

Ethics, social, legal, counselling

Affordable IVF for developing countries



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Abstract

Worldwide, more than 80 million couples suffer from infertility; the majority are residents of developing countries. Residents of developing countries encounter a lack of facilities at all levels of health care, but especially infertility diagnosis and treatment. Infertility defined as a disease has a much stronger negative consequence in developing countries compared with Western societies. Social isolation, economic deprivation and violence are commonly observed. Tubal infertility due to sexually transmitted diseases, unsafe abortion and post-partum pelvic infections are the main causes of infertility in developing countries. Very often those conditions are only treatable by assisted reproductive technologies. Although preventative measures are undoubtedly the most cost-effective approach, not offering assisted reproduction is not an alternative. This study proposes a specially designed infertility care programme leading to cost-effective simplified assisted reproduction as a valid treatment protocol in developing countries when prevention or alternative methods have failed. Special attention should be given to avoid adverse outcomes such as ovarian hyperstimulation and multiple embryo pregnancy.

Keywords: *affordable, assisted reproduction, developing countries, infertility treatment, IVF, simplified methods*

Introduction

In 1994, the United Nations International Conference on Population and Development in Cairo mentioned issues on future actions on 'prevention and appropriate treatment of infertility where feasible'. However, no guidelines or concrete actions and programmes were given for developing countries.

Worldwide, more than 80 million couples suffer from infertility; the majority of this population are residents of developing countries (Fathalla, 1992). New reproductive technologies are unavailable, scarcely available or very costly in so far that the large majority of the population cannot afford infertility treatment at all (Van Balen and Gerrits, 2001; Nachtigall, 2006). Developing countries have a large reservoir of infertility problems, of which bilateral tubal occlusion is the most important one (World Health Organization, 1987; Nachtigall, 2006), a condition that is potentially treatable by assisted reproductive technologies. Tubal factor infertility, the most common aetiological factor in developing countries, is mainly caused by sexually transmitted

diseases (STD), post-partum or post-abort infections, pelvic tuberculosis and schistosomiasis.

In most developing countries, reproductive health care is synonymous with family planning and contraception. In developing countries however, infertility, fetal and neonatal death constitute an important public health problem resulting in a high prevalence of childlessness (Bergstrom, 1992). Moreover, the negative consequences of childlessness are much stronger in developing countries when compared with Western societies. In many cultures childless women are stigmatized, which may lead to isolation, neglect, domestic violence, or they may end up as a second wife in a polygamous marriage (Gerrits, 1997; Sundby, 1997; Van Balen and Gerrits, 2001). Different religious customs, moral and legal rules may influence and explain the way a community regards childlessness. There is no doubt that in most developing countries infertile women are blamed for infertility, resulting in the social stigma of childlessness, even if they are not

the cause of it. On the other hand, dilatation and curettage and other harmful practices which are still used as a standard therapy for infertility in many low-income countries, demonstrate the outdated practices in these countries. These practices may even inflict infertility in otherwise healthy patients, indicating the need for rigorous training programmes (Sundby, 1997; FIGO, 2006).

During recent decades, politicians have always shown great interest in reducing the number of births in developing countries, the so-called political 'top-down' perspective (Hamberger and Janson, 1997), but infertility care received little or no attention.

Especially in developing countries, where poverty and infections are commonplace, fertility and fetal care are affected by many different cultural, environmental and socio-economic factors. The most cost-effective approach to tackle infertility problems in developing countries is prevention and education (Leke *et al.*, 1993). However, in those cases where prevention has failed, simplified assisted reproduction must be thought of as a valuable option (Malpani and Malpani, 1992). On the other hand, new reproductive technologies can only be successfully introduced in this part of the world if socio-cultural and economic prerequisites are fulfilled and politicians are persuaded to support the project. Quality of life will not only be achieved by a correct family planning and mother child programme, but also by an environmentally adapted reproductive health care programme. Limitations to introduction of IVF programmes in low-income countries also have to be faced.

In Egypt, it was previously stated that only 50–60% of couples could afford to pay for IVF and embryo transfer, induction/monitoring of ovulation, or artificial insemination with husband's spermatozoa, all of which only the private sector provided. These results demonstrate that prevention of infertility is still the most efficient option in developing countries (Serour *et al.*, 1991a,b).

In September 2001, a meeting on 'Medical, Ethical and Social Aspects of Assisted Reproduction' was organized by the WHO. For the first time, major attention was paid to ongoing developments in assisted reproduction technology together with their social and ethical implications in developing countries (Daar and Merali, 2002; Fathalla, 2002; Giwa-Osagie, 2002; Luna, 2002; Qiu, 2002; Serour, 2002; Tangwa, 2002; Vayena *et al.*, 2002; Widge, 2002). It was the first time that the WHO highlighted the issue of assisted reproduction in developing countries.

In the authors' view, goal-oriented population control is likely to be unsuccessful if it does not take into account all determinants of human reproductive failure. Optimizing a concurrent infertility treatment, family planning and perinatal care programme in so-called 'reproductive health centres' is probably the most important challenge for developing countries in the near future. As mentioned by van Balen and Gerrits (2001), traditional healers have some advantages over the Western approach because they understand the local people much better, they speak their local dialect and live according to the same culture. Their co-operation will be pivotal when formal strategies are planned.

After a fascinating period of almost 30 years of IVF and 15 years of intracytoplasmic sperm injection (ICSI), it must be admitted that only a small part of the world population benefits from these new reproductive technologies. The time has come to incorporate those new insights in a specially designed infertility

care programme, leading to a cost-effective simplified assisted reproduction programme with special attention to avoid ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy, as a valid treatment protocol in developing countries when prevention or alternative methods have failed.

Pros and cons of infertility treatment in developing countries

The direct and indirect costs of conventional reproductive technologies (IVF, ICSI) are extremely high and therefore only a small proportion of infertile women in developing countries will benefit from it. Subsequently the general attitude is that manpower and financial resources are not applied for introducing assisted reproductive technologies, but preferably for prevention and education. Sexually transmitted diseases, gender discrimination, pollution, poverty, among others may affect reproductive outcomes significantly; therefore, public funds used in education and preventive care are the most cost-effective approach to solving infertility problems in developing countries.

Nevertheless, history has taught us that even in countries where public health systems succeed in achieving well organized prevention and education programmes, 5–10% of couples remain infertile and should be helped. One should not forget that in affluent countries, infertility secondary to infection (female or male) is still an important reason for performing assisted reproduction. Neither should it be forgotten that the numerous IVF cycles performed in developed countries for iatrogenic tubal infertility secondary to improperly counselled couples before sterilizations.

Table 1 gives an overview of the arguments for and against the use of 'affordable IVF' in developing countries. The main reason why the idea of infertility treatment in developing countries still evokes a feeling of discomfort and indignation can be sought in the misconception that the expected overpopulation is only due to high fertility rates (number of children per woman).

According to the 2004 revision of the 'world population prospects' of the United Nations, the world population is expected to increase from 6.5 billion inhabitants in 2005 to reach 9.1 billion in 2050. The fertility rate at the world level was 5 in 1950–1955 and declined to 2.65 in 2000–2005. Realization of the fertility declines projected is contingent upon access to family planning and education, especially in the least developed countries. In 113 out of 148 developing countries, the mean fertility rate has already dropped as low as 2.58 per woman and is expected to decline to 1.92 by mid-century, i.e. below the replacement level of 2.1.

Even more important is population ageing. Global life expectancy at birth among the least developed countries is expected to rise from 51 years today to 67 years in 2045–2050. It seems that in the great majority of developing countries, the continuing population rise will be the result of population ageing and not because of high fertility rates.

Considering funding, the use of assisted reproduction in developing countries remains a contested issue. Because infertility is caused by bilateral tubal blockage in the majority of cases in developing countries, the use of assisted reproduction

Table 1. Arguments for and against IVF in developing countries. 'Men and woman of full age, without any limitation due to race, nationality or religion, have the right to marry and to found a family' (UN declaration of Human Rights, Article 16.1).*Arguments pro*

Infertility is a disease and needs medical treatment
 High prevalence of tubal factor infertility in DC
 Negative consequences of childlessness are much stronger in DC
 Equity: IVF should not only be available for the rich
 Prevention and alternative methods are not always successful
 Adoption is not an option in most DC (socio-cultural, religious)
 Possibility of simplifying diagnostic procedures
 Possibility of simplifying clinical procedures (IVF cycle)
 Possibility of simplifying laboratory procedures (IVF cycle)
 Reproductive Health Care Centres: go together with family planning/mother-care/infertility diagnosis and treatment (opportunity: cervical cancer and HIV screening)

Arguments contra

Reproductive Health Care in DC
 More important priorities
 family planning (contraception)
 prevention of infections
 education
 Limited budgets
 from government
 from non-governmental organizations
 Other important priorities: e.g. vaccinations, malaria, HIV
 Dilemma: overpopulation versus childwish
 IVF-related procedures: regarded as expensive and moderately effective
 High risk for complications (e.g. OHSS, multiple pregnancy, prematurity)
 Unknown outcome for women (? cancer risk)
 Unknown outcome for babies (immediate- and long-term risks)
 Limited professional experience for medics and paramedics in DC
 Low-level facilities in most DC
 ICSI and cryopreservation of gametes and embryos: doubts about cost-effectiveness in DC

DC = developing countries; ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome.

is usually needed. The option of treatment is not possible for many infertile couples due to the high cost of assisted reproduction. Therefore, the development of accessible and low cost assisted reproduction programmes will be crucial, and if assisted reproductive technologies cannot be simplified, public funding will be limited to education and preventive care in most developing countries.

Prevalence of infertility in developing countries

Only a limited number of papers report on the prevalence of subfertility and infertility in developing countries. Throughout the world, the core prevalence of infertility is probably about 5% due to endocrinological, genetic, anatomical and immunological causes (PATH, 1997). In sub-Saharan Africa up to one-third of couples are infertile, but the prevalence differs tremendously between regions, with figures as low as 9% in Gambia (Sundby *et al.*, 1998) compared with 21.2% in northwestern Ethiopia

(Haile, 1990) and between 20 and 35% in Nigeria (Ebomoyi and Adetoro, 1990; Adetoro and Ebomyi, 1991; Okonofua, 1996; Larsen, 2000). It was shown that infertility is the commonest reason for gynaecological consultation in Nigeria (Okonofua, 1996). Prevalence studies in Asia and South America are almost non-existent, and attention is only given to managing population size, with little attention to the issue of infertility, a condition that is not life threatening. The prevalence of infertility in India seems to be low, and according to the National Family Health Survey (2000), only 3.5% of married women are to be declared infertile and 3.8% of women between the ages of 40 and 44 have not had any children. A low prevalence of infertility (6–7%) has previously been reported in the state of Maharashtra, India in 1989 (Bang *et al.*, 1989).

It should be noted that a prevalence calculation is subject of a correct diagnostic process and registration modalities, both of which are very seldom present in developing countries (Anand Kumar, 2002, 2007).

Aetiological factors of infertility in developing countries

A study by the WHO indicates that most cases of infertility in Africa are caused by tubal occlusion secondary to infections, most frequently caused by *Chlamydia*, gonorrhoea and/or tuberculosis (Serour and Hefnawi, 1982; Serour *et al.*, 1982; WHO, 1987). Laparoscopy revealed a prevalence of bilateral tubal occlusion in 35–65% of infertility cases in Nigeria (Otolorin *et al.*, 1987; Okonofua *et al.*, 1989; Otubu *et al.*, 1990). In Durban, South Africa, a tubal factor was identifiable in 77% of the infertile population (Chigumadzi *et al.*, 1998).

Sexually transmitted diseases, unsafe abortion and post-partum pelvic infections are the main causes of (tubal) infertility in developing countries. Other confounding factors are urbanization, polygamy and resistant micro-organisms due to a delayed or lack of diagnosis, incomplete or no treatment at all (Giwa-Osagie, 2002).

Not only female infertility, but also the majority of male factor infertility in developing countries is caused by previous infections of the male genitourinary tract (Kuku and Osegbe, 1989).

Strategies for infertility treatment in developing countries

It is time to consider the possibility of implementing 'new reproductive technologies' in developing countries. The implementation of such a project is only possible if costs can be minimized to an acceptable level. Simplifying the diagnostic procedures in the infertility work-up, simplifying assisted reproduction technologies, minimizing the complication rate of assisted reproduction, organizing training-courses for medical and paramedical personnel and incorporating the infertility treatment programme into the existing family planning and perinatal care programmes will be the keystones for its success.

Simplifying diagnostic procedures

Tubal obstruction due to a previous pelvic infection is the most important reason for infertility in developing countries. Hysterosalpingography, hystero-salpingo-contrast-sonography and vaginal ultrasound are simple and accessible techniques to detect this problem without major costs (De Muylder, 1995; Hauge *et al.*, 2000, de Jonge *et al.*, 2001). Combining these techniques with an accurate anamnesis and a simple semen analysis will identify the majority of infertility causes such as ovulatory disorders, male subfertility and tubal infertility (Figure 1). Male factor infertility can be evaluated by a simple semen analysis, eventually in combination with rectal or scrotal ultrasound if male subfertility is suspected (Ombelet *et al.*, 1997; Gunalp *et al.*, 2001; Menkveld *et al.*, 2001). Light microscopy semen analysis is still the most powerful indicator for male infertility, with a much better predictive value in comparison with biochemical semen parameters (Ombelet *et al.*, 1998).

Endoscopic-based evaluation of the female reproductive tract has also been simplified in its instrumentation and technique, so

that it can be offered in a one-stop ambulatory approach, even in developing countries (Brosens, 2002; Campo *et al.*, 2002; Gordts, 2002). Office mini-hysteroscopy has become a non-expensive diagnostic technique accessible for every gynaecologist when using a small diameter optic, saline as distention medium and an atraumatic insertion technique (Campo *et al.*, 1999, 2005) (Figure 2). The value of an endoscopy based one-stop clinic for the diagnosis and treatment of infertility has to be assessed in well-organized studies performed in different developing countries.

Successful training programmes in diagnostic laparoscopy in developing countries have been described before (Serour and Hefnawi, 1982; Serour *et al.*, 1982).

Simplified assisted reproduction

One of the most challenging tasks will be to simplify assisted reproduction in such a way that it becomes affordable in developing countries. Simplifying should reduce the cost but not the quality, and special attention should be given to eliminate complications such as OHSS and multiple pregnancy. Both complications are unacceptable, certainly in developing countries.

Simplified inexpensive assisted conception techniques are needed that can be adapted for conditions in the developing world, so that infertile patients all over the world can benefit from them.

Ovarian stimulation protocols

Concerning the preparation of the oocytes for IVF, gonadotrophins and/or FSH (urinary or recombinant), gonadotrophin-releasing hormone (GnRH) agonists and GnRH antagonists are too expensive to be routinely used in developing countries. These drugs also carry a high risk for OHSS, a life threatening disease. OHSS can cause severe pain and trigger the release of fluid into the abdomen and lungs. If left untreated, OHSS can result in serious health complications. Severe cases of OHSS are rare, but they need intensive care treatment and have been known to lead to permanent injury and even death. There are enough reasons for being sceptical about the use of these drugs in developing countries, at least if the doses which are going to be used are comparable with the doses reported in the Western World, this means a median value of more than 2000 IU gonadotrophin or FSH per IVF cycle.

Natural cycle IVF could be an option, but the results have been disappointing until now. In a review of 20 selected studies reporting on a total of 1800 cycles of natural cycle IVF, embryo transfers were performed in only 45.5% of cycles with an ongoing pregnancy rate of only 7.2% per started cycle and 15.8% per embryo transfer (Pelinck *et al.*, 2002). High cancellation rates because of premature LH rise and premature ovulations must surely hamper the efficacy of natural cycle IVF.

Another low-risk and patient-friendly strategy is minimal stimulation IVF aimed at using the single oocyte that spontaneously develops to dominance. A GnRH antagonist to prevent untimely ovulation can be administered in the late follicular phase of the natural cycle together with recombinant

One-day clinic (diagnosis)

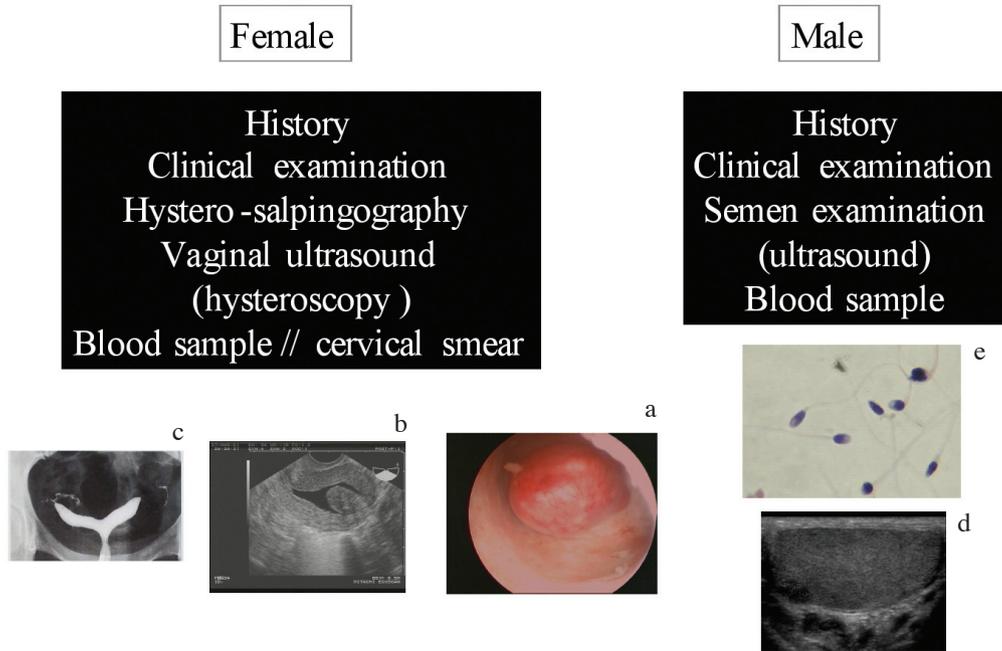


Figure 1. A non-expensive diagnostic work-up, affordable for health-care centres in most developing countries. Panels a–e show representative results from the techniques used during diagnostic work-up.

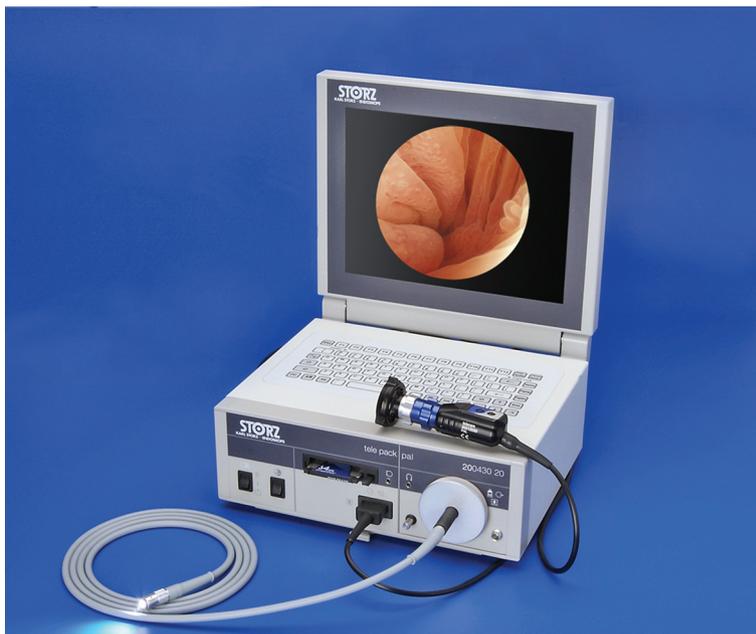


Figure 2. TELE PACK system: a comprehensive, multifunctional and compact documentation terminal with a camera control unit, illumination and an image display.

FSH for substitution (Pelinck *et al.*, 2006). The reported overall ongoing pregnancy rate per started cycle with this stimulation protocol was also low (8.3%), and the cumulative ongoing pregnancy rate after up to three cycles was only 20.8%.

Most interesting for developing countries is probably the use of low-dose clomiphene citrate regimen, which can be used with acceptable results and minimal complication rates (almost no OHSS) (Steinkampf *et al.*, 1992; Massey *et al.*, 1994; Ingerslev *et al.*, 2001). The use of clomiphene citrate stimulation seems to be superior to natural (unstimulated) or minimal stimulation IVF (Daya *et al.*, 1995; Ingerslev *et al.*, 2001; Nargund *et al.*, 2001).

It is well known that clomiphene citrate resistance is found in 20–30% of patients. For these patients, the best alternative ovarian stimulation protocol is the use of a low dose stimulation regimen with gonadotrophins or recombinant FSH. Identical results were reported when this protocol was compared with the commonly used more aggressive and hardly affordable high-dose stimulation protocols (Hohmann *et al.*, 2003).

Monitoring of the IVF cycle

Monitoring of the follicular development in an IVF cycle, as well as the timing of the human chorionic gonadotrophin administration can easily be done solely on sonographic criteria with basic inexpensive ultrasound equipment (Steinkampf *et al.*, 1992; Rojanasakul *et al.*, 1994). Training courses for fertility specialists and midwives can be organized in order to teach them how to perform accurate ultrasound monitoring of IVF cycles.

Simplified laboratory procedures and equipment

An interesting question arises as to whether it is possible to simplify the laboratory environment and procedures without compromising substantially the results?

The costs associated with fertilization and nurture of eggs in an IVF laboratory according to the new European regulations are far too high for developing countries. Instead of using an expensive laminar flow hood, it might be possible to use a converted 'humidicrib', a plastic box which is nowadays commonly used for keeping newborns snug (Pilcher, 2006). This box can be modified to create a portable, near-sterile environment which is necessary to handle eggs and embryos, and this for a tenth of the price of a laminar flow hood.

According to Trounson, instead of using an expensive cylinder with carbon dioxide for the incubation of embryos, it might be possible to exhale across the culture media before sealing it in a plastic bag (Pilcher, 2006). This bag, containing the Petri dish with the embryos, can be dropped into a warm bath, removing the need for an expensive incubator. This technique has been successfully used for more than 10 years for cow embryos in veterinary IVF (Pilcher, 2006).

Prevention of multiple pregnancies

Multiple pregnancy has to be considered as the most important adverse outcome following assisted reproductive technologies, and the reason is simple: perinatal mortality and morbidity in multiple pregnancies rises dramatically compared with singletons (Ombelet *et al.*, 2005). These are important considerations to keep in mind when organizing an infertility programme in a developing country, as facilities for perinatal care are often limited.

Prematurity is the most important problem concerning multiple pregnancies: half of all twin pregnancies cope with preterm labour and/or preterm prelabour rupture of membranes leading to premature delivery (<37weeks) and its related morbidity and mortality. The average gestational age for twins in Western Countries is 37 weeks, weighing 2.5 kg and for triplets it is 33.5 weeks weighing 1.8 kg (ESHRE, 2000). Two out of three twins will be small for gestational age or even growth retarded, which will obviously compound the problem of prematurity. Compared with singletons, there is an increased incidence of developmental problems and cerebral palsy (3- to 7-fold increase in twins, 10-fold increase in triplets) (Tanbo and Abyholm, 1996). Even when the babies are healthy, sensory deficits, speech, learning, attention and/or behavioural deficits are more commonly seen in cases of multiple pregnancy (Elster, 2000).

Among maternal complications associated with multiple pregnancies, gestational discomfort is often observed and there is a significant increase in early, severe pre-eclampsia. Bleeding problems are common due to an increased incidence of placenta praevia and post-partum haemorrhage following uterine atony.

Looking at these figures, keeping in mind that facilities are suboptimal in developing countries, it is necessary to stress the importance of avoiding multiple pregnancies as much as possible.

For IVF, transferring multiple embryos into the uterus maximizes pregnancy rates, at the expense however of an unacceptably high multiple pregnancy rate. The most important causal factor is the number of embryos transferred. After the transfer of three, four and five embryos the incidence of triplet pregnancies is respectively 8, 11 and 15% (Cohen, 2003). Nowadays, a policy of elective single embryo transfer in stimulated cycles becomes more popular and is the most efficacious measure to reduce the incidence of twin pregnancies (Wolner-Hanssen and Rydhstroem, 1998; Gerris *et al.*, 1999; Van Royen *et al.*, 1999; Tiitinen *et al.*, 2001; De Sutter *et al.*, 2003; Gerris 2005). In a large retrospective study, it was shown that with the implementation of elective single embryo transfer, multiple pregnancy delivery rates could drop from 25 to 5% (Tiitinen *et al.*, 2003).

The message is clear; the aim of assisted reproductive treatment in developing countries is not to achieve a successful conception, but to offer the parents a healthy and normal singleton child and to prevent multiple pregnancies by transferring only one embryo per trial.

Economical aspects of affordable IVF: will it be cost-effective?

Presently, the question of a real cost-benefit analysis of simplified assisted reproduction in developing countries is extremely difficult. Considering diagnostic techniques, little is known about the minimal costs needed in different countries of different continents. It is also hoped and expected that some companies of the pharmaceutical and medical industry are willing to provide cheap medication and low-cost equipment (e.g. ultrasound, endoscopy) to developing countries. It is not yet known what the exact reduction in cost and success rate will be when laboratory procedures and environment are available at minimal cost. The effect of the implementation of infertility clinics in existing reproductive health care centres on costs is also uncertain. Pilot studies to examine the real cost of a simplified diagnostic work-up are lacking and have to be organized and evaluated. Well organized studies on the real value of minimal stimulation IVF from an economical point of view are also urgently needed. One must be aware of the different population characteristics prevailing in developing countries when compared with developed countries. Whether to treat HIV-positive women with IVF will be the topic of further discussions. Whether ICSI and cryopreservation of embryos should be performed in developing countries is also very unlikely. Only the future can show the real benefit of simplified assisted reproduction in developing countries, but this may not be a reason for neglecting the problem without doing anything immediately.

Conclusion

Prevention and education remain the most important objectives considering the issue of infertility in developing countries. The public should be aware of the risk factors such as abortions and deliveries in unsafe circumstances and the immense problem of sexually transmitted diseases, including human immunodeficiency virus (HIV).

For those couples in whom prevention has failed, a specially designed infertility care programme should be provided for developing countries. The implementation of a cost-effective simplified assisted reproduction programme as a valid treatment protocol in developing countries is certainly the major challenge.

The introduction of simplified, cheap and effective methods might convince local politicians and insurance companies to formulate a policy concerning infertility treatment in their country. Tackling the issue of infertility in low-resource countries using simplified methods might improve the quality of life for numerous childless couples. To be successful family planning, prevention of infertility as well as diagnosis and treatment of infertility should be incorporated in existing health care centres.

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