OVARIAN STIMULATION FOR IVF: THE OPTIMAL BALANCE BETWEEN TOO MUCH AND TOO LITTLE

B.C.J.M. Fauser
Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, The Netherlands

The history of IVF has been characterized by profound ovarian stimulation, in an attempt to optimise pregnancy rates per cycle. These approaches, aiming at generating many oocytes, were meant to counterbalance inherent shortcomings in *in vitro* oocyte fertilisation, embryo culture, as well as embryo selection for transfer. Additional reasons put forward to justify "maximal" ovarian stimulation is the possibility to transfer multiple embryos and the ability to cryopreserve surplus embryos providing additional pregnancy chances in subsequent cycles. Over the years, ovarian stimulation protocols have become extremely complex and time consuming, associated with much patient discomfort, considerable complication rates. Moreover, drop-out rates are high due to the burden of treatment reducing cumulative pregnancy rates from multiple IVF cycles.

Mild IVF may involve mild ovarian stimulation, mild transfer policies (i.e. single embryo transfer in selected patients), or both. The tendency to go for fewer high quality embryos may go hand in hand with mild stimulation. Both strategies may result in a reduction in the pregnancy rate per cycle in case fresh transfer are considered. Only when cryopreserved embryo transfer cycles are included in success rates, overall pregnancy rates become comparable in IVF units with good laboratory performance. The aim of milder forms of ovarian stimulation is to render stimulation less complex, less time consuming and less costly, while improving patient acceptability by reducing side effects and chances for complications. Insufficient access to IVF treatment due to high cost and very few countries where IVF is reimbursed is the biggest threat to global IVF today. However, mild ovarian stimulation protocols do not work for all patients.

Indeed, cancellation rates are still unacceptably high in some mild stimulation regimens. On the other hand, a significant proportion of women show hyperresponse, even following mild stimulation. Hence, we have to acknowledge the fact that we will not succeed in the design of a single protocol which will work for all women. In clinical practice, many clinicians modify drug doses based on patient characteristics and ovarian response to stimulation. However, despite strong believes such approaches are rarely based on sound scientific evidence. Hence, individually tailored regimens should be developed, based on known ovarian response predictors such as female age, anti-Mullerian hormone (AMH) levels, antral follicle count (AFC) and other patient characteristics such as body weight and smoking habits. In the near future individual gene polymorphism profiles may also be added. Prospective studies are urgently needed, to assess whether individualized dose regimens based on objective patient characteristics will indeed result in a higher proportion of women eliciting the desired response of retrieving between 2 and 10 oocytes. IVF effectiveness and safety will benefit from achieving this aim. Such studies should focus on healthy children born following a given period of IVF treatment as the primary endpoint in the context of overall treatment cost, burden and complications.