In vitro fertilization is a complex treatment for infertility involving costly ovarian stimulation regimens, substantial patient discomfort and considerable chances for complications. Further development of IVF may be facilitated by challenging current concepts of success in assisted reproduction. IVF outcomes should be defined in broader terms which reflect the interests both of the couple and those providing health care (1). A couple embarking on IVF are presently focused on the traditional numerators and denominators of outcome, for example ongoing pregnancy rate per embryo transfer. The goal of their treatment is the chance of having a healthy baby after completing an IVF treatment consisting of series of IVF cycles and subsequent replacement of frozen embryos. This should be weighed against the associated discomfort complications and costs which they will encounter along the way. The outcome of a single cycle is of interest, but only as part of the whole treatment. The information patients, providers and policymakers require is the chance of delivering a healthy baby per treatment started or per defined treatment period (1).

Around 50% of those who initiate IVF will not conceive (2). This is partly due to the high drop out rates after an unsuccessful IVF cycle. European data reveal that up to 25% of patients who undergo a first IVF cycle refrain from further treatment, and are therefore deprived of additional chances of conceiving. This is not only due to costs, or poor prognosis but also to the stress and side effects of the treatment itself. By expressing results in terms of the delivery of a healthy baby per treatment started (or in a given time period), clinicians will be encouraged to develop and apply patient friendly stimulation protocols with less stress, discomfort, side effects and chances for complications such as the ovarian hyperstimulation syndrome.

The introduction of GnRH antagonists into clinical practice has enabled shorter, patient friendly treatment protocols to be applied since, in contrast to GnRH agonists, treatment can be limited to the days in the mid-to-late follicular phase truly at risk of a premature LH rise. Since the introduction of the GnRH antagonist, several studies have focused on optimizing the existing stimulation protocols. In 2006, a review has been published in Human reproduction update on behalf of the Brussels GnRH antagonist consensus workshop group concerning the recommended use of the GnRH antagonist co-treatment (3). In this review it has been concluded that the GnRH antagonist initiation on day 6 of stimulation appears to be superior to flexible initiation by a follicle of 14-16mm. The optimal timing for HCG administration needs to be further explored and replacement of HCG by a GnRH agonist for triggering of final oocyte maturation is associated with lower probability of pregnancy. Currently, data are not in favour of a need to increase the onadotropin dose at antagonist initiation. Alternative stimulation schemes such as the late initiation of FSH in the follicular phase and the application of IVF in a modified natural cycle have been explored. Extending the FSH window by administering low dose exogenous FSH from the mid to late follicular phase enables the endogenous inter-cycle FSH rise to be utilized rather than suppressed (4). This approach has opened the way to the development of mild patient friendly stimulation protocols. Mild stimulation protocols may reduce drop outs from IVF and therefore increase the overall number of cycles per patient resulting in increased overall birth rates per started treatment. Shorter, patient friendly stimulation protocols may increase efficiency, enabling more cycles to be carried out in a given period than is possible with conventional stimulation protocols. Natural cycle IVF is a low-risk and patient-friendly procedure with an ongoing pregnancy rate of about 7% per started cycle and about 16% per embryo transfer (5). The success rates of natural cycle IVF are hampered by high cancellation rates because of premature LH rise and premature ovulations. Recent reports using GnRH antagonists to prevent such a LH rise, or indomethacin to prevent rupture of the follicle before planned oocyte retrieval, appear promising in this respect.

The mild stimulation protocol has recently been tested in a 2-arm randomized controlled, non-inferiority, effectiveness trial using a more integrated outcome parameter (6). The aim of this trial was to establish whether a mild in-vitro fertilization treatment strategy can achieve the same term live birth rate within 1 year compared to standard treatment, while reducing patient discomfort, multiple pregnancies and cost. Patients were randomly assigned to undergo a mild ovarian stimulation with GnRH antagonist co-treatment combined with single embryo transfer (mild treatment) or a standard ovarian stimulation protocol including a GnRH agonist long-protocol combined with the transfer of 2 embryos (standard treatment). The cumulative...
pregnancy rate resulting in term live birth after 1 year was 43.4% in the mild treatment group and 44.7% in the standard treatment group. The respective multiple pregnancy rate per couple was 0.5% versus 13.1% (P<0.001) and total costs were €8,333 versus €10,745 (P=0.006) (6). The total patient discomfort was equal between the two treatment groups. The findings of this study highlight the medical, health economic and psychological benefits of mild strategies in IVF treatment. However, if these results are to be widely implemented IVF outcomes should be redefined in broader terms, better reflecting the interests of the couple, the child and providers of health care.

Adopting the endpoint 'term-delivery per time period' would encourage the adoption of patient friendly stimulation protocols.

Future trials should focus on developing patient friendly stimulation protocols and should also take the cost, patient discomfort and chances for complications into account.

Reference: