There is still a paucity of published real-life clinical experience with the use of first generation recombinant follicle stimulating hormone (rFSH) preparations. Ebulient reports, a major proportion of which originated from industry-sponsored or -associated research, have unanimously proclaimed the efficacy of both rFSH preparations that have come onto the market recently (Follitropin β; Puregon; NV Organon, Oss, The Netherlands; and Follitropin α; Gonal F; Ares-Serono, Geneva, Switzerland). The same group of reports, incidentally, have stressed the shortcomings of previously utilized, urinary-derived gonadotrophin preparations (uroG) in a manner which the industry never used prior to the recent marketing blitz of rFSH. It is not clear why one company (NV Organon, Oss, The Netherlands) tested its rFSH, Puregon, against an older generation and named uroG (Metrodin) of the competitor (Ares-Serono, Geneva, Switzerland) rather than use its own (named) products. No ‘conflict of interest’ declarations by industry employed or associated authors were in evidence and it was not indicated whether personnel in the collaborating international centres had any control over the content and penmanship of respective reports. The potency of one of the rFSH preparations has been challenged by an author–competitor, albeit on the basis of tenuous and indirectly-derived evidence. Finally, these reports have placed little emphasis on the shortcomings of the new gonadotrophin preparations and personal attempts to seek clarification on, for example, the extent of pain experienced during injection of rFSH have been met with evasive responses by industry representatives. For now, however, we have to accept these reports (e.g. Devroey et al., 1994; Hedon et al., 1995; Recombinant Human FSH Study Group, 1995; Aboulghar et al., 1996; Out et al. 1996a,b, 1997) as providing (reassuring) evidence from early drug trials, of the safety of rFSH and efficacy when used for ovarian stimulation during assisted conception treatment.

Another unsettling issue, especially for rFSH neophytes like me, has been the suggestion that the potency of Puregon is such that the 50 IU ampoule should be regarded as being equipotent to the 75 IU ampoule of the uroG (Out et al., 1995). I am not aware of the experimental basis for this claim but what this means is, that if one ignores the suggestion and assumes equipotency of both types of gonadotrophins, ovarian stimulation with ‘normal doses’ of Puregon may run the risk of over production of oocytes. More importantly, there will be an unacceptably high incidence of ovarian hyperstimulation syndrome (OHSS) and its attendant risks. There is also a potential liability to legal sanctions if a patient is so predisposed. Worldwide discussions with colleagues have not yet turned up anyone whose clinical experience with Puregon shows that its potency is as heightened as purported. Most agree that it is a ‘good’ preparation and, together with Gonal F, marks an advance in the production of more wholesome gonadotrophins for use in in-vitro fertilization (IVF) treatment. On the other hand, if one accepts that Puregon is a more potent preparation and decreases the starting dose as suggested, there is a risk of having a higher incidence of unsatisfactory treatment cycles.

A recent report (Jacob et al., 1998) showed more favourable IVF treatment outcome indices in women who had ovarian stimulation with uroG, when compared with those who were injected with Puregon. In determining the starting dose for patients who were administered Puregon, these workers had equated the potency of 50 IU of Puregon with that of 75 IU of uroG as suggested by the manufacturer, apparently based on the results of a previous study (Out et al., 1995). Other workers (Devroey et al., 1998) have also reported on their experience with the use of 100 IU of rFSH as a starting dose for ovulation stimulation and IVF treatment. Their patient population was small (43 patients) consisting of young females (mean age 31.7 years) who were predominantly of normal build (mean body mass index 23.2). In ~25% of patients, the response to the daily dose of 100 IU was considered adequate while the dose had to be increased in an attempt to achieve a better response in the remaining 75% of patients. The authors seem to believe that such an adequate response (25% of patients) to a starting dose of 100 IU is an exclusive preserve of Puregon but similar findings are common during the use of uroG; a significant subgroup of patients will respond adequately to daily doses of 75–100 IU, irrespective of the brand of product used.

However, the availability of 50 IU ampoules of Puregon is not necessarily a drawback because it may encourage greater use of smaller daily doses such as 100 IU (i.e. two ampoules) in certain groups of patients where the daily administration of 150 IU of even the uroG would have been excessive. In fact, the marketing of gonadotrophin injections as 25, 50, 75, 100, 150 and 200 IU ampoules will increase the ability of practitioners to individualize dosing regimens right from the start, avoid excessive waste of unused portions and, hence, use fewer ampoules to make up the required large dose for potential or proven poor responders. This proposal assumes that the cost of
packaging will not render production of the lower dose ampoules uneconomic. Staff will also be required to be more careful to avoid mistaking one dose preparation for another.

My strategy for using Puregon for the first time has been to assume equipotency of Puregon and uroG but, at the same time, to be cautious and reduce the starting dose in potential high responders, e.g. women with ultrasonic evidence of polycystic ovaries in conjunction with an age of <35 years and normal or low body mass index; these are the patients who are most likely to become overstimulated if the potency of Puregon is indeed above what we are used to for uroG. A total of 23 patients have so far been treated; ovarian stimulation was carried out using individualized dose regimens and starting dose levels (100, 150, 200, 250, 300, and 450 IU). The starting dose of 200 IU of Puregon was used for patients who would have had 225 IU if 75 IU ampoules had been available. It was assumed that there was no major difference between the bioactivity of 200 IU and 225 IU of Puregon; this made it possible to avoid wasting half of the contents of another 50 IU ampoule in a bid to obtain the required 25 IU. On the other hand, a starting dose of 250 IU was considered potentially excessive for this group of patients, especially if Puregon was indeed more potent than uroG. The rest of the treatment protocol was similar to contemporary practice. Of three patients who commenced on 100 IU daily, two required an increase in the dose of injection after 5 days but treatment had to be cancelled eventually for one of them after 15 days of injections due to continued poor response. Overall, 10 patients required an increase in their daily dose of Puregon injections while the starting dose was maintained throughout the period of ovulation stimulation in nine others, but the remaining four patients had a reduction of the dose of their daily injections. A total of 21 patients responded adequately and had oocyte retrieval; embryo transfers were carried out for 20 patients ~48 h later using Labotect catheters (Labotect GmbH Industries, Bovenden-Göttingen, Germany). Two embryos were transferred to each of 15 patients who completed the treatment, while the single embryo that was produced by one patient was transferred. The remaining four patients each had three embryos replaced. Positive pregnancy test results were obtained in a total of 11 patients including the single embryo transfer patient. One patient was later classed as having a biochemical pregnancy. Some of the patients are currently awaiting the confirmatory ultrasound scan at 7 weeks pregnancy. No case of OHSS has been encountered so far.

This patient population is obviously small and no claim is being made about the efficacy of Puregon, based on our favourable early experience. That has also not been the intention of this account; it is quite clear from the scientific literature that both Organon and Serono have produced good rFSH preparations in the form of Puregon and Gonal F. The contention of this writer is that the current and rather upbeat reports on rFSH (Puregon) have not been of much practical benefit to practitioners as they change over to the use of these new preparations. There has also been a blurring of the line between scientific information giving and marketing. If practitioners adhere to dosing proposals made in the reports they may not have a good experience with their first use of Puregon. Although there is a subgroup of patients who will obviously respond adequately to starting daily doses of as low as 100 IU Puregon for IVF treatment (Devroey et al., 1998), in none of the reports so far has any serious attempt been made to identify them. Instead, there has been a tendency to propose blanket dosing regimens which instinctively do not sound right and have now been documented (Jacob et al., 1998) as jeopardizing the treatment of some patients. Theirs is not likely to be the only experience that will be less than ideal in this regard and the following months may see publication of more real life results. Knowledge is still being built up worldwide on dosing regimens of rFSH. It will probably follow patterns that are somewhat similar to those used for uroG. This means that starting doses will depend on patient characteristics such as age, build, polycystic ovaries, previous experience with ovulation stimulation, history of ovarian or peri-ovarian surgery, pre-treatment concentrations of FSH and luteinizing hormone and other considerations.

Concern about contemporary (over)dosing regimens has been raised (Edwards et al., 1996). It is possible that stimulation with rFSH leads to the production of better quality oocytes. Furthermore, in-vitro culture conditions seem to have improved to the extent that good quality embryos are consistently being produced nowadays such that the number of transferred embryos can be confidently reduced to two, and eventually to one, still with the expectation of ‘normal’ pregnancy rates. Although embryo viability and embryo–endometrial interaction are strong determinants of successful IVF treatment outcome, the contribution of the transfer technique may have been underestimated previously as is suggested by recent findings (Lesny et al., 1998), regarding the translocation of transferred droplets following mechanical irritation of the uterus. Refinement of the embryo transfer technique, possibly with the use of potent uterine relaxants around the time of embryo transfer may improve pregnancy rates further. These factors actually may convince clinicians to aim for the production of fewer oocytes by using less medication rather than what the current suggestions about the potency of Puregon will achieve.

In conclusion, I suspect the medical community do not mind having rFSH preparations that are equipotent to uroG, provided they are free of contaminants, are readily available, do not show significant batch-to-batch variability in their bioactivity and can be used without fear of transmitting disease to patients. If any or both current rFSH preparations cause excessive pain during injection awareness by the medical community of this fact may lead to trial of methods that have been used in alleviating injection pain for other painful drug injections. This includes the use of pH buffers, warming the injection to 37–40°C before administration, prior application of topical anaesthetic cream or other agent at the injection site, rapid injection, adjusting the osmolarity and other interventions. These measures may suffice until the availability of hopefully less painful second generation rFSH products. Attempts to market Puregon as a ‘super drug’ may provoke a backlash that negatively affects the image of the product. Industry attention should, instead, be directed at more humane considerations such as reducing the presently punitive costs of both Puregon and Gonal F; the market is there and will not disappear anytime soon!
What are the clinical benefits of recombinant gonadotrophins?

References


