The prevalence of infertility is ~9% of married or co-habiting couples in all countries of the world (Boivin et al., 2007). In many cases, the infertility can be treated effectively only by means of assisted reproductive techniques (ART). In some developing countries, however, ART services are too expensive to be offered. Even in developed countries, ART is only available to women who can afford to pay and they often find that the time commitment, discomfort and complications are unbearable.

Innovative approaches are needed to dislodge the chief barrier to availability, which is the cost of in vitro fertilization (IVF). In a recent comment to Nature, Alan Trounson said ‘If you remove all the expensive stuff and use low-cost drugs (such as clomiphene) and remove just one or two oocytes, and only transfer one embryo, it can be done for <US$100’ (Pearson, 2008). Low cost drugs and less potent ovarian stimulation are one way to reduce the cost of IVF. Sensible as drastic cost reduction may be, some degree of ovarian stimulation is required, as shown by the difficult history of natural cycle IVF. Early pregnancy rates were disappointing to patients and clinicians (Lenton et al., 1992). Even now pregnancy rates are only 7% per cycle (or one in 14 cycles) and 44% overall in women who were able to complete an average of four cycles (Pelinck et al., 2007). Clearly, broad application of natural cycle IVF is a distant goal, as patients expect higher success rates and the time they must invest in a cycle is not negligible.

Although natural cycle IVF has not gained widespread acceptance, even a small reduction in the degree of ovarian stimulation could be an important step on the road to low cost treatment (Edwards et al., 1996). Mild ovarian stimulation, with the aim of reducing the number of developing follicles, could reduce cost and adverse events and would be consistent with the transfer of fewer embryos, resulting in fewer multiple births (Fauser et al., 1999).

The most common protocol for IVF involves up to 3 weeks of gonadotrophin releasing hormone (GnRH) agonist treatment, up to 2 weeks of FSH injections and frequent visits for ultrasound and hormone evaluation, as well as the essential luteal support after embryo transfer. The long GnRH agonist protocol is effective and its management has become a comfortable routine over the years, but it is costly and difficult for patients. The development of many follicles may lead to ovarian hyperstimulation syndrome and the transfer of multiple embryos increases multiple birth rates (van Voorhis, 2007; Andersen et al., 2008). Clearly, a milder stimulation protocol would reduce the complexity of IVF cycles, but can it do so without a significant reduction in success rates?

Two reviews in this issue evaluate the current literature on mild stimulation protocols. One explores broadly the value of different approaches to mild stimulation in IVF cycles (Verberg et al. 2008a). These authors find that (i) GnRH antagonist co-treatment to suppress a premature luteinizing hormone (LH) rise reduces FSH dosage and treatment days compared with the GnRH agonist long protocol, (ii) limited gonadotrophin dosage is associated with better pregnancy rates than anti-estrogens or aromatase inhibitors and (iii) the use of LH late in the follicular phase reduces total FSH dosage. In vitro maturation of oocytes also avoids ovarian stimulation, although its efficacy with respect to standard IVF has not been demonstrated in level I studies (Rao and Tan, 2005). The review found, however, that many mild stimulation studies involved poor prognosis patients, while it is mainly young patients with good ovarian responses who have the highest risk of complications from ovarian stimulation. The authors conclude that mild stimulation should yield more than one dominant follicle for the success rates to compete with those of standard stimulation protocols.

The second review has a narrower focus and a more in-depth analysis (Verberg et al., 2008b). This review asked whether retrieving a small number of oocytes after mild ovarian stimulation reflected a poor ovarian response and poor implantation rates, as it would with conventional stimulation. Only three studies met the search criteria for randomized controlled trials which compared milder stimulation protocols involving use of GnRH antagonist and lower dosage of...
FSH with conventional protocols involving GnRH agonist and standard FSH dosages. Since all three studies were published by their group, the authors were able to do a meta-analysis which made use of individual patient data. In 592 first treatment cycles, an average of six follicles was retrieved with mild compared to nine with standard stimulation. The highest implantation rates were similar in each group: 31% with mild and 29% with standard stimulation, but these rates were achieved with five oocytes in mild and ten oocytes in conventional stimulation cycles. Thus, the most functional ovarian responses occur with fewer oocytes in mild than in conventional stimulation cycles. On the other side of the coin, while five oocytes might reflect a poor ovarian response with conventional stimulation, it is an optimal response in mild stimulation cycles. These results are reassuring and informative about the dynamics of the ovarian response to exogenous FSH administration, but what is the clinical impact of mild stimulation?

In the largest of the three trials, the authors hypothesized that mild stimulation with GnRH antagonist co-treatment and single embryo transfer would be more tolerable than standard stimulation after long-GnRH agonist down-regulation with transfer of two embryos. They also hypothesized that there would be no more than a small decrease in effectiveness (Heijnen et al., 2007). This management trial was designed to compare four cycles of mild with three cycles of standard stimulation. The trial had a non-inferiority intent: it was designed to evaluate whether the birth rate (for all births that were initiated in 1 year after randomization) with mild stimulation would be within 12.5% of that for standard stimulation. The reasoning in non-inferiority trials is that the new approach will allow patients to gain from lower costs and/or fewer adverse effects while retaining nearly all (usually 90%) of the effectiveness of the standard treatment.

As expected, there were fewer term live births per cycle with mild (15.8%) than standard (24.0%) stimulation. Even so, with 444 versus 325 cycles in mild and standard protocols, respectively, the term birth rates after 1 year were similar: 43.4 and 44.7%. The lower 95% confidence interval of the difference in rates was −9.8%. Thus, over 1 year, the mild protocol was only 1.3% less effective than the standard protocol and it is unlikely that it would fall more than 10% below the birth rate with standard stimulation if a large number of trials were done.

Of course, with single embryo transfer there were significantly fewer multiple births, and costs were lower with mild stimulation (€8333 versus €10 745) (Heijnen et al., 2007; Polinder et al., 2008). Also, in the mild stimulation group the response to failure was better tolerated (de Klerk et al., 2007) and dropout rates were lower (Verberg et al., 2008c). Dropouts are important because these women no longer have a chance of conception with IVF. The main reason for dropout from IVF is patient distress, so that even where IVF is reimbursed, optimal access to treatment requires that the distress factor should be minimized. Furthermore, another of the three trials suggests that embryo aneuploidy rates are reduced in IVF cycles with mild stimulation (Baart, 2007).

Management trials such as that of Heijnen et al. (2007) play a key role in the application of evidence to clinical practice. In the hierarchy of trials, efficacy or explanatory trials test whether an intervention can work under ideal conditions, while management or effectiveness trials test whether the same intervention actually does work in the challenging and variable conditions of typical practices (Cochrane, 1972; Haynes, 1999). The trial methods differ in crucial respects. An efficacy trial would have a narrowly defined study population, a discrete intervention and possibly a surrogate outcome (Grimes and Schulz, 2005). In contrast, a management trial would enrol a typical range of patients and would not require clinicians to alter their routines appreciably. Under management trial conditions, the intervention must have a robust effect if it is to overcome the sources of variability that are typical among clinical practices.

Milder ovarian stimulation is sufficiently robust, although effectiveness does require more cycles. There is the usual need for additional trials of similar approaches in different clinical settings. Also, the protocol is far from the low-cost protocols envisaged by Edwards et al. (1996) or Trounson (Pearson, 2008). The combined use of gonadotrophin preparations and off patent oral drugs like anti-oestrogens or aromatase inhibitors seems worth pursuing. Nevertheless, mild stimulation can reduce gonadotrophin dosage, cutting costs, time commitments and the need for intense monitoring. Mild stimulation also diminishes patient distress and complications. When combined with the transfer of fewer embryos, multiple birth rates are reduced. Surely those are worthy achievements.

References


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