NEW DEBATE

Coming soon to your clinic: patient-friendly ART

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The current practice in medically assisted reproduction is still too exclusively focused on effectiveness and success rates. This has a number of considerable, and more importantly, avoidable drawbacks. Single embryo transfer was an important move away from this model to include safety and welfare of mother and child. Patient-friendly ART goes one big step further. It is composed of a mix of four criteria: cost-effectiveness, equity of access, minimal risk for mother and child and minimal burden for patients. All four components have a strong normative ethical basis: cost-effectiveness relies on the optimal use of community resources to maximise well-being; equity of access is based on justice, minimal risk is founded on the fundamental non-maleficence rule and minimal burden is largely based on the autonomy principle. The inclusion of the four criteria in decision-making about treatment would express these values in clinical practice.

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Introduction

A major objective of infertility specialists is to increase the effectiveness of IVF. This is understandable since one of the main criticisms from the outside world is that after 30 years the success rate of IVF is still pretty poor. Although the success rate is comparable to the chance in natural conception of fertile couples and although the rate is steadily rising, policy makers and health insurance providers are not happy with the present results. In several countries, this is a major reason for refusing reimbursement of IVF (Hughes and Giacomini, 2001). However, a high success rate also has more direct benefits for the practitioners: it attracts customers by giving the clinic a competitive edge over competitors, allows the practitioners to make more money and it gives a boost to their reputation among their colleagues. Therefore, the goal of maximising effectiveness has dominated the field for many years.

An important move away from this model occurred only a few years ago with the introduction of single embryo transfer (SET) (Wolner-Hanssen and Rydhstroem, 1998; Vilska et al., 1999; Gerris, 2005). Since both practitioners and patients believed that the replacement of several embryos increased the success rate, multiple embryo replacement was the rule. Very slowly one realized that this practice had considerable side effects. The price to be paid for the multiple births is enormous, both in financial and health terms, but also in terms of psychological suffering (Pennings, 2000; Ombelet et al., 2005).

The process that started with SET should eventually result in a global ‘patient-friendly’ approach. Patient-friendly ART includes four different aspects or criteria: cost-effectiveness, equity of access, risk minimisation and burden minimisation for the patients. Like SET, this proposal is founded on an altered ranking of these criteria compared with effectiveness. We believe that it is insufficient to give the patient the highest chance to take home a healthy child; one should offer the patient a fair chance to obtain a treatment that combines the highest chance of returning home with a healthy baby taking into account the cost of treatment for patient and society, the risks for mother and child and the burden for the woman and, to a lesser extent, for the man.

Cost-effectiveness

In the field of ART, there are numerous instances showing that ART can be performed in less costly ways. An efficient first line approach of infertility can be realised through fertility awareness programs. In a prospective randomised study by Gnoth et al. (2003) couples were instructed about the meaning and detection of cervical mucus secretion; 80% of the couples trying to conceive did so after 6 months. Despite the fact that these results were very promising and although this method is associated with considerable cost reduction, most fertility specialists are not interested in this first line option. A second example is the choice between...
human menopausal gonadotrophins, urinary follicle-stimulating hormone and recombinant follicle-stimulating hormone. The NICE report states that following pituitary down-regulation as part of an IVF treatment, all three products are equally effective in terms of pregnancy rates and incidence of ovarian hyperstimulation syndrome (OHSS) (National Institute of Clinical Excellence, 2004). That same report also notes that ‘consideration should be given to minimising costs when prescribing’. When ovarian stimulation is needed in intrauterine insemination (IUI) treatment cycles, clomiphene citrate can be used as a first line stimulation drug instead of gonadotrophins (Ombelet et al., 1997; Sovino et al., 2002). Recently, it was shown that in case of primary unexplained or male subfertility treated by IUI, no significant difference in live birth rates between clomiphene citrate and rFSH (recombinant FSH) could be observed. Being less expensive, clomiphene citrate seems the more cost-effective drug and can be offered as the first choice drug if ovarian stimulation is needed in IUI programmes (Dankert et al., 2007). In a large retrospective cohort study on 1759 IUI cycles in couples with unexplained infertility, it was shown that for older women aged >37 years, natural cycle (unstimulated) IUI seems to be associated with a significantly higher live birth rate compared to stimulated cycles (7.5 versus 3.5% per cycle), irrespective of the agent used (Kalu et al., 2007).

The final example is the recommendation to offer up to six cycles of IUI to couples with mild male factor fertility problems, unexplained infertility or minimal to mild endometriosis (Goverde et al., 2000; National Institute of Clinical Excellence, 2004). Data from Australia and New Zealand clearly show that almost 80% of centers are convinced of the cost-effectiveness of IUI, but nearly a third of centers still promote IVF as a first-line treatment even with patent tubes and normal semen. In cases of male subfertility, IUI is rarely considered as a first line option (Misky and Chapman, 2002) although the results of IUI in moderate male subfertility are encouraging (Ombelet et al., 2003). A study in The Netherlands also revealed that only about half of the recommendations for IUI are respected by less than half of the practitioners, leading to higher costs and more applications of IVF than necessary (ZonMw, 2005). The latter findings indicate that changing practice is more complex than it looks. Providing information about alternatives and composing guidelines regarding the use of certain methods is simply not enough. The tendency to stick to the routine treatment, the fear for a diminished success rate and other more material benefits all contribute to non-optimal procedures. The influence of drug companies on the way medicine is practiced should not be underestimated either (House of Commons Health Committee, 2005). Market incentives are posing serious challenges to the physicians’ commitment to altruism, putting the patient first and scientific integrity (Brennan et al., 2006). There is no reason to assume that medically assisted reproduction is immune to this danger. Equally powerful players, like the government or health insurers, may need to intervene to counteract the influence of the pharmaceutical companies.

The problem of the distribution of scarce resources presents itself at three different levels: at the community level between health care and other societal needs, at the health care level between infertility treatment and other diseases and at the level of infertility treatment itself between patients. First, there is increasing pressure to control the health care budget which has an inherent tendency to grow. No society will be able to cover all health care costs for all citizens since this would imply that other societal needs such as education and public transport will no longer be satisfied. Within the health care sector, each euro wasted in one sector deprives other sectors of their much-needed means. In a capitated health care system, money spend unnecessarily on some patients by treating them in a cost-ineffective way deprives other patients of treatment or may force them to end up on a waiting list. As a consequence, every citizen and physician has a duty towards the other parties who contribute to and may benefit from the common resource pool to reduce the costs as far as reasonably possible. Finally, using an expensive technology to obtain a pregnancy in one patient who was eligible for another less expensive technology harms other infertility patients. In countries with a global envelop granted to infertility treatment or with a limited number of reimbursed cycles, this link between patients is clear. In Belgium, for instance, the agreement with the Ministry of Health included 7000 cycles at 1182 euro, resulting in an envelop of 8 million euro (Ombelet et al., 2005). For these 8 million euro, more cycles could be done if the cost per treatment would be lowered, thus enabling the clinics to help more couples.

The adoption of cost-effectiveness as a criterion demands an evolution in the way we perceive the role of the physician. The physician has long been considered as the advocate of the patient without regard to costs or social obligations (Paris and Post, 2000). However, this concept is based on an outdated, one-sided and unrealistic picture of a physician’s practice. This attitude introduces an artificial dichotomy between quality of care and cost reduction and would lead to bankruptcy of the health care system. Although the first concern of the doctor should remain the individual patient and not the health care system or the budget plan, he or she should take into account the cost implications. A health care system that offers equitable access to basic health care services is only viable when both patients and physicians realise that the interests of the individual patient and of the social system must be balanced. This implies that patients do not have a right to the most effective treatment (regardless of the cost) but only to the most cost-effective treatment.

Access
Reproduction and family building are important parts of most people’s life plan. As a consequence, societies have a good reason to recognise and remedy the need created by infertility. If the child wish is considered as a basic health need, it is part of the society’s duty to ensure equity. Given the high cost, there is widespread concern about equity in access to reproductive health care. In the USA, for instance, racial, ethnic and socioeconomic status are important factors determining access to infertility treatment (Bitler and Schmidt, 2006). In countries like Finland on the contrary, different socioeconomic groups

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have almost equal access to infertility services (Klemetti et al., 2004).

ART is a relatively expensive treatment in most countries. This is especially true in countries in which infertility is primarily private treatment without (private of public) insurance coverage. In the USA expenses for infertility, including IVF, account for 0.4–0.8% of the total health care costs (Griffin and Panak, 1998). The costs of IVF/ICSI to individual couples range from 10% of annual household expenditures in European countries to 25% in Canada and the USA (Collins, 2002). Costs linked to infertility treatment should not only include the cost of the treatment procedures but also the costs for health care of the pregnant women and their offspring (Collins et al., 1995; Laufer et al., 1995; Goldfarb et al., 1996; Wolner-Hanssen and Rydstroem, 1998; Collins and Graves, 2000). Even when couples are paying for the ART procedures out-of-pocket, the care for their offspring remains a burden on the community if neonatal, paediatric, social and educational services are financed by public funds.

The public financial support through social health insurance largely eliminates ‘ability to pay’ as a criterion for access to treatment. While reimbursement is surely part of the solution, simultaneous efforts from the provider side are also needed. Practitioners cannot campaign for reimbursement of infertility treatment if they are not prepared to take on their part of the deal. The allocation of public funds to infertility care generates an obligation on the part of the practitioners to work cost-effectively. The Belgian project in which reimbursement of ART-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction, is a good example of cost-effective health care through responsibilisation (Ombelet et al., 2005).

In a patient-friendly system, all criteria should be taken into account simultaneously. Focusing on one only may lead to aberrations. Take reimbursement and cost-effectiveness. Full reimbursement of all costs (including drugs and laboratory fees) solves the problem for the patient but not for the health care system. Ironically, reimbursement by public health insurance may even eliminate the incentive for practitioners to reduce costs. The personal financial capacity of patients becomes irrelevant when full reimbursement is offered. Recently, several politicians in Belgium have expressed the fear that the present Belgian reimbursement strategy promotes the unnecessary use of IVF over other less technical and less costly treatments such as IUI. It is cheaper for patients to move directly to IVF because this treatment is fully reimbursed while IUI is not. Patients will opt for the treatment that costs them personally the least even if that option means a more aggressive technique for themselves and a much more expensive option for society. The reimbursement system should avoid such pitfalls. This demands a thorough rethinking of the present procedures. The strategy to fund a strictly limited number of IVF cycles, for instance, makes both SET and minimal stimulation procedures unattractive as they do not lead to the maximal pregnancy rate. Patients with limited resources will opt for treatment that gives the highest success rate even if this may result in multiple births and complications like OHSS. The most effective treatment for the patient may not be the most cost-effective treatment for society. It is a challenge for the field to try to invent a reimbursement system that avoids these aberrations. One possible solution is the adoption of a system that no longer works with a single cycle or treatment for measuring success but with a larger unit like the cumulative pregnancy rate within a fixed time span for similar costs (Heijnen et al., 2004). This would make comparisons of techniques in terms of cost-effectiveness easier.

Risk minimisation

Generally speaking, a number of cost reducing measures involve the rejection of the ‘aggressive’ standard hormonal stimulation. This movement has been given several labels: ‘soft’, ‘natural cycle’, ‘minimal stimulation’ IVF etc. A major advantage of these procedures is the lower risk of OHSS. Feminist and patient groups have been focused on the dangers associated with the hormonal stimulation from the very beginning of IVF. The most remarkable thing is that the ways to lower the risk of OHSS are known (Guibert and Olivennes, 2004). The current rate of severe OHSS (estimated around 1%) and moderate OHSS (estimated around 6%) can be brought down significantly (ESHRE Task Force on Ethics and Law, 2007). The incidence of OHSS may be decreased by the investigation of predisposing factors like polycystic ovaries, the use of milder or minimal stimulation protocols and the use of GnRH agonist to trigger ovulation instead of human chorionic gonadotrophins. The reduction or even elimination of health risks for women would deprive the opponents of a very strong argument.

The second main advantage is the significantly lower risk of multiple pregnancies. As mentioned above, standard IVF aimed at increasing the pregnancy rate by replacing several embryos. The resistance to change the policy of transferring multiple embryos was (and in some countries remains) considerable even after it had been shown that SET barely diminishes the success rate in specified groups (Gordts et al., 2005). In some countries, the policy break was only implemented when the government intervened and forced it upon the practitioners (Ombelet et al., 2005). It is a real pity that infertility specialists were not able to impose this rule on themselves (Pennings, 2000). SET was a consequence of the realisation that the ultimate goal of assisted reproduction was not to create as many children as possible or to achieve a successful conception but to offer the parents a healthy singleton, a twin pregnancy being regarded as an adverse outcome (Land and Evers, 2003). It is obvious that in case of non-IVF assisted reproduction, minimal ovarian stimulation also reduces the risk for multiple pregnancies and OHSS.

Burden minimisation

From the beginning, it was clear that IVF was not an easy procedure for the women undergoing it. The psychological, physical and emotional stress experienced by both women and men during assisted conception treatment is high and surely underestimated (Boivin and Tafekman, 1995; Verhaak et al., 2001). The psychological distress is also the main
reason why patients drop out (Olivius et al., 2004). In addition, there are indications that ovarian suppression with GnRH agonists can cause depression, anxiety, headache, lower back and muscle pain. Mild stimulation in combination with SET represents a patient-friendly alternative for conventional IVF (de Klerk et al., 2006). Moreover, the duration of treatment is considerably shorter and the medication is administered for a few days only (Pelink et al., 2006). Milder stimulation protocols have fewer side effects and are also less stressful for the patients (Fauser et al., 1999; Nargund et al., 2001). The stress can partially be explained by fear for the unknown, worry about the injections and the possible side effects of the drugs (Hammarberg, 2003). If a woman is really concerned about the possible effects of the hormones on her health, it will make a huge difference if she is offered a minimal stimulation protocol. In general, adaptation of the treatment to the patients’ psychological concerns may reduce the stress and improve their well-being.

Here too, there is a normative component involved. When there are different options for treatment, the principle of respect for autonomy demands that all options are discussed with the patients in order to allow them to choose. Treatments are not only different in terms of success rate but also in terms of psychological burden and financial implications. Although it has become standard practice in the last decade to stress patient’s rights and to allow patients to participate in treatment decision-making, patient preferences are only rarely studied in the field of reproductive medicine (Bayram et al., 2005). We suspect that the patient’s preference is often assumed rather than expressed. Are patients given the choice to opt for a less effective but considerably less burdensome treatment? If this information is not provided by the physician, the patient will not even realise that an alternative exists and that a choice can be made on these points. In a Dutch study, a questionnaire was send to patients and physicians on their choice between one stimulated cycle and three natural cycles (Braat and Kremer, 2004; Pistorius et al., 2006). The survey revealed that about 30% of both patients and physicians were willing to trade off 6% success in live birth of the stimulated cycle for the three natural IVF cycles. An important predictor of the patient preferences was the anxiety about hormone injections. In another study, Hoijgaard et al. (2001) concluded that patients preferred the simplicity and short duration of a low stimulation regimen in spite of drawbacks such as high risk of cancellation of the cycle and a corresponding necessity for more treatment cycles. Generally speaking, patients counterbalance the disadvantages of low stimulation (less efficiency per cycle, more cancellations) by the advantages on other aspects (few side effects, short duration, simplicity).

It is important that more studies on the emotional, psychological and physical advantages and disadvantages of alternative stimulation protocols are conducted. Moreover, the studies should be designed to measure the burden in combination with the other relevant factors. One stimulated cycle should not just be replaced by one natural or low stimulation cycle. Within a certain reimbursement context, the latter would never be chosen by patients given the decrease in success rate that is expected. But one could offer patients a choice between three or five natural IVF cycles and one standard IVF cycle, which leads to a comparable success rate and comparable cost (Janssens et al., 2000). The study designed by Eijkemans et al. (2006) is almost perfectly fitted to the proposal of patient-friendly care we propose here. This study compared the effectiveness, health economics (costs) and patient discomfort (quality of life or psychological burden) of two treatment strategies that differ in ovarian stimulation protocol and embryo transfer policy. They showed that cumulative rates of term livebirths and patients’ discomfort are comparable for mild ovarian stimulation with SET and for standard stimulation with two embryos transferred. On the other hand, after a mild IVF treatment protocol multiple pregnancy rates and overall costs are substantially lower (Heijnen et al., 2007).

Conclusion

The current practice in medically assisted reproduction is still too exclusively focused on effectiveness and success rates. This has a number of considerable, and more importantly, avoidable drawbacks. SET was the first adaptation of the practice to include safety and welfare of mother and child. Patient-friendly ART goes one big step further. It is composed of a mix of four criteria: cost-effectiveness, access, minimal risk and minimal burden. All four components have a strong normative ethical basis: cost-effectiveness relies on the optimal use of community resources to maximise well-being; access should be equitable and fair; minimal risk is founded on the fundamental ‘do-not-harm’ rule and minimal burden is largely based on the autonomy principle. We believe that it is high time to refocus on these values in clinical practice.

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