DEBATE

Are we on the verge of a new era in ART?

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Since the birth of the first test tube baby in 1978 assisted reproduction has developed a great deal (Steptoe and Edwards, 1978). While at that time only the natural cycle was considered to be able to allow a fertilization of the oocyte, controlled ovarian hyperstimulation (COH) using urinary human menopausal gonadotrophins (HMG) was a major step forward (Edwards, 1981; Trounson et al., 1981; Trounson, 1983). More oocytes to be rescued meant more oocytes to be fertilized in vitro and more embryos to be transferred during each attempt at treatment. This greatly raised the success rate in terms of pregnancies achieved.

By introducing gonadotrophin-releasing hormone (GnRH) agonists into COH, the premature luteinization as major drawback of a stimulation with HMG only could be avoided almost completely. In particular, the ‘long protocol’, aiming at complete desensitization of the pituitary gland before starting the stimulatory therapy has become a widely accepted treatment of first choice (Wildt et al., 1986; Smitz et al., 1992). Since 1992, we have experienced a veritable revolution in infertility treatment of the male in consequence of the inauguration of intracytoplasmic sperm injection (ICSI) with its excellent fertilization outcome irrespective of sperm morphology (Palermo et al., 1992; Van Steirteghem, 1994; Küpker et al., 1995). However, it seems as if our therapeutic approach has been overdone in the meantime. Burden and risks for our patients as well as costs have sky rocketed. It is agreed that excessive ovarian stimulation with rescue rates of more than 30 oocytes is not uncommon, as large numbers of follicles and aspirated oocytes are almost regarded as criteria of success (Balen, 1995). On the other hand, the incidence of moderate and severe ovarian hyperstimulation syndromes (OHSS) has increased from <1% to ~7%, while our therapeutic possibilities still remain poor (Golan et al., 1988; Ron-El et al., 1991; Bauer et al., 1996). If the healthy single fetus pregnancy is the goal to aim for, a multiple pregnancy rate of ~20% demonstrates how often we fail in our attempt (ART World Collaborative Report, 1993). Increasing concerns on current approaches to ovarian stimulation brought up a demand for milder forms of ovarian stimulation which should be applied in tailormade modes for each patient. It seemed to revolutionize ovarian stimulation (Edwards et al., 1996). The development of recombinant gonadotrophins and their introduction onto the market entailed an important scientific advance, while treatment costs were increased tremendously (Recombinant FSH Study Group, 1995). Although lowering the price for these compounds would be expected to replace the urinary ones almost totally, recombinant gonadotrophins remain extremely expensive.

After years of intensive clinical trials, GnRH antagonists are now to be introduced onto the market. They will probably replace GnRH agonists within COH for assisted reproduction techniques (ART), due to the advantages of their mode of action as compared to agonistic analogues (Bouchard et al., 1990). Different protocols of antagonist administration within COH have been developed. While the French group of Oliwennes, Bouchard and Frydman favour a single or dual administration in the late follicular phase, the ‘Lübeck protocol’ involves a multiple dose application of the GnRH antagonist in the midcycle phase concomitant with COH with HMG or recombinant FSH (Oliwennes et al., 1994, 1995; Diedrich et al., 1994; Felberbaum et al., 1996; Albano et al., 1997). Both dose applications proved to be safe and effective in avoiding the premature luteinizing hormone (LH) surge during COH. Pregnancy rates of ~30% look most promising. However, results are contradictory regarding a possible reduction of the amount of gonadotrophins needed for ovarian stimulation. While the first studies to establish the dose for the multiple dose application, using 3, 1 and 0.5 mg/day, seemed to show a clear tendency to lower amounts as compared with the long agonistic protocol, subsequent studies using 0.5 and 0.25 mg/day could not confirm these results. The French group, however, reported a reduction of ~50% in gonadotrophins in comparison with a long protocol (Oliwennes et al., 1997). Earlier studies found no deleterious effect of GnRH antagonists on the luteal phase (Ditkoff et al., 1991). However, when a dose of 0.5 mg of Cetrorelix was applied in the multidose fashion in six patients, and no luteal phase support was given, the luteal phase was shortened and no pregnancies occurred (Albano et al., 1997). Nothing is yet known about the luteal phase following lower dosages. It may be assumed that corpus luteum function is abolished as a result of the long action of the antagonist via suppression of pituitary gonadotrophin secretion, as was demonstrated in the animal model (Fraser et al., 1997).

Although our knowledge regarding oocyte and embryo quality after COH with concomitant GnRH antagonist treatment may still be limited, the rates of excellent embryos transferred seem to be satisfactory (Felberbaum et al., 1996; Albano et al., 1997). The long agonist protocol was regarded as advantageous since recruitment of a larger follicle cohort could be stimulated by gonadotrophins at a very early point of folliculogenesis.
Costs of controlled ovarian hyperstimulation: a matter of debate.

(Fleming et al., 1986). As in the short agonistic protocol, this is not the case in protocols for COH using antagonists, where stimulation starts almost immediately after having completed the recruitment of follicles in the spontaneous cycle (Hillier et al., 1993). From a theoretical point of view, this could lead to a larger number of small and intermediate follicles at the time for ovulation induction by HCG. This would actually enhance the risk of onset of an OHSS. In spite of this very reasonable hypothesis, all data available up to now seem to indicate a remarkably lower incidence of moderate and severe OHSS after COH with gonadotrophins and concomitant GnRH antagonist treatment, which may be <2% (K. Diedrich and P. Devroey, unpublished data).

Overall, the most promising aspect of introducing GnRH antagonists into COH may be the possibility of making this treatment less aggressive and much gentler than an agonistic long protocol, using old-fashioned schemes of stimulation such as clomiphene citrate (CC) in combination with HMG. It has been proved that ovarian stimulation with CC only for the purpose of ICSI is perfectly feasible, applying the simplest, least aggressive and least expensive form of stimulation (Felberbaum et al., 1997; Ludwig et al., 1997; Diedrich et al., 1998). However, these results have been ignored. This could change very rapidly, if it could be shown that CC/HMG under the coverage of midcycle GnRH antagonist treatment ('soft protocol') will allow the rescue of three to five mature metaphase II oocytes to be treated by ICSI. This would reduce the risk of OHSS to almost zero. The idea of 'the more oocytes, the better' is totally wrong in view of the restrictions of the German embryo protection law (Keller et al., 1992). The first feasibility studies using Cetrorelix for this purpose are in progress at the moment. Just as a matter of debate a glimpse into the costs of these regimens in comparison with the recruitment of follicles in the spontaneous cycle (Hillier, S.G. (1994) Current concepts of the role of FSH and LH in folliculogenesis. *Hum. Reprod.*, 9, 188–191.


References


