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## Patient-Friendly Protocols for Controlled Ovarian Stimulation

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Ovarian stimulation protocols have been developed for ovulation induction in anovulatory women and for so-called controlled ovarian stimulation (COS) which induce multiple follicular development prior to assisted reproductive technologies (ARTs) such as IVF and intracytoplasmic sperm injection (ICSI). The development of COS, from no stimulation in natural cycles to sophisticated protocols using GnRH analogues and recombinant gonadotropins, has been one of the most significant advances in ARTs. So far, physicians and scientists tend to focus on the technological aspects of COS and pay less attention to the patients' comfortability and easy-to-use. Pregnancy rates in IVF cycles have been stabilized. It seems that there are no new amazing technologies for the time being. For optimization of COS, it must be more 'patient friendly'. Multiple, painful needle puncture, long treatment period and complex or confusing protocols can frustrate patients and cause patients to discontinue treatment. Therefore, one of strategies for optimization of COS is making COS 'patient-friendly' and easier for patients. Methods for making COS easier and patient-friendly are 1) abandonment of blood sampling, 2) reduction of pain and treatment duration, 3) convenient use of drugs and so on.

For reducing painful and multiple injections and treatment period, the use of recently introduced recombinant gonadotropins, GnRH antagonist and vaginal progesterone are very useful. Moreover, pen administration device which enables subcutaneous administration of recombinant FSH (rFSH) with dose fine-tuning has contributed to a more convenient, patient-friendly and more successful treatment of infertility. The use of GnRH antagonist for COS makes treatment less aggressive and more patient-friendly, using clomiphene citrate (CC) and even applying the natural cycle. Our prospective, randomized study demonstrated that the soft stimulation protocol using GnRH antagonist/CC/rFSH for IVF/ICSI results in a comparable pregnancy outcome despite smaller numbers of mature and fertilized oocytes in normal responders, compared with standard GnRH antagonist multidose protocol (MDP). Soft stimulation protocol may become a convenient and cost-effective choice requiring smaller dose of rhFSH. Therefore, it can be considered as a 1st line COS for IVF in normal responders. GnRH antagonists can be also used for patients undergoing natural cycle IVF and its use can decrease a cancellation rate and increase a pregnancy rate with minimal use of gonadotropins. Recently, it was reported that in women aged 40 and above with abnormal FSH levels, minimal stimulation in natural cycles resulted in a similar pregnancy rates despite the higher cancellation rate, lower number of oocytes retrieved and embryos compared with standard GnRH

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antagonist protocol, and thus represented a cost-effective alternative. Our prospective study also demonstrated that in women aged 40 or above or with basal antral follicles less than 4, the minimal stimulation significantly decreased a cancellation rate and yielded significantly higher number of oocyte and mature oocyte, compared with natural cycle IVF. Our another prospective study showed that in women of advanced age or with low ovarian reserve, the minimal stimulation protocol produced a comparable pregnancy outcome despite the lower numbers of oocytes, good quality embryos and embryos transferred, compared with a standard antagonist MDP. This minimal stimulation may be a cost-effective alternative to standard COS protocols for women of advanced age and with low ovarian reserve, and can be considered as the last chance before egg donation.

Now, we are entering an new era in which patient-friendly COS protocols considering a convenience as well as an efficacy are preferable and individualized approach is necessary to increase the cost-effectiveness.

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