This year, Louise Brown, the first baby conceived through in-vitro fertilization (IVF) (Steptoe and Edwards, 1978) will be 20 years old. Since then, IVF techniques have improved in various areas to raise the success rate, to extend the list of pathologies which can be overcome and, therefore, to break down the barriers of infertility.

However, this ‘explosion’ in the available technologies has increased the burden on the couple and, more recently, on the gametes and embryos themselves. The ovarian stimulation protocols have increased the amount of drug injected from clomiphene citrate to the association of gonadotrophins and gonadotrophin-releasing hormone agonist (GnRHa). GnRHa have almost suppressed the onset of premature luteinizing hormone (LH) surges and, therefore, reduced the cancellation rate. They also allow us to manage the activity of IVF teams more easily. However, the price paid by the patients (literally and physically!) is not negligible. Ovarian hyperstimulation syndrome (OHSS) is more frequent with the use of GnRHa (Navot et al., 1991) and the side-effects of the long protocol (used in the majority of the cases) are frequent and not always well tolerated by the patient (Frydman et al., 1988). As discussed by Edwards et al. (1996), such stimulation protocols may not be good for women’s health and may not be the optimal treatment for achieving the best implantation rates (Edwards et al., 1996). Some authors have found a correlation between the number of oocytes retrieved and pregnancy rates. However, most of these studies are retrospective and under comparable stimulation regimens, patients with fewer oocytes are very likely to respond poorly to IVF, with diminished pregnancy rates (Meniru and Craft, 1997).

The man, after being almost ignored for many years, can now share with his partner the various invasive medical techniques which may be proposed. The onset and results of intracytoplasmic sperm injection (ICSI) with a very limited number of spermatooza started the race to collect spermatooza and sperm recovery now involves the use of needles, ‘guns’, or open biopsy (Hovatta et al., 1995; Nagy et al., 1997).

Finally, the gametes and embryos themselves are not left in peace. Oocytes are injected with a single spermatoozoon (Palermo et al., 1992), and cytoplasmic transfer or pronucleus aspiration have been tried recently (Cohen et al., 1997). Spermatooza have been exposed to various physical and chemical procedures to enhance their fertilizing potential (Oeninger and Alexander, 1991). Embryos have been bathed in acidified solution (Tucker et al., 1993), and their zona pellucidae are slit (Alikani and Cohen, 1992), drilled with acid (Cohen et al., 1992), with lasers (Laufer et al., 1993) or simply removed before transfer (Fong et al., 1997).

Of course, all these improvements in IVF techniques have one final goal: the improvement of the success rate of a technique which can help couples to have children. The pregnancy rates of the best IVF teams today approaches 50% (Rosenwaks et al., 1995). This should please both R.G.Edwards, and the late P.Steptoe, considering their struggle at the start of IVF.

Even when pregnant, the couple can still be exposed to complications. Multiple pregnancies expose the children and their families to complications and difficulties which are usually underestimated (Garel et al., 1997). Multiple pregnancies should not be considered as an IVF success, even though progress in obstetrics and neonatology has considerably reduced perinatal mortality rates. In comparison with singleton pregnancies, the chances of having a healthy child are reduced in triplet pregnancies (Albrecht and Tomich, 1996) as well as, to a lesser extent, in twin pregnancies (Olivennes et al., 1996). The latter being generally considered as ‘a nice opportunity for a childless couple to have a boy and a girl at the same time!’ It is appalling to attend medical meetings and see the number of teams routinely transferring four or more embryos and being proud of their 50% multiple pregnancy rates including 15% triplets! The availability of selective embryo reduction should not mask the terrible paradox of suppressing the development of a medically assisted conception. In addition to the ethical controversy, the potentially adverse effects of this technique on the outcome of the pregnancy (Evans et al., 1990) and on the patient (Schreiner-Engel et al., 1995), should not be underestimated.

The number of embryos transferred may be increased to overcome a poor implantation rate. The resulting high multiple pregnancy rates and their related complications and costs result in an interesting debate on why such high numbers of embryos are transferred (Faber, 1997). There is also discussion on the need for legal regulation (already in place in some countries) on the maximum number of transferred embryos (Bronson, 1997; Bustillo, 1997; Palmer, 1997). The excess observed in some countries and the obvious absence of self-regulation clearly advocates some sort of control (Faber, 1997).

Out of the physical burden arises a high social cost. The multiple blood samples drawn, controls, tests and intervention impact the patient’s life and could compromise a women’s career. Finally, all this progress has increased the costs of the IVF procedure and, in certain parts of the US, this can now reach US$20 000. The estimated cost of an IVF baby (Goldfarb...
et al., 1996; Van Voorhis et al., 1997) has led to some questioning on the necessity of covering medical expenses for IVF.

Being close to ‘the top of the wave’, it is interesting to see the growing interest in the reduction of the burden of IVF on the couple (Edwards et al., 1996). Perhaps we should try to come back to the goal of P. Steptoe and R. G. Edwards – to produce in vitro an embryo which can implant and lead to the birth of one healthy child. Maybe it is time to put together our ideas to diminish the weight of the IVF procedures and related complications. We should think of giving a couple the chance to conceive using procedures which are less costly in terms of physical, emotional, social and financial burden both for the patient and the potential child. It is time to propose a more gentle assisted reproductive technology – time to think of ‘friendly IVF’.

The first step of friendly IVF is probably the most difficult – how to reduce the complexity of the procedure without altering the success rate? However, one should consider the possibility that some women might want to try three times using a very simple procedure which has a 10% success rate, rather than having a single attempt using a procedure which could give a 30% success rate, but which could also have a 30% multiple pregnancy rate, and/or, 4 months of coping with the physical and emotional consequences of failure. This is in addition to the side-effects of the procedure itself (headaches, hair loss, weight gain, libido modification, abdominal pain etc...) and its cost. Comparisons will have to be made on the respective costs of repeated simple treatments with the classical ovarian stimulation protocols.

Simplification of the stimulation protocol can go in various directions. Reducing the amount of drug used, reducing the amount of control procedures involved in the monitoring of the cycle, improving our knowledge on embryo implantation and our in-vitro handling of gametes and embryos to give the best implantation rate possible. New approaches to non-invasive assessments of human oocytes and embryos will be a determinant in the better understanding and prediction of the developmental competence of human IVF embryos (Van Blerkom, 1997). This is, of course, dependent on embryo research, which could be a major problem in the European Community. Embryo research is forbidden in the majority of European countries apart from Italy, UK and Belgium. If such legislation was extended to all European countries, the progress in improving our knowledge of embryos could be compromised. Probably, we should be experimenting more on the embryo and less on the couples, with all the ethical controls needed for these research projects.

In an effort to attenuate the stimulation protocols, the development of GnRH antagonists, and their recent availability for safe clinical use in humans, represent an interesting perspective (Olivennes et al., 1994a; Albano et al., 1997). We have recently presented data on the use of a GnRH antagonist with a single injection protocol which suppresses the inconvenience associated with GnRHa and reduces both the length of the treatment procedure and the amount of human menopausal gonadotrophin (HMG) needed (Olivennes et al., 1994a, 1995). More recently, we have investigated the potential of using GnRH antagonists in spontaneous menstrual cycles (Frydman et al., 1997). The spontaneous cycle is probably the ‘gold standard’ of friendly IVF. Moreover, higher quality embryos might be obtained with the natural cycle as suggested by Edwards et al. (1996). What could be more natural than a natural cycle? However, spontaneous cycles have been almost abandoned, due to their poor pregnancy rates and the frequency of cycle cancellations due to premature ovulation. GnRH antagonists could help to prevent LH surges in spontaneous cycles (Leroy et al., 1994) and could, therefore, reduce cancellation rates.

In the preliminary results of an ongoing study, we propose preventing a LH surge in a spontaneous menstrual cycle by administering a single dose of 0.5 or 1 mg Cetrorelix. Patients were selected among couples where ICSI was indicated for severe male factor infertility, since higher implantation rates could be expected in these women, who were generally free from infertility factors. The injection was performed when a follicle of 14 mm was observed, in association with a plasma oestradiol concentration of >100 pg/ml. The preliminary results have been encouraging; a total of 30 patients were included of which four were cancelled (13%). In a total of 26 oocyte retrievals, 21 led to at least one oocyte with a 81% fertilization rate. A total of 16 transfers were performed leading to four pregnancies (15% per retrieval, 25% per transfer) of which three are ongoing. These results need to be confirmed in a larger number of patients, but they could lead to an interesting alternative in some selected patients.

The success of using spontaneous cycles might be increased by trying to obtain a blastocyst with an extended culture period. Until recently, the blastocyst retrieval rate with cell-free culture media was disappointing (Olivennes et al., 1994b). Recently, sequential culture media have produced interesting data and a good implantation rate has been reported with blastocysts obtained using cell-free culture media (Behr et al., 1997; Bongso et al., 1997). If one can dream of an implantation rate of 20–30% per blastocyst, the association of spontaneous cycle and blastocyst transfers could represent a very interesting alternative to an intense IVF protocol. Potential benefits of blastocysts transferts might be extended to routine IVF if co-culture is not longer required to obtain good quality blastocysts (Bavister and Boatman, 1997).

Coming from a different direction, in vitro maturation of oocytes would be the simplest method of producing more than one embryo, and with a limited burden on the couple. After a few reported pregnancies (Cha et al., 1991), some teams are now working extensively on in vitro maturation of oocytes (Trounson et al., 1994; Barnes et al., 1996; Russell et al., 1997). If the results of maturation, fertilization and embryo development are good, the results in terms of pregnancy rate are extremely disappointing, confirming that a ‘good looking embryo’ is not always a good embryo as far as implantation is concerned. These studies point to a new goal in reproduction research and demonstrate that nuclear maturity may be variable and/or that the cytoplasmic maturation of the oocyte is of first importance in the competence of the oocyte and the embryo. Preliminary experience with cytoplasmic transfers seems to have produced some interesting results recently (Cohen et al., 1997).
1997), but the lack of identifying markers for cytoplasmic maturation complicates the assessment of cytoplasmic maturity. The relative success of in-vitro maturation of oocytes in animal species, e.g. bovine (Trounson et al., 1994a), gives us hope for the future. A drug-free IVF procedure would represent enormous progress, but will probably take some years to become a successful procedure which could be proposed routinely. In the meantime, simplifying the stimulation protocol should be proposed. This could be achieved by reducing the amount of stimulatory drugs used in different protocols, e.g. the step-down scheme (Antoine et al., 1997) or the ‘old fashioned’ clomiphene citrate protocol, which has recently been making a come-back in IVF (Felderbaum et al., 1997), or by minimal monitoring (Wikland et al., 1994). Another way would be to propose a minimal stimulation protocol to obtain a lower number of embryos with a high implantation rate. This could be enhanced by the constant improvement of embryo culture techniques. The development of long-acting gonadotrophins could also improve the stimulation protocol by reducing the number of injections (Heikoop et al., 1997). Finally, coming back to the spontaneous cycle and improving its success rate, could represent an interesting alternative with a limited burden for the couple and without multiple pregnancy: the most friendly IVF.

References
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