

The Arusha project: Accessible infertility care in developing countries – a reasonable option?

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Abstract

Infertility is a central issue in the lives of many couples who suffer from it. In developing countries the problem of childlessness is even more pronounced compared with Western societies due to different socio-cultural circumstances. It mostly causes severe psychological, social and economic suffering and access to infertility treatment is often limited to certain procedures and certain costumers.

The issue of infertility in developing countries is underestimated and neglected not only by the local governments but also by the international non-profit organizations.

Simplification of the diagnostic and therapeutic procedures, minimising the complication rate and incorporating fertility centres into existing reproductive health care programmes are essential measures to take in resource-poor countries if we want to make infertility treatment accessible to a larger part of the population.

The debate about assisted reproduction in developing countries has entered a new constructive phase. The common picture of ART (assisted reproductive technologies) as a *luxury item* not suitable for impoverished people in the developing world is not accepted anymore as such. Initiatives to make infertility care accessible and technically appropriate for poor resource settings are gaining momentum. To achieve this goal it remains important to acknowledge the socio-cultural differences of developing countries as well as their different phases in development.

Because a lot of people still throw doubt upon the value of affordable ART in developing countries, time has come *to start a debate* on this controversial subject.

Key words: accessible, assisted reproduction, developing countries, fertility care, intrauterine insemination, IVF.

Introduction

Infertility should be recognized as a public health issue worldwide, including developing countries and research is needed on innovative, low-cost ART procedures that provide safe, effective, acceptable and

affordable treatment for infertility: These were two of the 13 recommendations on infertility and ART in the developing world formulated on the occasion of the WHO-meeting on “Medical, Ethical and Social Aspects of Assisted Reproduction” which was held in Geneva in 2001 (Vayena *et al.*, 2002a).

Reproductive Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity in all matters relating to the reproductive system and to its functions and processes (WHO, 2004). Reproductive health therefore implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so (Fathalla, 2007).

It should be realised that in developing countries, despite overpopulation and resource-poor health care systems, unwanted childlessness is an important psychological, social and economical burden that needs attention (Dyer *et al.*, 2004, 2005; Ombelet *et al.*, 2008, Van Balen and Bos, 2009). The magnitude of the problem differs between different geographic areas and is highly influenced by religious, ethical and socio-cultural influences (Leke *et al.*, 1993; Serour, 2002; 2006; Van Balen and Bos, 2009).

Nevertheless, until very recently the problem of infertility in developing countries has been ignored at all levels of health care management. This attitude is not only the result of a serious underestimation of the problem of childlessness but also due to a lack of facilities and affordable treatment options in most resource-poor countries.

The most common underlying cause for infertility in developing countries, especially in the sub-Saharan region, is severe male infertility and bilateral tubal occlusion caused by sexually transmitted infections (STDs), unsafe abortions and postpartum infections (WHO, 1987; Nachtigall, 2006). This means that the majority of infertile couples in developing countries can only be treated by assisted reproductive technologies (ART). On the other hand, new reproductive technologies are either unavailable or very costly in so far that the large majority of the population cannot afford it (Malpani and Malpani, 1992; van Balen and Gerrits, 2001; Nachtigall, 2006).

The most important question to answer is whether expensive techniques with a low success rate can be justified in countries where poverty is still an important issue, taking into account that in most developing countries the problems of infectious diseases such as malaria, tuberculosis, gonorrhoea and HIV are still very prevalent. During the past decades, the majority of health strategies in Western Countries focussed on reducing total fertility rates while infertility care received little or no attention (Hamberger and Janson, 1997). The biggest obstacle in implementing health policies which consider infertility as a problem is the (1) widespread belief that infertility is not a pressing problem in poor developing countries where fatal and contagious diseases remain uncontrolled and (2) because infertility as such is

not directly life-threatening (Vayena *et al.*, 2002b; Anonymous, 2006), neglecting totally the devastating social, psychological, economical and personal burden of being childless in most poor societies. Another frequently used argument holds that supporting infertility treatment is unacceptable in countries struggling to decrease their fertility rate and failing to support their fast-growing populations. This argument is no longer valid in most developing countries. It was reported by the United Nations that in the great majority of developing countries the mean fertility rate nowadays already dropped as low as 2.58 per woman and is expected to decline to 1.92 by mid-century (<http://esa.un.org/unpp/>). Unfortunately, in the least developed countries such as Mali, Angola, Afghanistan, Republic of Congo, Uganda and Burundi, the fertility rate is still more than 6 but is also expected to drop to 2.57 by 2045-2050.

It is easy to understand that if infertility diagnosis and treatment, including assisted reproduction, has to be accessible for many couples in developing countries, procedures need to be simplified as much as possible without decreasing the safety and quality of care. On the other hand, it should be stressed that the plea for infertility care in developing countries is not limited to affordable IVF, on the contrary. The most important goal, apart from prevention of infertility, should be to make infertility discussable and accepted as a disease, taking into account the social and psychological suffering which is observed nowadays in many poor countries. On the other hand, affordable and easy diagnostic procedures have to be introduced to select patients for different treatment strategies such as endoscopic surgery, non-IVF assisted reproduction and IVF/ICSI. Education on reproductive health should be promoted by the government and implemented at schools and at primary health care facilities.

The stigma and social taboos of infertility in developing countries

The severity and impact of infertility differ significantly between developing and developed countries. Although considerable variation is found among different regions, in many developing countries the social stigma of childlessness still leads to isolation and abandonment (Ebomoyi and Adetoro, 1990; Leke *et al.*, 1993; van Balen and Gerrits, 2001; Giwa-Osagie, 2002; Zaar and Merali, 2002; Ombelet *et al.*, 2008). In South Africa it was shown that infertility has a very strong effect on the psychological well-being of both men and women (Dyer *et al.*, 2002a, 2002b, 2004, 2005). In the Western World, the problem of infertility is frequently associated with guilt, self-blame, helplessness and even depres-

sion. Furthermore, childlessness may lead to social alienation, marital or social violence and abuse, loss of social status, divorce and severe economic deprivation, violence-induced suicide and even a loss of dignities in death (Daar and Merali, 2002). The burden of infertility mainly falls on women and they are mostly blamed for it. In certain ethnic communities, the diminished status of women compared to men is associated with a strong negative attitude towards infertile women. Childless women can be ostracized and assaulted by their families and motherhood is often the only way to enhance their status within the family and community.

History of promises

“Men and woman of full age, without any limitation due to race, nationality or religion, have the right to marry and to raise a family”. This statement was adopted 60 years ago at the 1948 UN Universal Declaration of Human Rights and can’t be misunderstood: it implies the right to access to fertility treatments when couples are unable to have children (Table I).

At the United Nations International Conference on Population and Development in Cairo in 1994 the following statement was made “Reproductive health therefore implies that people have the capability to reproduce and the freedom to decide if, when and how often to do so ... and to have the information and the means to do so ...” (Table I).

Political statements and commitments need to result in appropriate actions but progress towards the attainment of these goals on the subject of infertility in developing countries remains however slow. The reasons are multiple and include, among others, the problem of ‘brain drain’, lack of collaboration, budgetary constraints and lack of political commitment (Fathalla *et al.*, 2006). Another reason might be that the most important non-profit international organisations, including Family Health International, International Planned Parenthood Federation, WHO and The Population Council still focus on safe motherhood, the reduction of unsafe abortions and the prevention of STDs and HIV/AIDS (Ombelet *et al.*, 2008). The implementation of infertility treatment in developing countries is until today not a priority for these organizations.

The present situation

In many developing countries about 10 % of all visits to doctors are related to problems of childlessness (Bergstrom, 1992). The problem is mostly underestimated or neglected by health care providers, most of the time, because they do not know how to

Table I: International statements on the subject of universal access to fertility care

1. “Men and woman of full age, without any limitation due to race, nationality or religion, have the right to marry and to raise a family”. This statement was adopted 60 years ago at the 1948 UN Universal Declaration of Human Rights and can’t be misunderstood: it implies the right to access to fertility treatments when couples are unable to have children.
2. At the United Nations International Conference on Population and Development in Cairo in 1994 the following statement was made “Reproductive health therefore implies that people have the capability to reproduce and the freedom to decide if, when and how often to do so ... and to have the information and the means to do so ...”
3. United Nations Millennium Declaration, signed in September 2000: “Achieve, by 2015, universal access to reproductive health”.
4. In 2001, on the occasion of a WHO meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction" in Geneva, a call for the integration of infertility into existing sexual and reproductive health care programmes in developing countries was made.
5. In 2004 the World Health Assembly proposed five core statements, including “the provision of high-quality services for family-planning, including infertility services”.
6. At the World Summit in 2005, the largest-ever gathering of world leaders called for achieving these goals by the year 2015.
7. In 2006 the International Federation of Obstetricians and Gynaecologists (FIGO) stated that “women and men have the right to the highest available standard of health care for all aspects of their sexual and reproductive health”.
8. December 2006 the Executive Committee of the European Society of Human Reproduction and Embryology (ESHRE) established a new “Special Task Force” dedicated to infertility in developing countries.
9. At the Oslo Ministerial Declaration in 2007 health was recognised as one of the most important long-term foreign policy issues by the Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand. In a Ministerial declaration the following statement was made: “The well functioning health systems that are needed to reduce maternal newborn and child mortality and to combat HIV/AIDS, tuberculosis and malaria will also help countries to cope with other major health concerns such as sexual and reproductive health ...”

deal with it. Prevention and management of STDs and infections related to childbirth and abortion is frequently considered the only priority for service delivery, not only by the local governments but also by the international non-profit organizations. Treatment of infertility is not considered a priority and because of limited resources most governments

focus on primary reproductive health care with two main objectives, namely promoting family planning and reducing maternal mortality (Ombelet *et al.*, 2008). It is very striking that although most cultures value motherhood, infertility treatment comes low down on the agendas of health authorities. Most women consider infertility treatment of utmost importance, even more important than the treatment of morbidity generated by their own illnesses (Bergstrom, 1992). In most developing countries the public health service agenda is very distant from the people's agenda. Due to a lack of interest of health care providers, a lot of infertile patients are prone to exploitation and potentially damaging practices (van Zandvoort *et al.*, 2001; van Balen and Gerrits, 2001). The first priority is and should remain the prevention rather than cure of infertility. Education in sexuality and safe sex are the best measures to prepare the adolescent and to prevent infertility. However, many developing countries struggle with the ignorance of teachers in matters related with sexuality. Because of this, many governments are unable to implement simple education programs such as the use of condoms for the prevention of STDs and infertility.

Although the United Nations International Conference on Population and Development in 1994 (Cairo) clearly highlighted "prevention and appropriate treatment of infertility where feasible" and despite the recommendations of the WHO-meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction", Geneva, 2001 (Table 1, Vayena *et al.*, 2002a) almost no progress is made in education and service in South Asia and sub-Saharan Africa due to a lack of guidelines or concrete actions and programmes (Fathalla *et al.*, 2006).

Affordable infertility diagnosis

Standardized investigation of the couple at minimal costs will enhance the likelihood that infertile couples, both men and woman, will come to the centre. Which centres and how they have to reach their goal has to be seen in the context of the heterogeneity of developing countries (Vayena *et al.*, 2002b). The best option would be to develop specific primary health care facilities located near tertiary health care hospitals, where women can obtain sexual and reproductive health care (prevention of cancer, STDs, diagnostic procedures for infertility, etc.). Concerning infertility diagnosis, the concept of primary health care should include trained personnel capable of using a microscope and ultrasound equipment (incorporated in existing reproductive health care centres, if they exist at all). Reproductive Health Care Centres are mostly located in big hospitals with long waiting lists and far away from villages. The advantage of a "specialized primary health care facility" is that it can become a place for both medical activities, educational activities and a place where women can discuss their problems. Since tubal obstruction associated with previous pelvic infections is the most important reason for infertility in some developing regions, hysterosalpingography, and hystero-salpingo-contrast-sonography are simple and accessible techniques to detect this problem without major costs (Hauge *et al.*, 2000, de Jonge *et al.*, 2001). Combining these techniques with an accurate anamnesis will identify the majority of women's infertility causes such as ovulatory disorders and tubal infertility. Male factor infertility can easily be evaluated by a simple semen analysis. Training courses on how

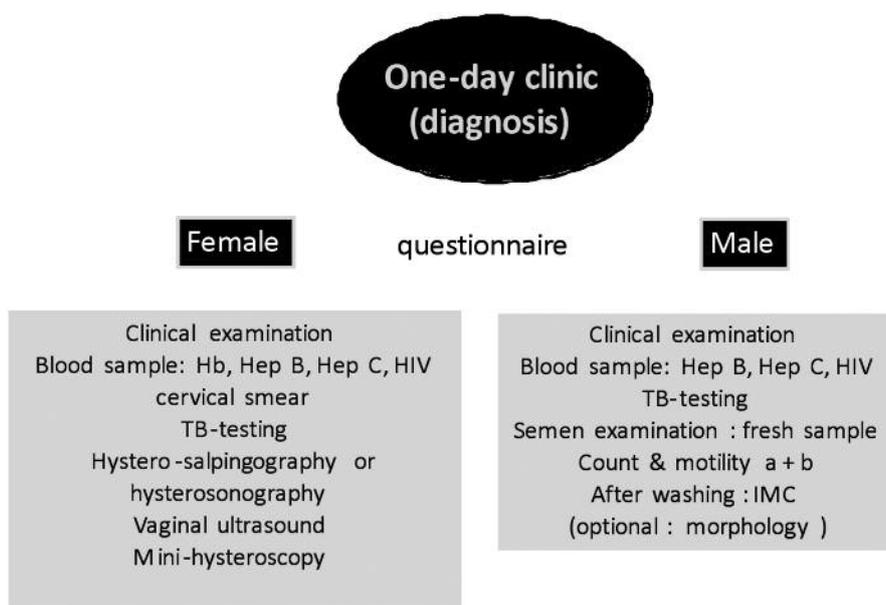


Fig. 1. — One-day diagnostic phase for infertility work-up in a resource-poor setting

to interpret semen analyses were already successfully organised in sub-Saharan Africa (Franken *et al.*, 2000). Semen analyses can be also performed by well-trained paramedicals, another very important advantage for developing countries.

Office mini-hysteroscopy to investigate intrauterine abnormalities has been simplified in its instrumentation and technique so that it 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.*, 2005; Ombelet and Campo, 2007).

The value of a “specialized primary health care facility” for the diagnosis of infertility at minimal cost has to be assessed in well-organised studies performed in different developing countries. Whether or not HIV-testing should be included in the routine procedure of the investigation of an infertile couple remains a debatable subject. If HIV-testing is a requisite, we have to face the risk that many couples will not come to the centre because the stigma of infertility might be replaced by the stigma of HIV. On the other hand, laboratory people claim that it is necessary for them to be informed about the infectious profile of their patients and it was argued before that in the presence of chronic viral diseases (HIV, Hepatitis C) a separate high security laboratory should be available to ensure minimal cross-contamination risk to unaffected gametes and embryos (Englert *et al.*, 2004; Gilling-Smith *et al.*, 2005). It's obvious that this strategy is almost impossible in a low-cost laboratory setting. It also seems logical that HIV positive women can only be treated in those countries where antiretroviral therapy is provided, whether by the government or by non-profit organizations.

Accessible infertility care

IUI as a first line treatment

Provided tubal patency has been proven, intrauterine insemination (IUI) with husband's semen can be promoted as a first-line treatment in most cases of unexplained and moderate male infertility, without major costs and without very expensive infrastructure (Ombelet *et al.*, 2003; Verhulst *et al.*, 2006). A threshold level of inseminating motile count (IMC) after washing procedure below which IUI is not successful enough to be used as a first line treatment is not known but most studies indicate that a threshold IMC of 0.8 - 1 million should be recommended (Ombelet *et al.*, 2003; Verhulst *et al.*, 2006).

Satisfying results are obtained when clomiphene citrate (CC) - stimulation is used and cost-effectiveness studies have shown that three IUI's using CC

are as successful, but much cheaper compared to one IVF/ICSI cycle (Peterson *et al.*, 1994; Goverde *et al.*, 2000; Philips *et al.*, 2000; Van Voorhis *et al.*, 1997, 2000).

IUI programs can easily be run by well-trained paramedicals, another advantage for resource-poor countries. In case of CC-resistancy a minimal stimulation protocol using urinary gonadotrophins or recombinant FSH aiming at monofollicular growth should be recommended. One should be aware of the fact that in controlled ovarian hyperstimulation (COH), with or without IUI, the prediction of multiple gestation is highly uncertain especially when gonadotrophins or rec-FSH are used (Gleicher *et al.*, 2000). This is a very important issue since multiple pregnancies have to be avoided, especially in developing countries, for obvious reasons.

The chances of performing a thorough examination of the pelvis and uterine cavity (laparoscopy and hysteroscopy) is remote or will be available to very few. If couples fail to get pregnant after three – four trials of IUI they may be referred to IVF/ICSI.

Simplified IVF

It is important to realize that simplifying the procedures has to reduce cost but not quality. We also have to avoid complications such as ovarian hyperstimulation (OHSS) and multiple pregnancy as much as possible. Concerning the recruitment of oocytes for IVF, gonadotrophins and/or follicle stimulating hormones (urinary or recombinant), GnRH agonists and GnRH antagonists are presently too expensive to be routinely used in developing countries.

Natural cycle IVF could be an option, but the results are disappointing until now due to high cancellation rates because of premature LH rise and premature ovulations. A review of 20 selected studies showed an ongoing pregnancy rate of only 7.2% per started cycle and 15.8% per embryo transfer (Pelinck *et al.*, 2002).

Probably more promising is the use of clomiphene citrate regimen (Figure 2). More acceptable results when compared to natural cycle and minimal stimulation IVF are described for CC-IVF, also with minimal complication rates (Steinkampf *et al.*, 1992; Massey *et al.*, 1994; Daya *et al.*, 1995; Ingerslev *et al.*, 2001; Nargund *et al.*, 2001). In case of clomiphene citrate resistance the use of low dose stimulation regimen with gonadotrophins or recombinant FSH could be recommended.

Monitoring of the follicular development as well as the timing of hCG administration can easily be done solely on sonographic criteria with basic inexpensive ultrasound equipment (Steinkampf *et al.*, 1992; Rojanasakul *et al.*, 1994).

Low-cost IVF stimulation

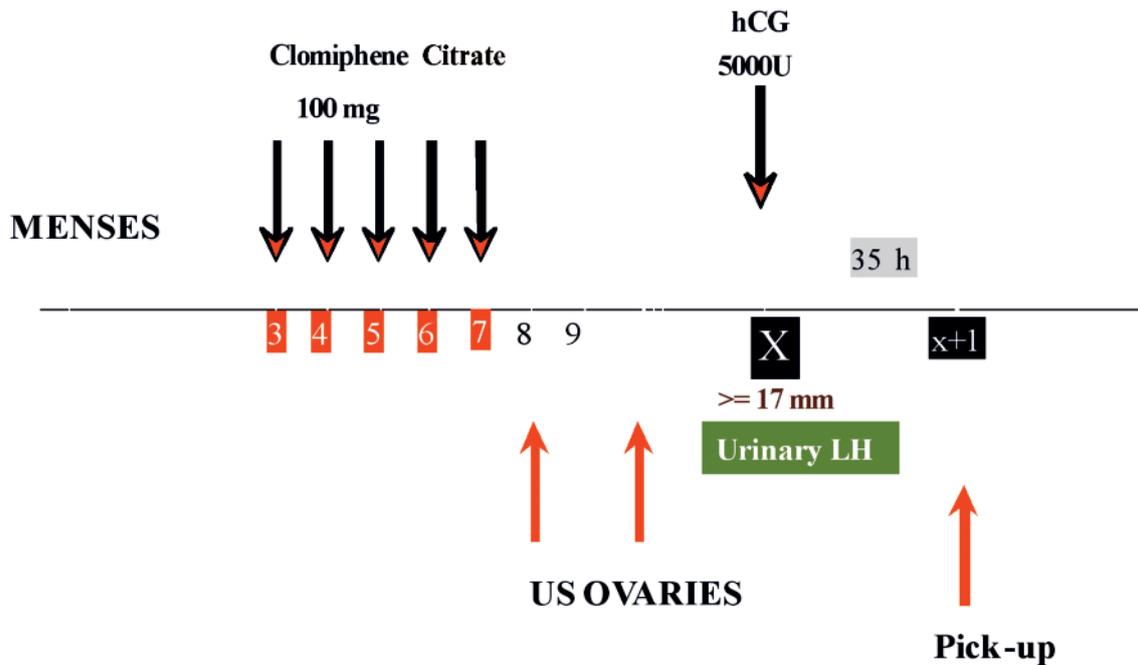


Fig. 2. — Suggested ovarian stimulation protocol for IVF (suggested by Working Group 2, coordinator AN Andersen)

Considering laboratory procedures different options have to be examined:

It is possible to use a converted 'humidicrib', a plastic box which is nowadays commonly used for keeping newborns snug instead of using an expensive laminar flow hood (Hovatta and Cooke, 2006; Pilcher, 2006). With this method the handling of eggs and embryos can be done for a tenth of the price. Instead of using an expensive cylinder with carbon dioxide to incubate the embryos, a plastic bag, containing the Petri dish with the embryos can be used. By dropping this bag into a warm bath culturing can effectively be done without the need for an expensive incubator. This technique has been successfully used for more than ten years for cow embryos in veterinary IVF (Vajta *et al.*, 1997; Pilcher, 2006).

More research is urgently needed on the value of intravaginal or intrauterine fertilization and culture. Intravaginal culture was described about 20 years ago (Ranoux *et al.*, 1988, 1990; Taymor *et al.*, 1992). A tube completely filled with 3 ml of culture medium containing 1 to 5 oocytes with 10,000 to 20,000 washed spermatozoa per ml is hermetically closed and is placed in the vagina and held by a diaphragm for incubation for 44 to 50 hours. Comparable success rates with conventional IVF were reported (Ranoux *et al.*, 1988).

Another interesting *in vivo* culture system using an encapsulation technology was recently described by Blockeel *et al.* (2009). In their pilot study it was shown that this new system appears to be feasible and safe, supporting normal fertilization, embryo development and normal chromosomal segregation. It also showed that live births are possible after the transient presence of a silicone device in the uterus.

Culturing and fertilization of one or two oocytes in the tip of a transfer catheter, between two air bubbles, using a small number of sperm in a 100 μ L of HEPES buffered medium, incubated simply at 37°C, without CO₂. No special incubation is needed and the embryos are transferred in the uterus after 24 hours of insemination, with the same catheter.

Conclusion

Compared to Western societies the negative consequences of childlessness are more pronounced in developing countries. Infertility may lead to social isolation, stigmatization, economical deprivation, domestic violence and even suicide.

Bilateral tubal occlusion due to sexually transmitted diseases and pregnancy-related infections is the most common cause for infertility in developing countries, especially in sub-Saharan Africa. Male infertility is very common, also due to STDs. Both

Table II: Arusha Project: Working and Study Groups // ESHRE Special task Force on “Developing countries and infertility”

Coordinator: W Ombelet (Belgium)

Working Groups

1. The One Day Diagnostic Phase

Coordinator: R Campo (Belgium)

Aim: To examine the feasibility of a model of centralized expertise with a one stop diagnostic strategy in developing countries. The one stop approach implement the responsibility of diagnosis and immediate management policy providing in the one stop environment all expertise and facilities of reproductive health care. The consequences of the results for the management of the couple have to be discussed with them on that same day. To make a protocol for the anamnesis and examination of the infertile couple and to determine which simple diagnostic tests have to be performed when and where.

2. Ovarian stimulation for IUI and IVF/ICSI

Coordinator: AN Andersen (Denmark)

Aim: To determine which stimulation schemes are most appropriate for IUI and IVF/ICSI in developing countries. How to monitor the cycle? How to give simple and effective information to the couple about this phase?

3. Laboratory phase for IUI and IVF/ICSI

Coordinator: J Van Blerkom (USA)

Aim: To translate the often complex and expensive procedures and instruments used for IVF in Western countries into the circumstances of developing countries. To investigate the value of intrauterine and intravaginal culturing techniques as an alternative for conventional culturing in IVF.

4. Funding

Coordinator: H Sallam (Egypt)

Aim: To raise funds for the project of assisting developing countries in incorporating infertility services within their reproductive health programmes.

Study Groups

1. Reproductive health education, prevention and awareness

Coordinator: G Serour (Egypt)

Aim: Public education on prevention of infertility including life style, prevention of STDs and postpartum and past infection, iatrogenic infertility, environmental contamination and pollution, incorporation of reproductive health education in general health education, raising awareness of health care providers on importance of reproductive health education and prevention of infertility and raising awareness of politicians on importance of infertility- its prevention and treatment.

2. Burden-of-disease and Cost-Effectiveness

Coordinator: D Habbema (the Netherlands)

Aim: To study if it is possible to measure the reduction in the quality of life by infertility and compare this to the reduction caused by other common diseases in developing countries. How cost-effective is fertility treatment in comparison with other measures aimed to improve health.

3. Training courses

Coordinator: I Cooke (UK)

Aim: To establish integrated, simple and standardized training courses for personnel of fertility clinics on the anamnesis and examination of the infertile couple, semen analysis, embryology, traditional hysterosalpingography, modern imaging techniques, documentation and quality control.

4. Social sciences, ethics and law

Coordinator: F van Balen (the Netherlands)

Aim: (1) To collect studies and stimulate research on social, cultural, ethical, religious and juridical aspects of infertility in poor-resource countries, including pathways to healthcare and access to treatment. (2) To initiate and expand an international network of social science research (in broad sense) of researchers in this field, (3) To publish overviews of findings and communicate this to (a) the members of the task force and (b) a wider audience (including patients, medical professionals, press, NGO's and political and governmental institutions), (4) To monitor and assess the social, cultural, ethical and juridical aspects of the pilot-projects for low cost IVF and (5) To analyse ethical issues arising during the implementation of the project and discuss ethical objections against the project in general

conditions are preferably treated by assisted reproductive technologies but most infertile couples in developing countries can't afford ART because the techniques are too expensive and mostly limited to private centres or not available at all.

While recognising the important and crucial role of education and prevention, the issue of infertility in developing countries requires greater attention at national and international levels for reasons of social justice. For a successful implementation of fertility

centres in resource-poor settings, simplification of the diagnostic procedures, minimising the complication rate, organizing training-courses for health care workers and incorporating fertility centres into existing reproductive health care programmes is essential.

ART units in developing countries should be safe, effective and affordable. Identifying the right couples for treatment will be crucial and the support from the community will be very important. The equipment and the products used have to be robust, effective and affordable.

To conclude, even if we have the knowledge and aspiration to make infertility diagnosis and treatment affordable for a large part of the population, a lot of questions concerning this issue will remain the same and a lot of people still throw doubt upon the value of accessible infertility care in resource-poor countries. Therefore we believe that time has come to debate this controversial subject. *To initiate the debate, Table III summarizes a few of the most common asked questions concerning the issue of infertility treatment in developing countries.*

Table III — Infertility and developing countries (DC): frequently asked questions (ART = assisted reproductive technologies)

1. How can we reduce the stigma of infertility and childlessness in DC?
2. Does the value of children and the motive for parenthood differ between developed and developing countries, and if yes, what can we do about it?
3. Is it necessary and/or advisable to introduce accessible low-cost infertility services in DC?
4. Is it reasonable and feasible to incorporate infertility care in 'Reproductive Health Care Centres' and what will be the hurdles?
5. Which geographical areas should have priority in developing ART in resource-poor economies and what have to be the selection criteria for accessible IVF in DC?
6. Is access to acceptable perinatal care an unconditioned requirement for the delivery of infertility care in DC?
7. Is access to antiretroviral therapy an unconditioned requirement for the delivery of infertility care in HIV-infected couples?
8. Although the need for single embryo transfer (SET) is obvious, which may be the best algorithm to follow in developing countries. Who should have double embryo transfer (DET)?
9. Can endoscopic surgery (diagnostic and therapeutic) be implemented in a project of low cost infertility care in DC?
10. How can Public-Private partnership assist in the development of simplified ART to the advantage of developing countries? Private versus Public or Public-Private?

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