 controlled natural IVF (nIVF) cycles were reviewed retrospectively and compared with 370 stimulated IVF (sIVF) cycles <sup>8</sup>). The clinical pregnancy rate per embryo transfer following nIVF was 27% and 47% in sIVF cycles for patients aged less than 35. However, natural cycle patients could attempt consecutive cycles with much less impact on their lives, both medically and financially. In patients under 35 years of age, the choice of controlled nIVF reduces the cost and risk to the patient, permitting her to have multiple, consecutive attempts, and cumulatively offers a clinical pregnancy rate which approaches that of sIVF <sup>8</sup>. The multiple pregnancy rate in nIVF is significantly reduced compared with sIVF treatment cycles <sup>8</sup>.

Minimal Stimulation IVF is obviously very close to routine IVF, and differs mainly in its utilization of smaller doses of hormones or just clomiphene citrate. Administration of 50 mg clomiphene citrate is initiated on cycle day 3, and from day 8 patients receive 150 IU of FSH every other day <sup>9</sup>. When the size of the dominant follicle and the estradiol concentration reach the predefined values, gonadotrophin-releasing hormone agonist is administered to induce follicular maturation. Oocytes are then retrieved 32-35 h later. Because the short half-life of enclomiphene (24 h) is of critical importance in this protocol, it is necessary to continue oral administration of clomiphene citrate until the day before maturation is triggered. Of all 43,433 cycles initiated, the rates for oocyte retrieval and embryo cleavage were 83% and 64% respectively. The mean number of oocytes retrieved was 2.2. The rates for live births, miscarriages, and ectopic pregnancies, in relation to initiated cycles, including cases of frozen-thawed transfer, were 11.1%, 3.4% and 0.2% respectively. Another recent study confirmed the efficacy of OC

use for down-regulation followed by ms IVF using CC as a simple, low-cost and low-risk alternative to stimulated IVF with comparable pregnancy rates <sup>10</sup>.

The clinical application of IVM has been described in detail by Tan et al <sup>11</sup>. Today, many clinics now achieve results with IVM that are equivalent to routine IVF. Methods initially successful when used for patients with polycystic ovaries have now been applied to those with normal cycles. Bleeding from aspirated small follicles has been reduced by modifying structure of aspirating needles. As many as 50 or more oocytes can be plucked from available follicles on some occasions, which challenge success rates attained with routine IVF. Improvements in oocyte cryopreservation imply that follicles can be aspirated at any stage of the menstrual cycle and their oocytes preserved for later use <sup>12</sup>. Lim et al concluded that Natural cycle IVF/M together with IVM-alone treatment can offer more than 50% of infertile women with an acceptable pregnancy and implantations rates <sup>13</sup>.

## Conclusions

Mild stimulation protocols reduce the mean number of days of stimulation, the total amount of gonadotropins used and the mean number of oocytes retrieved. The proportion of high quality and euploid embryos seems to be higher compared with conventional stimulation protocols and the pregnancy rate per embryo transfer is comparable. Moreover, the reduced costs, the better tolerability for patients and the less time needed to complete an IVF or an IUI cycle make mild approaches clinically acceptable and cost-effective over a given period of time. The use of aromatase inhibitors in conjunction with gonadotropins is associated with a significant reduction in the gonadotropin dose required for optimum controlled ovarian hyperstimulation <sup>14</sup>. Recent research suggests that IVF in modified natural cycle/mild stimulation with antagonist is likely to replace the current conventional approach in down-regulated cycles <sup>15</sup>.

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