

Infertility and the provision of infertility medical services in developing countries

Willem Ombetel^{1,6}, Ian Cooke², Silke Dyer³, Gamal Serour⁴ and Paul Devroey⁵

¹Department of Obstetrics and Gynaecology, Genk Institute for Fertility Technology, Schiepse Bos 6, 3600 Genk, Belgium; ²Emeritus Professor of Obstetrics and Gynaecology, 80 Grove Road, Millhouses, Sheffield S7 2GZ, UK; ³Reproductive Medicine Unit, Department of Obstetrics and Gynaecology, Grootte Schuur Hospital and Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; ⁴Department of Obstetrics and Gynaecology, Al Azhar University, The Egyptian IVF-ET Center, 3 Street 161, Hadayek El-Maadi, Cairo 11431, Egypt; ⁵The Center for Reproductive Medicine of the Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Jette, Belgium

⁶Correspondence address. E-mail: willem.ombetel@telenet.be

BACKGROUND: Worldwide more than 70 million couples suffer from infertility, the majority being residents of developing countries. Negative consequences of childlessness are experienced to a greater degree in developing countries when compared with Western societies. Bilateral tubal occlusion due to sexually transmitted diseases and pregnancy-related infections is the most common cause of infertility in developing countries, a condition that is potentially treatable with assisted reproductive technologies (ART). New reproductive technologies are either unavailable or very costly in developing countries. This review provides a comprehensive survey of all important papers on the issue of infertility in developing countries. **METHODS:** Medline, PubMed, Excerpta Medica and EMBASE searches identified relevant papers published between 1978 and 2007 and the keywords used were the combinations of ‘affordable, assisted reproduction, ART, developing countries, health services, infertility, IVF, simplified methods, traditional health care’. **RESULTS:** The exact prevalence of infertility in developing countries is unknown due to a lack of registration and well-performed studies. On the other hand, the implementation of appropriate infertility treatment is currently not a main goal for most international non-profit organizations. Keystones in the successful implementation of infertility care in low-resource settings include simplification of diagnostic and ART procedures, minimizing the complication rate of interventions, providing training-courses for health-care workers and incorporating infertility treatment into sexual and reproductive health-care programmes. **CONCLUSIONS:** Although recognizing the importance of education and prevention, we believe that for the reasons of social justice, infertility treatment in developing countries requires greater attention at National and International levels.

Keywords: developing countries; infertility; low-cost ART; politics; simplified infertility treatment

Introduction

One of the most important and underappreciated reproductive health problems in developing countries is the high rate of infertility and childlessness (Bergstrom, 1992; Leke *et al.*, 1993). The inability to procreate is frequently considered a personal tragedy and a curse for the couple, impacting on the entire family and even the local community. Negative psychosocial consequences of childlessness are common and often severe (Daar and Merali, 2002; Dyer *et al.*, 2002a,b, 2004, 2005; Umezulike and Efetie,

2004; Dyer, 2007, Table I, Fig. 1). In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple’s inability to conceive. Moreover, in the absence of social security systems, older people are economically completely dependent on their children. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy (Gerrits, 1997; Sundby, 1997; Papreen *et al.*, 2000; van Balen and Gerrits, 2001; Richards, 2002; van Balen, 2002; Araoye, 2003; Hollos, 2003; Wiersema *et al.*, 2006).

© The Author 2008. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology. All rights reserved.

For Permissions, please email: journals.permissions@oxfordjournals.org

The online version of this article has been published under an open access model. Users are entitled to use, reproduce, disseminate, or display the open access version of this article for non-commercial purposes provided that: the original authorship is properly and fully attributed; the Journal and Oxford University Press are attributed as the original place of publication with the correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oxfordjournals.org 605

Table I. Psychological and social consequences of infertility in developing countries.

-
- (1) Loss of Social Status (Dyer *et al.*, 2002a,b, 2004)
- Fertility = blessing of God → Infertility = curse, punishment
 - Social status of woman = dependent of number of children (sons)
 - Burdened with additional social tasks by extended family
- (2) Social Isolation (Dyer *et al.*, 2004)
- Subject to ridicule, scorn and gossip
 - Marginalized in family/community
 - Excluded from community functions
 - Accusations of ‘witch craft’, ostracism
 - Excluded from contact with children
- (3) Marital Instability (Dyer *et al.*, 2002a,b, 2004; Orji *et al.*, 2002; Umezulike and Efetie 2004)
- Unhappiness, sexual dissatisfaction
 - Alcohol abuse
 - Migrant Labour
 - Psychological, emotional and physical abuse
 - Abandonment//divorce
 - Return of bride wealth
 - Poverty
 - Second wife
 - Strategy to overcome infertility
 - Increased risk of STDs including HIV
- (4) Loss of Social Security (Sundby *et al.*, 1998; Papreen *et al.*, 2000; Hollos, 2003)
- Marital instability ⇒ lack of assistance in domestic tasks
 - Land claims negotiated through number of children
 - Lack of old age security
 - Death of a spouse: -few rights to inherit from husband
 - right to live in deceased husband’s compound dependent on the presence of a son.
- (5) Gender Identity (Hollos, 2003; Dyer *et al.*, 2004)
- Infertility arrests transition from child to adult
- (6) Psychological consequences (Papreen *et al.*, 2000; Dyer *et al.*, 2004)
- Most common: guilt, depression, shame, grief, disbelief, sense of worthlessness
 - Greater width and depth of distress when compared with Western Societies
- (7) Continuity: Funeral Tradition (Leonard, 2002; Hollos, 2003)
- No child to conduct funeral/mourn for deceased
 - No burial//fear for diminished fertility of the soil
 - Infertile women excluded from reincarnation
-

Although good documentation of the prevalence of infertility is lacking, it is generally believed that more than 70 million couples suffer from infertility worldwide (Fathalla, 1992; Boivin *et al.*, 2007). Bilateral tubal occlusion is the most common underlying cause (World Health Organization, 1987; Nachtigall, 2006), a condition that is potentially treatable by assisted reproductive technologies (ART). Unfortunately, a large majority of the population cannot afford infertility treatment since new reproductive technologies are either unavailable or very costly (Malpani and Malpani, 1992; Van Balen and Gerrits, 2001; Nachtigall, 2006). When reflecting on the possible role of ART in developing countries, many concerns and barriers become apparent (Dyer *et al.*,

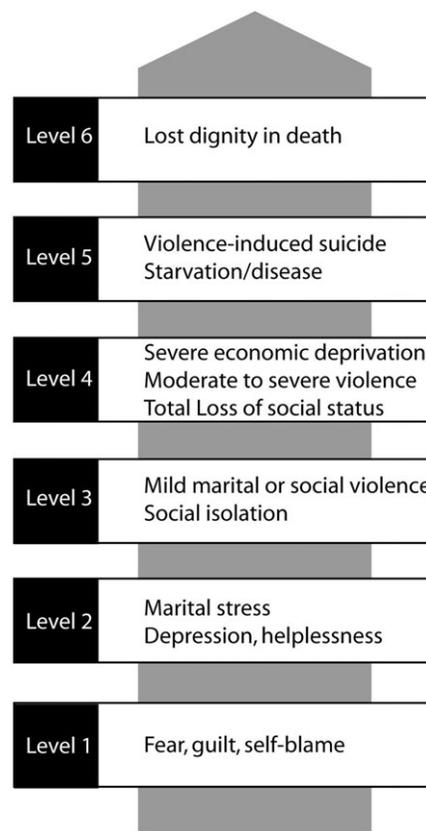


Figure 1: Consequences of infertility: in developed countries, the consequences of infertility rarely extend beyond level 2, in developing countries (especially Asia and Africa) the consequences are infrequently as mild as level 3.

The distinction between social alienation, social isolation, economic stress, severe economic deprivation and mild to very severe physical violence was clearly described before (Daar and Merali, 2002; Vayena *et al.*, 2002a, p. 18).

2002a,b; Fathalla, 2002; Vayena *et al.*, 2002b). Central to these is the question whether expensive techniques, which have a low success rate (live birth rate < 25% per cycle), can be justified in countries, where poverty is still an important issue. A related concern involves many shortcomings of health-care systems, which struggle with the immense problem of infectious diseases, such as malaria, tuberculosis, gonorrhoea and HIV. Further barriers include national and international health strategies, which during the past decades have focused on reducing total fertility rates (the so-called political ‘top-down’ perspective), while infertility care has received little or no attention (Hamberger and Janson, 1997).

In this paper, we will discuss controversies and common misconceptions surrounding this subject, outline the magnitude of the problem, evaluate infertility-related health policies of international organizations tasked with promoting global reproductive health care, and present strategies for infertility prevention and treatment in resource-poor settings.

Methodology—search strategy

This search aimed to identify all valuable and relevant information considering the problem of infertility in developing countries published between January 1978 and May 2008. We referred the information databases of Medline, PubMed, Excerpta Medica and

EMBASE, and the keywords used were the combinations of 'affordable, assisted reproduction, ART, developing countries, health services, infertility, IVF, simplified methods, traditional health care'. In our view, ART include any form of assisted reproduction, including IVF/ICSI and ovarian stimulation with or without artificial insemination.

Abstracts had to be written in English and if the abstract was pertinent and relevant to the topic, the full article whether in English, German or French was sought and critically studied in detail.

Other sources include Google using the same keywords and the websites of different organizations, such as ESHRE, IFFS, FIGO, WHO, Population Council, Family Planning International, Joyce Fertility etc. We also referred books and monographs on the issue of childlessness in developing countries. In addition, the reference lists and bibliography of all relevant studies and papers were reviewed and manually searched for additional papers.

We excluded studies and reports with minimal importance on the topics, and we wanted to study prevalence of infertility, aetiological factors, ethical and sociocultural influences, diagnostic and therapeutic procedures and governmental and non-governmental initiatives. We also excluded studies with a small group size since these reports are frequently associated with a poor methodological quality. Some opinions in the paper are influenced by several personal contacts with experts in the field. Since no randomized trial could be found on our subject, only observational and descriptive studies are discussed in this review.

For the classification of developing countries, different measures have been described by the World Bank and the United Nations Development Programme (UNDP). The World Bank classifies countries according to their gross national income whereas the UNDP takes into consideration three criteria for the evaluation of countries' development: the low-income criterion, the economic vulnerability criterion and the human resources weakness criterion (Sallam, 2008). In our review, we included studies and reports from all countries outside Europe, North America, Japan and Australia/New Zealand because most of these countries are known to need assistance for reproductive health care regardless of their exact classification.

Prevalence of infertility in developing countries

Only a limited number of papers report on the prevalence of infertility in developing countries. According to Boivin *et al.* (2007), the 12-month prevalence rate ranges from 6.9 to 9.3% in less-developed countries. Substantial geographical differences in the prevalence are noted, and these differences are largely explained by different environmental, cultural and socioeconomic influences.

In sub-Saharan Africa, the prevalence differs widely from 9% in the Gambia (Sundby *et al.*, 1998) and 11.8% in Ghana (Geelhoed *et al.*, 2002) compared with 21.2% in northwestern Ethiopia (Haile, 1990) and between 20 and 30% in Nigeria (Ebomoyi and Adetoro, 1990; Adetoro and Ebomyi, 1991; Okonofua, 1996; Larsen, 2000). Even less data are available from Asia and Latin-America, but a report compiled by the World Health Organization (WHO) indicated that the prevalence of infertility in these regions fell within the globally expected range 8–12% of couples of reproductive age and was thus lower when compared with African countries (World Health Organization, 1991).

Aetiology and risk factors for infertility in developing countries

In a large study performed by the WHO Task Force on the Diagnosis and Treatment of Infertility, 8504 infertile couples in 33 different countries were examined through a standard approach in all participating centres (Cates *et al.*, 1985; World Health Organization, 1987). In Africa, over 85% of women had an infertility diagnosis attributable to an infection compared with 33% of women worldwide. In another study from sub-Saharan Africa, a history of sexually transmitted diseases (STDs) was reported by 46% of participating men (Gerais and Rushwan, 1992). A study of 5800 couples in 33 World Health Organization centres in 25 countries showed that almost 50% of the African couples and 11–15% of other patients in other parts of the world had infectious tubal disease (Sciarra, 1994). Individual studies from Nigeria, South Africa and Egypt have reported a prevalence rates of tubal factor infertility ranging from 42 to 77% (Otolorin *et al.*, 1987; Okonofua *et al.*, 1989; Otubu *et al.*, 1990; Serour *et al.*, 1991; Chigumadzi *et al.*, 1998; Ikechebelu *et al.*, 2003). It has been estimated that ~70% of pelvic infections are caused by STDs while the other 30% are attributable to pregnancy-related sepsis (Ericksen and Brunette, 1996). Similarly, most cases of male factor infertility are caused by previous infections of the male genitourinary tract (Kuku and Osegbe, 1989; Meheus *et al.*, 1986). Nigerian studies have shown a prevalence of male infertility in 26–43% of cases (Adeniji *et al.*, 2003; Ikechebelu *et al.*, 2003; Olanunji and Sule-Odu, 2003). Studies from non-African developing countries on the causes of infertility are lacking but available data would indicate that infection-related causes also play a prominent role (Barten, 1978; Makush *et al.*, 2000).

Moreover, infectious diseases other than STDs may also cause infertility. Lepromatous leprosy is associated with an increased risk of semen abnormalities and azoospermia with testicular biopsies showing features of spermatogenic arrest as well as complete hyalinization of both seminiferous tubules and interstitial tissue (El-Beheiry *et al.*, 1979; Saporta and Yuksel, 1994). Data from Tanzania have suggested lower fertility in men and women suffering from malaria although the pathogenesis remains to be explained (Larsen, 1996).

Sexually transmitted diseases

STDs are, as outlined above, prominent risk factors for infertility in developing countries. The organisms most commonly involved are *Chlamydia trachomatis* and *Neisseria gonorrhoea* (Walker and Hoffer, 1989; Mascie-Taylor, 1992; Mayaud *et al.*, 1995; Sciarra, 1997). Pelvic tuberculosis can also result in tubal infertility, and high incidences have been reported in studies from the Indian subcontinent as well as from Ethiopia (Mascie-Taylor, 1992; Parikh *et al.*, 1997; Sekadde-Kigundu and Machoki, 2002; Shaheen *et al.*, 2006).

Another sexually transmitted organism associated with infertility is HIV-1. Several studies have documented reduced fecundity in HIV-infected individuals (Brocklehurst and French, 1998; Glynn *et al.*, 2000; Sekadde-Kigundu and Machoki, 2002). Mechanisms involved include tubal factor infertility through the greater susceptibility to other STDs, male hypogonadism, altered spermatogenesis, increased risk of miscarriages as well as behavioural

factors (Lyerly and Anderson 2001; Gilling-Smith *et al.*, 2006). On the other hand, marital instability and polygamy secondary to infertility may in turn increase the spread of HIV-1 infection (Nabaitu *et al.*, 1994).

The high prevalence of infections is commonly compounded by a delayed or a complete lack of diagnosis together with incomplete, inappropriate or no intervention at all (Adler, 1996; Giwa-Osagie, 2002a,b). Related risk factors include, among others, poor education, poverty, negative cultural attitudes to women, early age at first marriage, polygamy, lack of access to contraception and the adverse effects of migrant labour (Bambra, 1999). Effective and appropriate educational, preventive and curative sexual and reproductive health programmes are urgently required (Leke *et al.*, 1993; Temmerman, 1994). A diagram of the most important aetiological factors associated with infertility in developing countries is shown in Fig. 2.

Unsafe abortion practices

Worldwide estimates for 1995 indicate that ~20 million illegal abortions took place every year and almost all unsafe abortions (97%) occur in developing countries (Henshaw *et al.*, 1999; World Health Organization, 2004). Unsafe abortions are commonly carried out by unqualified personnel without the requisite skills, or in unsafe and unsterile conditions (Leke *et al.*, 1993;

Grimes *et al.*, 2006). Even if performed under legal circumstances abortion practices are, however, often not within the required standard of care. In the case of complications, access to appropriate medical treatment is often insufficient (Leke *et al.*, 1993).

Post-partum pelvic infections

Post-partum pelvic infections are extremely common in developing countries. They are often the result of lack of access to appropriate medical care, especially in rural areas. Home deliveries, performed in unhygienic circumstances by inadequately trained or equipped birth attendants, increase the risk of complications and post-partum infections dramatically. In sub-Saharan Africa, only 40% of births are attended by trained personnel (Stanton *et al.*, 2007). The most important complications of obstructed or unassisted labour are trauma and sepsis, both of which increase the risk of future infertility. In addition, obstetric fistulas may also compromise reproductive potential. The mechanisms involve chronic inflammation as well as social isolation, which these women often suffer as a result of incontinence and subsequent rejection by their husband, family and community (Leke *et al.*, 1993).

Female genital mutilation

It has been estimated that between 100 and 140 million girls and women have been subjected to some form of female genital

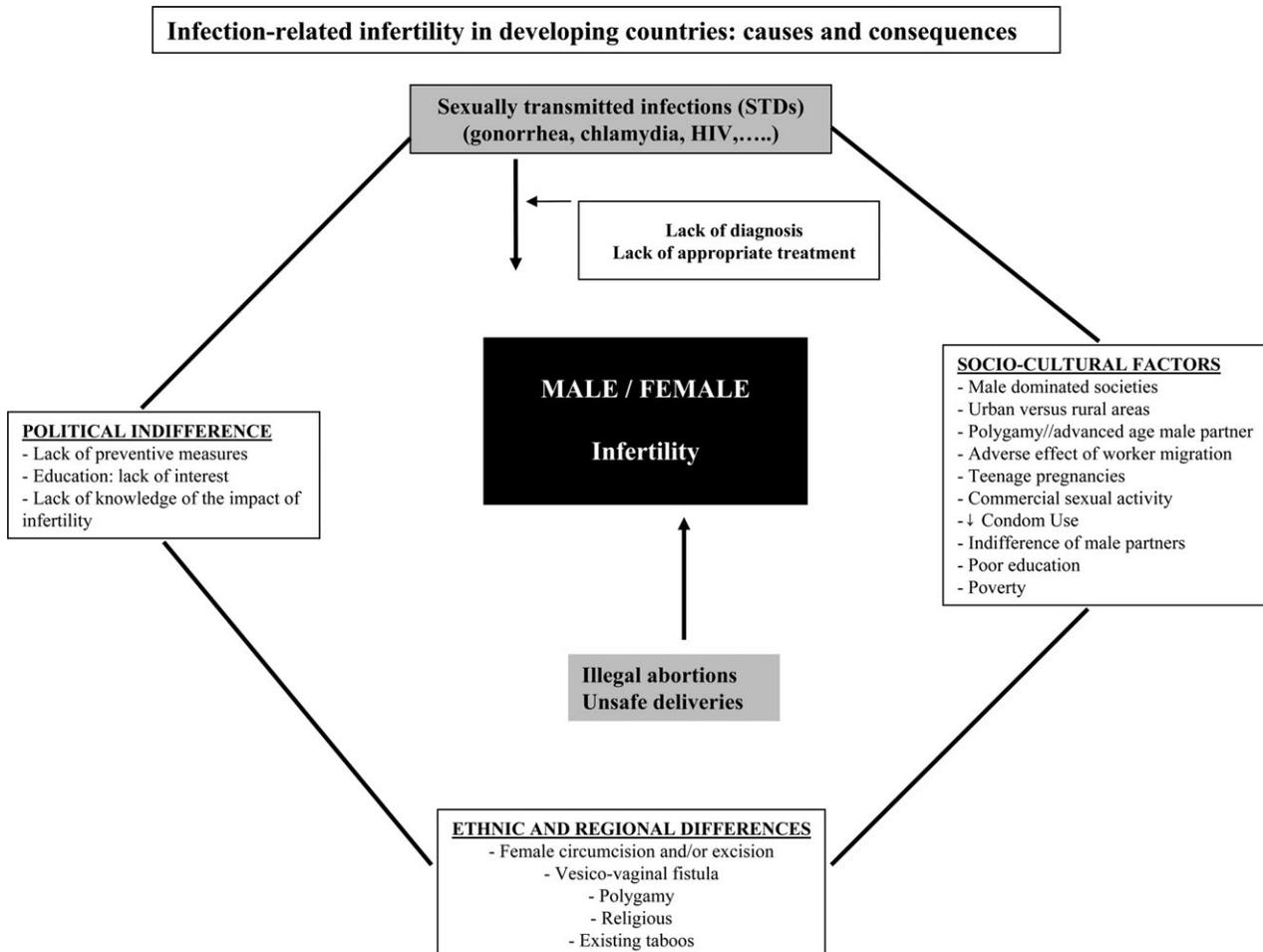


Figure 2: Infection-related infertility in developing countries: causes and consequences.

mutilation in Africa and, to a lesser extent, in some countries in the Middle East (World Health Organization, 2005). Traditionally, the procedure is performed by local midwives or elderly female villagers who have learned the techniques from their predecessors and who often have limited knowledge about the principles of aseptic techniques and the underlying anatomy (Davis *et al.*, 1999). The procedure is associated with immediate and long-term complications which include haemorrhage, sepsis, haematocolpos, dysmenorrhoea, dyspareunia, obstructed labour, fistula formation and infertility (Davis *et al.*, 1999; Obermeyer, 2005). In order to avoid these complications, some parents choose to use biomedical services if these can be accessed, indicating that the procedure may be gradually modernized but not necessarily abandoned.

Controversies and common misconceptions surrounding the issue of infertility treatment in developing countries

Population growth perception

In the Western industrialized World, the idea of infertility treatment in developing countries often evokes a feeling of discomfort and disbelief. It is generally thought that the problem of overpopulation can only be solved by well-organized family planning programmes and education, leaving little room for other initiatives. In this context, some believe that the infertile couple should be encouraged to courageously accept their condition of childlessness rather than be offered intervention (Tangwa, 2002).

A few questions around this subject are crucial: (1) Is it still true that the expected overpopulation in developing countries is mainly caused by the high fertility rate? (2) Can we succeed at reducing the high fertility rate through promotion of contraception and at the same time offer infertile couples the opportunity of simplified diagnosis and treatment? and (3) What would be the expected implication on population growth if affordable infertility treatment, including ART, could be offered to infertile couples in developing countries?

Considering the first question: according to the United Nations data the world population is expected to increase from 6.7 billion inhabitants in 2005 to reach 9.2 billion in 2050 (United Nations, 2007, p. vii). By 2050, the population of the more developed countries will decline slowly by ~1 million a year, while that of the developing world would be adding 35 million annually, 22 million of whom would be absorbed by the least developed countries. On the other hand, it should be noticed that if fertility remains constant at the levels estimated for 2000–2005, the population of the less developed regions would increase to 10.6 billion instead of the 7.9–9.2 billion. To achieve reductions against these estimates, it is essential that access to family planning services expands in the least developed countries. Therefore, it should be clear that the figures are based on assumptions of future fertility rates declining (United Nations, 2007, p. viii).

The global fertility rate (number of children per woman) was 5.0 in 1950–1955, 4.5 in 1970–1975 and 2.75 in 2005–2010 (United Nations, 2007, p. 74). This rate is projected to decline further to 2.02 per woman by 2045–2050, i.e. below the replacement level of 2.1. In the majority of 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.

On the other hand; expected population growth in developing countries can not only be attributed to high fertility rates but will also be caused by improved life expectancy (United

Nations, 2007, p. 14). Because of a rapid decline in mortality, even in the least developed countries life expectancy is set to rise from an average of 54 years currently to 67 years in 2045–2050, which highlights the important issue of population ageing. For Africa, the life expectancy at birth is expected to rise from 53 years nowadays to 66 years in 2045–2050.

Concerning the second question, although family planning and educational programmes have already resulted in a substantial fertility decline in most developing countries, there is still a need to support and optimize these programmes. The focus, however, should be on reproductive autonomy and not primarily on fertility reduction. The message of including infertility care in Reproductive Health Care Centres might convince some politicians to increase their awareness for better family planning strategies (A. Tezikuba, personal communication). The objective of supporting family planning programmes while providing treatment to the infertile couple can be achieved through the integration of family planning, fertility and maternal health services in well-organized existing or newly created Reproductive Health Care Centres.

Lastly, data from Belgium have shown that ART accounted for only 4.3% of all neonates born in 2004 (source: Study Centre for Perinatal Epidemiology, Brussels). However, in Belgium, six cycles of IVF are reimbursed by the government, which implies that there is no financial burden for patients in starting ART procedures. Even if ART could be made more accessible in developing countries, it would probably still account for < 1% of all deliveries. Increasing effort on family planning and health education should readily overcome this small contribution to the fertility rate.

An overview of the pros and cons of infertility treatment in developing countries is shown in Table II.

Competition for funding—the limited resources argument

Bilateral tubal blockage is the leading cause of infertility in developing countries (see section on ‘aetiology of infertility’). While ART remains the most effective intervention for this condition, funding remains a contested issue. This can be explained by the scarcity of health resources against a backdrop of limited funds. In Nigeria the cost of starting a new IVF-programme in a teaching hospital has been estimated at \$2 million, which is more than half of the total financial resources of the hospital (Okonofua, 1996). Such a strategy is of course unrealistic because hospitals also have to provide other important (life-saving) health-related services within the existing limited budget.

Health authorities focus on primary health care such as the reduction of maternal mortality and the promotion of family planning (Aboulghar, 2005). Although prevention of STDs and pregnancy-related sepsis should be considered a reproductive health priority, public investment in infertility treatment must also become a subject for discussion. We can, however, anticipate that public funding of infertility-related health care will be restricted to education and preventative care unless we succeed in substantially simplifying ART procedures.

Geographical differences in attitudes on infertility with emphasis on sociocultural, religious and political health issues

In communities which place a high value on fertility and children, the inability to conceive creates many psychological, social and

Table II. Pros and cons of infertility treatment in developing countries (DC).**Arguments pro**

- Infertility is a disease and needs medical treatment
- High prevalence of tubal factor infertility in developing countries (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)
- Opportunity of establishing 'Reproductive Health Care Centres' with possibilities for family planning/mother-care/infertility diagnosis & treatment
- Opportunity for cervical cancer and HIV screening for subfertile couples

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: vaccinations, malaria, HIV,...
- Dilemma: overpopulation versus childwish
- IVF-related procedures: regarded as expensive and moderately effective
- High risk for complications (ovarian stimulation syndrome (OHSS), multiple pregnancy, prematurity,...)
- Unknown outcome for women in this population (? cancer risk)
- Immediate and long-term-risks for ART babies
- Limited professional experience for medical and paramedical staff in DC
- Low-level facilities in most DC
- ICSI and cryopreservation of gametes and embryos: doubts about cost-effectiveness in DC

Reprinted from an article in Reproductive BioMedicine Online by Ombelet and Campo (2007) with permission from Reproductive Healthcare Ltd.

economic burdens, particularly for women (Dyer *et al.*, 2004, 2005; Wiersema *et al.*, 2006). Infertility has a profoundly negative impact on reproductive health in developing countries, although this impact varies between different regions and is influenced, among others, by religious, sociocultural and legal factors.

The middle east

Three major religions, Islam, Judaism and Christianity, continue to influence behaviour, attitudes and policy-making in the Middle East (Serour, 2000, 2002). To date, ART guidelines for Christians and Muslims are almost the same. For all religions, artificial insemination with husband's semen is permissible. For the Jewish masturbation should be avoided if possible, so that coitus interruptus or the use of a condom become preferred methods for semen collection. Judaism allows the practice of all techniques of assisted reproduction when the oocyte and spermatozoon originate from the wife and husband, respectively (Schenker, 2005).

Ultraorthodox Jews use infertility treatment as citizens of a pronatalist state and pronatalist religious system (Kahn, 2002). Third party gametes are also unacceptable to Muslims, so gamete-donation, embryo-donation and surrogate motherhood are not allowed. In contrast, for the Shari'ah sect, oocyte donation, embryo donation and surrogacy within a frame of temporary marriage arrangements are permitted (Serour, 2006). The attitude towards reproductive practice differs among the various divisions of Christianity. The practice of assisted reproduction is not accepted by the Vatican, however, it may be practiced by Protestant, Anglican and other denominations (Schenker, 2000).

Sub-Saharan Africa

Fertility and parenthood are highly valued in Africa to the extent that procreation is usually considered the most important purpose of marriage (Okonofua *et al.*, 1995; Hollos, 2003). As a result, infertility is often associated with marital instability and many other psychosocial consequences (Table I). Moreover, the high premium placed on fertility may act as a relevant barrier to the success of family planning strategies due to the wide-spread belief that contraception may result in permanent infertility.

There is, in principle, an enormous demand for ART in African countries, especially because most infertility cases are infection-related and therefore best treated by ART. Clinics providing ART are, however, still few and mostly in private settings (Giwa-Osagie, 2002a,b,c). Before ART can be made more accessible, many challenges will need to be negotiated. These relate to funding, geographical barriers and to the infrastructure required for ART (e.g. human skills and resources, equipment and supplies, electricity etc). The up-to-date management of the adverse effects of ART, and the need for adequate obstetric and neonatal care are also very important (Okonofua, 1996; Inhorn, 2003). Moreover, ART should be implemented with due recognition of the importance and influence of traditional systems of health and healing (Sundby, 1997; Leonard, 2002; Tangwa, 2002).

Latin America

Latin America is a heterogeneous region with many different cultural and sociological influences (Luna, 2002). The high prevalence of catholicism has a great impact on reproductive issues. Although infertility is a social stigma in Latin American societies, most countries do not consider ART a priority. Public hospitals generally provide only infertility investigations but cannot offer ART. Private centres exist but are very expensive, and therefore ART is commonly perceived as a luxury for wealthy couples (Zegers-Hochschild *et al.*, 2008). Paradoxically, those who cannot access ART are those who are most in need of treatment, as they are most likely to suffer from STDs, be subjected to unsafe abortion practices or work in conditions with pollutants influencing their reproductive capacity (Luna, 2002).

In 1995, a multinational registry of ART was initiated. Today this registry comprises ~135 centres in more than 10 countries in Latin America (Registro Latinoamericano de Reproduccion Asistida, www.redlara.com). Legislation on ART procedures differs between countries and is only well regulated in Mexico and Brazil. In these countries, ART can only be offered to married couples or those with a stable relationship. Embryo cryopreservation can and embryo donation cannot be done. While there is a need for better

regulation in many countries, the fear of the emergence of very restrictive laws due to the influence of a strong Catholic lobby may act as a deterrent in this regard. At the same time the lack of regulation is associated with a greater degree of fear regarding laboratory procedures and ART (Guilhem, 2001). Clearly, there is a need for open dialogue and debate surrounding the issue of ART in Latin America in order to improve access and quality of infertility care.

India

Motherhood is the most important goal for Indian women. Children, especially boys, give the woman status as well as psychological and emotional security within the patriarchal family. Childlessness is associated with stigmatization, social isolation and sometimes violence (Unisa, 1999; Riessman, 2000). Even in the case of male infertility, women usually bear the negative consequences of their inability to conceive. Preventive and curative services for infertility have not yet been a priority in India despite the importance of motherhood. ART is only provided in private centres and is only accessible by those who can afford this treatment. Owing to the stigma of infertility, secrecy is an important component of assisted conception, especially where donor gametes are involved (Bharadwaj, 2003). Owing to the lack of laws and regulation, there is great concern about quality and safety within existing ART centres. The problem of infertility in India has to be interpreted in a context of poverty, class and gender inequality and unequal access to health-care resources (Widge, 2002).

The Far East—China

China has developed a unique culture influenced by the teachings of Taoism, Confucianism and Buddhism. People with Confucian or Buddhist beliefs consider infertility as retribution for wrongdoing either by the man, woman or even ancestors (Handwerker, 1995; Qiu, 2002). Excessive sexual activity is believed to be the reason of infertility. With this belief, one can expect that infertile people are mostly blamed for their condition.

IVF-related procedures are acceptable when a couple's own gametes are used. On the other hand, donor insemination is also widely practised although the availability of donors does not meet the demand. In general, any intervention in natural reproduction is not desirable, but interference seems to be more acceptable than childlessness. Another form of interference relates to sex-selection which is especially practised in rural areas where boys are more highly desired than girls, and which may create devastating consequences for female embryos (Handwerker, 2002).

Suggested strategies for affordable infertility management in developing countries

The time has come to consider the possibility of implementing 'new reproductive technologies' in developing countries. We consider the integration of infertility management into sexual and reproductive health-care programmes and a reduction of costs a prerequisite in this regard. Simplifying diagnostic procedures in the infertility work-up, simplifying ART, minimizing complication rates and organizing training courses for medical and paramedical personnel will be mandatory if new reproductive

technologies are becoming available and affordable, especially outside the private health-care sector.

Preventive strategies

The first priority should always be prevention rather than cure (Inhorn, 2003). Therefore, prevention of STDs and pregnancy-related sepsis should be regarded as the most important and cost-effective strategy to decrease infertility rates. Many variables influence the success of the different prevention strategies. These include a number of elements: the target group, the constraints to overcome and the right strategies for prevention (Table III, Sekadde-Kigundu *et al.*, 2002; Kiros, 2002; Leke, 2002; Leke *et al.*, 2002).

The importance of education was documented by Okumu *et al.* (1990) who studied the past reproductive and sexual characteristics of patients with tubal infertility. When compared with fertile controls, women with tubal disease were younger at first coitus, were more likely to have had first coitus pre-menarche, had more sexual partners, more abortions before marriage, more

Table III. Prevention of Infertility in developing countries.

Target Group

- Adolescents and young adults with high-risk behaviour
- Low socio-economic class
- Migrants from rural to urban areas
- Refugees
- High-risk professions: tourist guides, long distance truck drivers, sex workers etc.

Constraints to overcome

More urgent issues: HIV pandemic, high maternal and perinatal mortality rates,

Lack of political commitment

Lack of knowledge on societal impact on the magnitude of 'infertility problems'

Stigmatization and gender issues associated with HIV/STDs

No integration of infertility in Reproductive Health Care Centres

- understaffing, lack of training, no knowledge of prevention and management of infertility

Poorly organized fertility clinics

- lack of space for proper counselling and laboratory facilities

Lack of clear guidelines//lack of well-organized referral system

Poor planning of preventive strategies

Men's lack of interest in a 'fertility exploration'

Popularity of traditional healers performing harmful traditional practises

Lack of available drugs and restrictions on drug prescription

Strategies for prevention

Education: ↑ public awareness
 ↑ knowledge of adolescents in human sexuality, reproductive biology, awareness of fertile period, causes of infertility etc.

Community mobilization: target groups = NGOs, health committees, opinion leaders

Prevention and effective treatment of STDs in men is vital: primary source of infection

Prevention of unplanned pregnancies (friendly family planning)

Safe delivery and post-natal care

Safe abortion services when law permits

Linkage of family planning, mothercare and infertility care

→ creation of centres of excellence

STD, sexually transmitted disease; NGO, Non-governmental organization

induced abortions, were more likely to have been diagnosed with STDs and had fewer years of schooling. These data suggest that reproductive and sexual events during teenage years determine the future prospects of fertility and highlight the importance of education. Paradoxically, education will not only help to safeguard future fertility but will also reduce total fertility rates as studies have demonstrated that education, especially of women, is an important variable determining the desired number of children (Potts and Marks, 2001; Bauer *et al.*, 2006).

Simplifying diagnostic procedures

An accurate history of couple's personal and medical details together with a simple light microscopy semen analysis will identify the majority of infertility problems related to ovulatory disorders and male subfertility (Ombelet *et al.*, 1997a, 1998; World Health Organization, 1999; Menkveld *et al.*, 2001; Gunalp *et al.*, 2001). The diagnosis of tubal factor infertility can be made by hysterosalpingography (HSG) or hystero-salpingo-contrast-sonography. These techniques are simple, reliable and comparatively inexpensive (De Muylder, 1995; Hauge *et al.*, 2000; De Jonge *et al.*, 2001; Kiguli-Malwadde and Byanyima, 2004). Laparoscopic techniques have been simplified over the years and can now be conducted in a one step ambulatory approach (Brosens *et al.*, 2002; Gordts *et al.*, 1998, 2002; Campo *et al.*, 2005). Even office mini-hysteroscopy can be done without major costs and side-effects, provided there has been appropriate training (Campo *et al.*, 1999; Ombelet and Campo, 2007).

Moreover, all of these procedures can be performed by a small team of health-care providers within a short period of time in an inexpensive setting (Ombelet and Campo, 2007). Future studies should assess the value and potential costs of 'one-stop infertility clinics' in different developing countries.

Simplified infertility treatment and non-IVF assisted reproduction

Fertility awareness programmes are an inexpensive and efficient first line approach to infertility management, provided tubal patency is demonstrated and severe male factor subfertility has been excluded (Gnoth *et al.*, 2002). In a prospective randomized study by Gnoth *et al.* (2003), couples were instructed about the meaning and detection of cervical mucus secretion, with good results. Fertility awareness counselling, which should also incorporate education on infertility prevention, can be given by nurses and paramedical staff working in existing reproductive health-care centres.

For ovulatory dysfunction, representing almost 20% of female infertility, clomiphene citrate (CC) can initiate ovulation. This medication is very cheap, can be taken orally with minimal discomfort and the results are rewarding. Ovulation can be induced in 50–70% of cases and, together with timed intercourse, the pregnancy rate varies between 15 and 25% per cycle with a low multiple pregnancy rate of 6–8% (Ombelet *et al.*, 1996, 1997b; Sovino *et al.*, 2002). In case of resistance to CC, a low-dose ovarian stimulation regimen with gonadotrophins aimed at mono-follicular growth is advisable, although this medication is more expensive. Alternatively, the use of aromatase inhibitors (AI) such as anastrozole and letrozole may be considered (Begum *et al.*, 2006; Verpoest *et al.*, 2006; Casper, 2007; Kafy and Tulandi, 2007). Although more expensive than CC, success rates

may be slightly higher when compared with CC, probably due to a better endometrial, receptivity (Atay *et al.*, 2006).

In the case of unexplained and moderate male factor infertility and provided tubal patency has been documented, intrauterine insemination (IUI) with husband's semen in natural cycles or after CC-stimulation can be promoted as a first-line treatment without major costs and without expensive infrastructure (Ombelet *et al.*, 1995, 2003; Verhulst *et al.*, 2006). Cost-effectiveness studies showed that three IUIs were as successful, but much cheaper than one IVF/ICSI cycle (Peterson *et al.*, 1994; Zayed *et al.*, 1997; Goverde *et al.*, 2000; Philips *et al.*, 2000; Van Voorhis *et al.*, 1997; Van Voorhis and Syrop, 2000). Moreover, IUI programmes can be run by well-trained paramedical staff, another advantage for resource-poor countries. Controlled ovarian hyperstimulation (COH), with or without IUI, is associated with the risk of multiple gestation, especially when gonadotrophins are used (Gleicher *et al.*, 2000). A high degree of awareness must be maintained, underpinned by appropriate protocols in order to minimize this risk. This is a particularly important issue in developing countries where the consequences of multiple pregnancies can be devastating.

Endoscopic surgery

Laparoscopy is an important tool, not only in the diagnosis of infertility, but also in the treatment of selected cases. Hysteroscopy may be used to diagnose and treat uterine septa, endometrial polyps, submucosal myomas and intrauterine adhesions. At laparoscopy, ovarian drilling can be performed in the case of ovulatory disorders associated with polycystic ovary syndrome (PCOS) when weight reduction and/or CC are unsuccessful (Guzick, 2007). Laparoscopic surgery can be recommended in the case of large ovarian cysts or hydrosalpinges, before starting assisted reproduction (Strandell *et al.*, 2005). This implies that training in endoscopic surgery should be regarded as an important issue in developing countries.

Simplified assisted reproduction

The development of ART associated with low cost and a very low complication rate is mandatory if governments in developing countries are to be convinced to fund infertility clinics. IVF procedures can be modified to make them affordable. Presently we do not know if IVF, even minimal stimulation IVF, is feasible in less than ideal conditions when compared with centres with high standards of laboratory equipment and using standard stimulation protocols. Therefore, studies on simplified, low-cost diagnostic procedures and ART techniques are urgently required in a low-cost setting.

Recruiting oocytes for IVF: ovarian stimulation

Gonadotrophins and/or follicle stimulating hormones, GnRH agonists and GnRH antagonists are too expensive to be used routinely in developing countries. If used without sufficient experience they also carry a high risk of ovarian hyperstimulation syndrome (OHSS), a life threatening disease. Mild ovarian stimulation should therefore be considered as a potential option in resource-poor countries (Philips and Kadoch, 2007).

The results of natural cycle IVF are, however, disappointing. The efficacy is hampered by high cancellation rates because of

premature LH rise and premature ovulation (Pelinck *et al.*, 2002). A low-risk and patient-friendly strategy is minimal stimulation IVF aiming at monofollicular growth. In the late follicular phase, a GnRH antagonist is given to prevent ovulation together with FSH for substitution (Pelinck *et al.*, 2006). The overall ongoing pregnancy rate per started cycle is low (8.3%) with an acceptable cumulative ongoing pregnancy rate of 20.8% after three cycles. Alternatively, low-dose hCG can be administered in the later stages of controlled ovarian stimulation. This results in a significantly reduced dose of recombinant FSH/hMG while the outcome is comparable to traditional COH regimens (Filicori *et al.*, 2005a,b).

The use of a low-dose CC regimen in IVF is another option with reportedly acceptable results, minimal side effects and a very low complication rate (Steinkampf *et al.*, 1992; Massey *et al.*, 1994; Ingerslev *et al.*, 2001; Hovatta and Cooke, 2006). The use of CC-stimulation seems to be superior to natural or minimal stimulation IVF (Daya *et al.*, 1995; Ingerslev *et al.*, 2001; Nargund *et al.*, 2001). Another option might be the use of letrozole or low-dose stimulation with gonadotrophins or recombinant FSH (more expensive). Identical results were reported with this low-dose protocol of recombinant FSH when compared with the commonly used high-dose stimulation protocols (Hohmann *et al.*, 2003). A higher cancellation rate before oocyte retrieval was compensated by improved embryo quality concomitant with a higher chance of undergoing embryo transfer. Cumulative rates of term live birth and patient discomfort are much the same for mild ovarian stimulation with single embryo transfer and for standard stimulation with two embryos transferred. The important advantage is that a mild IVF treatment protocol can substantially reduce multiple pregnancy rates and overall costs (Heijnen *et al.*, 2007).

Monitoring of the IVF cycle

Monitoring of follicular development in an IVF cycle, as well as the timing of the hCG administration can be done solely on sonographic criteria with basic inexpensive ultrasound equipment thereby avoiding the need of expensive endocrine investigations (Steinkampf *et al.*, 1992; Rojanasakul *et al.*, 1994).

Simplified laboratory procedures and equipment

Lowering the cost associated with laboratory procedures, namely fertilization and culture of embryos, represents another challenge. One possible approach is the use of a 'humidicrib', a plastic box which is commonly used for keeping newborns snug, instead of an expensive laminar flow hood (Hovatta and Cooke, 2006; Pilcher, 2006). For a tenth of the price, this box can be modified to be used as a portable, near sterile environment for the handling of gametes and embryos. Expensive cylinders of carbon dioxides required to incubate the embryos may be abandoned in favour of exhaling across the culture medium before sealing it in a plastic bag. This bag, containing the Petri dish with the embryos, can be dropped into a warm bath without the need for expensive incubators. This technique has been successfully used for more than 10 years for cow embryos in veterinary IVF (Vajta *et al.*, 1997, 2004).

Another possibility is intravaginal or intrauterine fertilization and culture. Intravaginal culture was already described about 20 years ago (Ranoux *et al.*, 1987, 1988; Ranoux and Seibel, 1990; Taymor *et al.*, 1992). A tube filled with 3 ml of culture medium containing 1–5 oocytes with 10 000–20 000 washed spermatozoa

per millilitre is hermetically closed and is placed in the vagina and held by a diaphragm for incubation for 44–50 h. Comparable success rates with conventional IVF were reported (Ranoux *et al.*, 1988). For unknown reasons, this simple and safe method of culture did not receive wide attention.

Semen decontamination through sperm processing is very important in countries with a high rate of seminal infection. The use of a novel washing method combining multiple density gradients and trypsin for removing human immunodeficiency virus-1 and hepatitis C virus from semen seems to be very promising (Loskutoff *et al.*, 2005; Huyser *et al.*, 2006).

Table IV summarizes the most important recommendations to consider when starting an ART unit in developing countries.

Minimizing the risks and complications of ART—OHSS and multiple pregnancy

The two most important complications of ART are OHSS and multiple pregnancies. If left untreated, OHSS can result in serious health complications and even death. OHSS is mostly associated with the high serum estradiol level from the use of high dose gonadotrophins and/or recombinant FSH.

Multiple pregnancy is the most important adverse outcome of ART. Perinatal and maternal mortality/morbidity rise dramatically compared with singleton pregnancies (Elster, 2000; Cohen, 2003; Ombelet *et al.*, 2005). Almost 50% of twin pregnancies are associated with preterm labour and/or preterm prelabour rupture of membranes (PPROM) often leading to premature delivery (<37 weeks) and its related morbidity and mortality (The ESHRE Capri Workshop Group, 2000). Two out of three

Table IV. Most important recommendations to consider when starting low-cost ART in developing countries: a proposed strategy (C. Huyser: personal communication at the Arusha Expert meeting, 2007).

-
- (1) Risk analysis of the country
 - (2) De-stigmatizing of fertility problems
 - (3) Identifying patients through reproductive health screening
 - (4) The community/region should be empowered to support the program (communication channels, ...)
 - (5) Be aware of infectious conditions and STDs
 - Aseptic conditions to perform procedures
 - Screening of patients
 - Prevention of STD transmission
 - Unique profiles and risks in different countries
 - Effective semen decontamination methods for sperm processing
 - (6) ART should be designed to be robust, repeatable and efficient
 - (7) Equipment should be basic, sturdy and strong
 - (8) Products should be solid, ready to use and with a long half-life
 - Sperm processing materials are best aseptically packaged (set or kit) and stored at room temperature
 - Embryo culture media should be robust, short-term, pre-packaged in small quantities
 - Disposables (pipette tips, screening dishes, ...) can be pre-packaged as 'a set per patient'
 - (9) The use of silastic condoms might be needed in some communities
 - (10) Information to the community should be discrete and applicable, taking into account sociocultural and religious differences
 - (11) A training program (with follow-up/audits) for the medical and paramedical staff should be designed.
-

twins will be small for gestational age, compounding the problem of prematurity. Furthermore, an increasing risk of handicap has been reported with an increasing number of fetuses (Luke and Keith, 1992), and at least one handicapped child is found in 7.4, 21.6 and 50% of twin, triplet and quadruplet pregnancies, respectively (Yokoyama *et al.*, 1995). Cerebral palsy seems to occur respectively 5–6 and 17–20 times more often in twin and triplet pregnancies compared with singletons (Pettersen *et al.*, 1993; Pharoah and Cooke, 1996; Tanbo and Abyholm, 1996). The importance of avoiding multiple pregnancies cannot be overemphasized when considering these risks against a backdrop of inadequate health-care facilities.

Nowadays, a policy of elective single embryo transfer (eSET) is reported as the most efficacious measure of reducing the incidence of multiple pregnancies in ART (Wolner-Hanssen and Rydhstroem, 1998; Gerris *et al.*, 1999, 2004; Van Royen *et al.*, 1999; Gerris, 2000; Tiitinen *et al.*, 2001; De Sutter *et al.*, 2002, 2003; Gerris and Van Royen, 2005). In a large retrospective study, it was shown that with the implementation of eSET multiple pregnancy delivery rates could drop from 25 to 5% (Tiitinen *et al.*, 2003). IUI in natural cycles and/or CC or letrozole-stimulated cycles have a reported multiple pregnancy rate of <8% which is acceptable (Ombelet *et al.*, 1996, 1997b). With the use of human gonadotrophins (hMG) or recombinant FSH, IUI success rates are significantly higher but multiple pregnancy rates rise to 20–30% (Guzick *et al.*, 1999).

Education and training

The implementation of new reproductive technologies will require education and training. In the past physicians working in developing countries mostly covered the cost of their training in ART and related procedures themselves, which also commonly included expenditure associated with living abroad for prolonged periods of time. This may account at least in part for the fact that many of them subsequently seek to make their profit in the private sector (Inhorn, 2003). Training courses on semen analyses and laparoscopic procedures have already been successfully conducted in African countries (Serour and Hefnawi, 1982; Serour *et al.*, 1982; Franken *et al.*, 2000a,b). Since 2005, efforts have intensified under the auspices of the IFFS education programme, which facilitated workshops in many different countries such as Uruguay, the Philippines and Nigeria.

Following training, quality control, regular audit and systems of accreditation and registration should be implemented in order to maintain appropriate standards of care.

The Arusha-project

December 2006, the Executive Committee of the European Society of Human Reproduction and Embryology (ESHRE) started with a new 'Special Task Force' dedicated to infertility in developing countries. This Special Task Force aimed to encourage more and affordable infertility diagnosis and treatment in developing countries. December 2007, an expert meeting on the topic of 'Developing countries and infertility' was organized in Arusha, Tanzania. A summary of most Arusha presentations are summarized in the ESHRE Monograph (July 2008). As a result of this meeting, an action-plan and a road-plan to the future have been outlined with the establishment of five Working-Groups

and five Study-Groups. Optimizing a concurrent and affordable infertility diagnostic and treatment programme will be the most important challenge. One of the Study-Groups will also deal with health economics, quality-of-life and cost-effectiveness of ART in resource-poor settings. One of the questions will be how cost-effective fertility treatment will be in comparison with other measures aimed to improve health. Whether we will not create false expectations by introducing relatively expensive and sophisticated fertility treatment will be another important subject (<http://www.eshre.com>). Looking at the different strategies we proposed, we still have to acknowledge that the question 'would the implementation of ART in developing countries result in relief or grief' should be discussed seriously all the way.

Funding and supporting the project of affordable art in developing countries

Infertility programmes in developing countries can only be implemented and sustained if they are supported by local policy makers as well as the international community. A critical aspect of this process is funding, and this is likely to require input and collaboration from various role players.

Governments

Expenditure on health as a percentage of gross domestic product differs significantly between different continents and different countries (World Health Statistics, 2007). The American (12.7%) and the European regions (8.6%) have the highest score compared with the African (6%), the Western Pacific (5.8%), the Eastern Mediterranean (5.0%) and the South-East Asia regions (4%). Evidently, these discrepancies translate into gross inequalities with regard to global health care. From the perspective of reproductive health, political statements and commitments need to result in appropriate action in order to achieve 'sexual and reproductive health for all' by 2015 as agreed to by 179 governments at the United Nations International Conference on Population and Development in Cairo in 1994 (Fathalla *et al.*, 2006).

More recently, health was recognized 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 need for integration of health services was emphasized by stating that '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 ...' (Oslo Ministerial Declaration, 2007).

There is consensus that stronger health systems, which are able to deliver an integrated approach to health, are key elements to achieve improved health outcomes (Van Zandvoort *et al.*, 2001; Travis *et al.*, 2004). There are many reasons for fragile and fragmented health services in developing countries, which include political instability, poor quality governance, lack of work force, inadequate drug supply and lack of functional information systems. Research is urgently required on how to overcome these barriers and strengthen health systems in resource-constrained settings (Travis *et al.*, 2004; Kumar, 2007).

International organizations dealing with 'reproductive health in developing countries'

United Nations—World Health Organization

The World Health Organization is the United Nations specialized agency for health. WHO's objective is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's Constitution as 'a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity'.

WHO sponsored the largest study on the epidemiology of infertility and has created a standardized approach to the diagnosis in infertile couples (Cates *et al.*, 1985; World Health Organization, 1987). At present, infertility prevention is the main objective of WHO's infertility-related reproductive health programme. At a more recent meeting on 'Medical, Ethical and Social Aspects of Assisted Reproduction' in 2001, WHO called for the integration of infertility into existing sexual and reproductive health-care programmes and for highlighting the issue of ART in developing countries. Table V summarizes part of the recommendations agreed at the meeting (Vayena *et al.*, 2002a). Progress towards the attainment of these goals remains, however, slow. The reasons for this 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; Kumar, 2007).

The population council

The Population Council (www.popcouncil.org) is an international, non-profit, non-governmental organization (NGO) that conducts biomedical, social science and public health research. For more than 50 years, the Council has been a leader in conducting studies on a range of reproductive health issues. Council research emphasizes the synergy of reproductive health and family planning services and seeks to combine them successfully and cost-effectively. The Population Council conducts reproductive health research in reducing unsafe abortion, prevention of STDs and promoting and supporting safe motherhood and post-partum care. Establishing fertility centres in developing countries are not a priority.

Family Health International

Family Health International (FHI) (www.fhi.org) is a leader among not-for-profit international public health organizations, managing research and field activities in more than 70 countries to meet the public health needs of some of the world's most vulnerable people. This organization tries to help countries and communities to prevent the spread of HIV/AIDS and STDs and care for those affected by them, to improve people's access to quality reproductive health services, especially safe, effective and affordable family planning methods and to improve the health of women and children, especially those who live in resource-constrained settings. The implementation of ART in developing countries is not a goal of this organization.

International Federation of Gynaecology and Obstetrics

The International Federation of Gynaecology and Obstetrics (FIGO) (www.igo.org) brings together professional Societies of obstetricians and gynaecologists of 113 countries. Its mission is to promote the wellbeing of women and their children and to raise the standard of practice in obstetrics and gynaecology around the world. This organization strives to ensure respect for women and advancement of their status.

FIGO commits its resources through educational, research and advocacy activities to strengthen its links with and between its member societies. FIGO initiatives in developing countries focus on reducing perinatal and maternal morbidity and mortality. The FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health elaborated on the ethical obligation in preventing infertility and on ethical guidelines for ART practice to minimize complications particularly in developing countries (www.igo.org).

International Federation of Fertility Societies

The International Federation of Fertility Societies (IFFS) was born in 1968. At present, 57 National Fertility Societies are affiliated. It is estimated that over 40 000 fertility specialists worldwide are brought together under one umbrella organization (www.iffs-reproduction.org). The most important objectives of IFFS are to stimulate basic and applied research and the dissemination of knowledge in all aspects of reproduction and fertility. The IFFS education

Table V. Report and Recommendations of the WHO-meeting on 'Medical, Ethical and Social Aspects of Assisted Reproduction', Geneva, 2001 (Vayena *et al.*, 2002a).

-
- (1) Infertility should be recognized as a Public Health issue worldwide, including developing countries.
 - (2) Research is needed on innovative, low-cost ART procedures that provide safe, effective, acceptable and affordable treatment for infertility.
 - (3) Policy makers and health staff should give attention to infertility and the needs of infertile patients.
 - (4) Governments should improve education in infertility and reproductive health for the general public and health-care professionals.
 - (5) A gender perspective needs to be applied by healthcare providers to infertility management and treatment.
 - (6) Infertility management should be integrated into national reproductive health education programmes and services.
 - (7) Physicians should provide adequate investigation facilities and treatment for the infertile couple in a culturally sensitive and ethically acceptable manner.
 - (8) Where appropriate, traditional healers should be included in the dialogue between patients and health-care providers concerning the treatment of infertility.
 - (9) Where public funding is insufficient, alternative sources of funding for public sector ART programmes should be sought.
 - (10) Cost-effective options, including the establishment of national networks of satellite clinics to screen and refer appropriate couples to specialist centres, should be examined as a means of improving access to ART.
 - (11) ART should be complementary to other ethically acceptable, social and cultural solutions to infertility.
 - (12) Public awareness of infertility and its causes should be increased to improve preventative behaviour and to diminish the stigmatization and social exclusion of infertile men and women.
 - (13) The dissemination of public information on the options for treatment of infertility, including adoption and the ethical and legal issues involved, should be improved.
-

programme is organizing successful workshops on ART, especially in developing countries. This initiative, which is the first of its kind, was met with great enthusiasm by various developing countries indicating the need for the advancement of infertility care.

The European Society for Human Reproduction and Embryology

The European Society of Human Reproduction and Embryology (ESHRE) was officially founded in Bonn (1985). The main aim of ESHRE is to promote interest in, and understanding of reproductive biology and medicine (www.eshre.com). It also aims to promote improvements in clinical practice by organizing teaching, training and continuing medical educational activities, developing and maintaining data registries and implementing methods to improve safety and quality assurance in clinical and laboratory procedures.

In 2006, the executive committee of ESHRE agreed upon the foundation of a new 'Special Task Force (STF)' on 'Developing countries and infertility'. This STF aims to document the problem of infertility in developing countries, to develop and test the effectiveness of a simplified 'one-step clinic' for the diagnosis of infertility, to develop and test the effectiveness of simplified IVF-related procedures, to develop strategies for minimizing the risks of ART and to promote the linkage of family planning, maternal and neonatal care and infertility treatment. The STF also aims to search for the optimal management strategy for subfertile couples in developing countries with emphasis on non-IVF treatment and other (surgical or medical) options before starting IVF. Other plans for the STF are to organize expert meetings and training courses for fertility specialists and paramedical staff from developing countries, to approach the media and to work together with other non-profit organizations with common interests.

Patient support networks

From a political point of view, it is very important that patient organizations claim the right to equitable access to infertility treatment all over the world (Dill, 2007). The International Consumer Support for Infertility (iCSI—www.icsi.ws) is a global family of patient associations of 39 countries in all world regions. In sub-Saharan Africa, the Joyce Fertility Support Centre Uganda was founded in 1998 to bring forward the idea of providing a holistic approach to the problem of infertility. Joyce Fertility Support is breaking with tradition by openly talking about infertility, its causes and its treatments. This patient network tries to convince local people that infertility affects both men and women, and that methods to prevent and to treat it are available (www.joyce-fertility.org). Recently Joyce Fertility Support launched the African Infertility Alliance which brings together the countries of Uganda, Kenya, Zimbabwe and Israel to share issues concerning infertility. Patients' voices will be crucial when the issue of infertility has to be discussed with policy makers.

The role of industry

It will be essential to convince industry of the value of infertility treatment in developing countries and to gain their support for Foundations and NGOs in this area of reproductive health. Apart from general support, the industry can make several relevant contributions. Providing cheap medication will be an important issue, as will be the manufacturing of basic ultrasound and laboratory

equipment at low price. Industry has also become an important source of funding for clinical research and this source should be utilized in developing countries. As for all clinical research, ethics committees and review bodies are needed for the appropriate monitoring of studies (Abbas, 2007).

Ethical aspects of 'infertility treatment in developing countries'

The wish for a child is a basic need for all people. In developing countries, childlessness has important psychological, social and economic consequences as previously outlined. The question is not whether fertility care is ethically justified in resource-poor developing countries but whether we can propose the more widespread use of ART as a valuable strategy. In our view, reproductive autonomy and equity justify our efforts to make ART available and affordable worldwide subject to political stability and a basic level of medical infrastructure. This does not mean that fair access to scarce resources, non-maleficence and treatment effectiveness are not equally important, of course.

Even if we succeed in implementing low-cost IVF, it remains however unlikely that treatment will become universally accessible. We may speculate that those who can afford treatment in low-resource settings are also able to raise a child in reasonable circumstances. In contrast, men and women living in extreme poverty cannot and should not access infertility treatment but require socio-political interventions, which improve their economical situation.

Another controversial question is whether infertility treatment should be offered to HIV positive couples in countries with a high HIV-related mortality and morbidity. While the answer to this question is likely to centre on the availability of antiretroviral medication, all HIV-infected couples require in-depth counselling on the pregnancy-related risks as well as on different reproductive choices, including, where indicated and accessible, ART. Unilateral promotion of contraception contradicts the concept of reproductive autonomy (Myer *et al.*, 2005; Delvaux and Nöstlinger, 2007).

Economic aspects of 'infertility care in developing countries'

A cost-benefit analysis of simplified and affordable ART in developing countries does not exist and the subject is extremely difficult to study (Ombelet and Campo, 2007). The results will depend largely on the cost of the diagnostic procedures and the ART treatment itself. Pilot studies are urgently needed to examine the precise cost of ART when the laboratory environment and equipment are available at minimal cost and when minimal stimulation protocols with cheap medication and minimal monitoring are used. The economic value of a newborn in developing countries has never been studied and will likely depend on the economic and demographic situations.

Conclusion

Infertility is a common reproductive health problem in developing countries, which frequently carries negative psychosocial implications. In many instances, infertility is caused by genital tract

infections. This highlights the need for both preventative health care measures and ART. New reproductive technologies can only be successfully introduced in developing countries if socio-cultural and economic prerequisites are fulfilled and governments can be persuaded to support their introduction. We have to liaise with the relevant authorities to discuss the strengthening of infertility services, at the core of which lies the integration of infertility, contraceptive and maternal health services within public health-care structures. Beyond this, the success and sustainability of ART in resource-low settings will depend to a large extent on our ability to optimize these techniques in terms of availability, affordability and effectiveness. It is our duty to give correct information to the governments, health-care providers and infertile couples to avoid the situation where couples would sacrifice everything they have or could borrow, for low-quality low success IVF.

After a fascinating period of almost 30 years of IVF and 15 years of ICSI, only a small part of the world population benefits from these new technologies. Time has come to give adequate attention to the issue of infertility in developing countries.

Funding

Funding to pay the Open Access publication charges for this article was provided by GIFT NPO.

References

- Abbas EE. Industry-sponsored research in developing countries. *Contemp Clin Trials* 2007;**28**:677–683.
- Aboughar MA. The importance of fertility treatment in the developing world. *BJOG* 2005;**112**:1174–1176.
- Adeniji RA, Olayemi O, Okunlola MA, Aimakhu CO. Pattern of semen analysis of male partners of infertile couples at the University College Hospital, Ibadan. *West Afr J Med* 2003;**22**:243–245.
- Adetoro OO, Ebomoyi EW. The prevalence of infertility in a rural Nigerian community. *Afr J Med Sci* 1991;**20**:23–27.
- Adler MW. Sexually transmitted diseases control in developing countries. *Genitourin Med* 1996;**72**:83–88.
- Araoye MO. Epidemiology of Infertility: social problems of the infertile couple. *West Afr J Med* 2003;**22**:190–196.
- Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *J Int Med Res* 2006;**34**:73–76.
- Bambra CS. Current status of reproductive behaviour in Africa. *Hum Reprod Update* 1999;**5**:1–20.
- Barten J. Screening for infertility in Indonesia. Results of examination of 863 infertile couples. *Andrologia* 1978;**10**:405–412.
- Bauer M, Chytilova J, Streblov P. *Effects of Education on determinants of high desired fertility: Evidence from Ugandan Villages*. Charles University, 2006. IES Working Paper 239/2006, IES FSV. <http://ies.fsv.cuni.cz>.
- Begum MR, Quadir E, Begum A, Begum RA, Begum M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. *J Obstet Gynaecol Res* 2006;**32**:502–506.
- Bergstrom S. Reproductive failure as a health priority in the Third World: a review. *East Afr Med J* 1992;**69**:174–180.
- Bharadwaj A. Why adoption is not an option in India: the visibility of infertility, the secrecy of donor insemination, and other cultural complexities. *Soc Sci Med* 2003;**56**:1867–1880.
- Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007;**22**:1506–1512.
- Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol* 1998;**105**:836–848.
- Brosens I, Campo R, Puttermans P, Gordts S. One-stop endoscopy-based infertility clinic. *Curr Opin Obstet Gynecol* 2002;**14**:397–400.
- Campo R, Van Belle Y, Rombauts L, Mestdagh G, Lauwers M, Braekmans P, Brosens I, Van Belle Y, Gordts S. Office mini-hysteroscopy. *Hum Reprod Update* 1999;**5**:73–81.
- Campo R, Molinas CR, Rombauts L, Mestdagh G, Lauwers M, Braekmans P, Brosens I, Van Belle Y, Gordts S. Prospective multicentre randomized controlled trial to evaluate factors influencing the success rate of office diagnostic hysteroscopy. *Hum Reprod* 2005;**20**:258–263.
- Casper RF. Aromatase inhibitors in ovarian stimulation. *Steroid Biochem Mol Biol* 2007;**106**:71–75.
- Cates W, Farley TM, Rowe PJ. Worldwide patterns of infertility: is Africa different? *Lancet* 1985;**2**:596–598.
- Chigumadzi PT, Moodley J, Bagratee J. Infertility profile at King Edward VIII Hospital, Durban, South Africa. *Trop Doct* 1998;**28**:168–172.
- Cohen J. Associated multiple gestation–ART. *Clin Obstet Gynecol* 2003;**46**:363–374.
- Daar AS, Merali Z. Infertility and social suffering: the case of ART in developing countries. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,15–21.
- Davis G, Ellis J, Hibbert M, Perez RP, Zimbleman E. Female circumcision: the prevalence and nature of the ritual in Eritrea. *Mil Med* 1999;**164**:11–16.
- Daya S, Gunby J, Hughes EG, Collins JA, Sagle MA, YoungLai EV. Natural cycles for in-vitro fertilization: cost-effectiveness analysis and factors influencing outcome. *Hum Reprod* 1995;**10**:1719–1724.
- De Jonge ETM, Hartman CR, Swaenepoel HM, Pistorius LR, Ombelet W. Hysterosalping-contrast-sonography as a triage for tubal patency in a population at risk for pelvic infection. *Middle East Fertil Soc J* 2001;**6**:239–244.
- Delvaux T, Nöstlinger C. Reproductive Choice for women and men living with HIV, contraception, abortion and fertility. *Reprod Health Matters* 2007;**15**(Suppl. 29):46–66.
- De Muylder X. Role of hysterosalpingography in the evaluation of infertility in Black Africa. *Med Trop (Mars)* 1995;**55**:160–164.
- De Sutter P, Gerris J, Dhont M. A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI. *Hum Reprod* 2002;**17**:2891–2896.
- De Sutter P, Van der Elst J, Coetsier T, Dhont M. Single embryo transfer and multiple pregnancy rate reduction in IVF/ICSI: a 5-year appraisal. *Reprod Biomed Online* 2003;**6**:464–469.
- Dill SK. International treatment differences: Policy, politics, partnership and ART. *Pharm Policy Law* 2007;**9**:147–156.
- Dyer SJ. The value of children in African countries: insights from studies on infertility. *J Psychosom Obstet Gynaecol* 2007;**28**:69–77.
- Dyer SJ, Abrahams N, Hoffman M, van der Spuy ZM. 'Men leave me as I cannot have children': women's experiences with involuntary childlessness. *Hum Reprod* 2002a;**17**:1663–1668.
- Dyer SJ, Abrahams N, Hoffman M, van der Spuy ZM. Infertility in South Africa: women's reproductive health knowledge and treatment-seeking behaviour for involuntary childlessness. *Hum Reprod* 2002b;**17**:1657–1662.
- Dyer SJ, Abrahams N, Mokoena NE, van der Spuy ZM. "you are a man because you have children": experiences, reproductive health knowledge and treatment-seeking behaviour among men suffering from couple infertility in South Africa. *Hum Reprod* 2004;**19**:960–967.
- Dyer SJ, Abrahams N, Mokoena NE, Lombard CJ, van der Spuy ZM. Psychological distress among women suffering from couple infertility in South Africa: a quantitative assessment. *Hum Reprod* 2005;**20**:1938–1943.
- Ebomoyi E, Adetoro OO. Socio-biological factors influencing infertility in a rural Nigerian community. *Int J Gynaecol Obstet* 1990;**33**:41–47.
- El-Beheiry A, Abou-Zeid S, El-Ghazzawi E, El-Mansy E, Salama N. The leprous testis. *Arch Androl* 1979;**3**:173–176.
- Elster N. Less is more: the risks of multiple births. *Fertil Steril* 2000;**74**:617–623.
- The ESHRE Capri Workshop Group. Multiple gestation pregnancy. *Hum Reprod* 2000;**15**:1856–1864.
- Ericksen K, Brunette T. Patterns and predictors of infertility among African women: a cross-national survey of twenty-seven nations. *Soc Sci Med* 1996;**42**:209–220.
- Fathalla MF. Reproductive health: a global overview. *Early Hum Dev* 1992;**29**:35–42.
- Fathalla MF. Current challenges in assisted reproduction. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,3–12.

- Fathalla MF, Sinding SW, Rosenfield A, Fathalla MMF. Sexual and reproductive health for all: a call for action. *Lancet* 2006;**368**:2095–2100.
- Filicori M, Cognigni GE, Gamberini E, Parmegiani L, Troilo E, Roset B. Efficacy of low-dose human chorionic gonadotropin alone to complete controlled ovarian stimulation. *Fertil Steril* 2005a;**84**:394–401.
- Filicori M, Fazleabas AT, Huhtaniemi I, Licht P, Rao ChV, Tesarik J, Zygmunt M. Novel concepts of human chorionic gonadotropin: reproductive system interactions and potential in the management of infertility. *Fertil Steril* 2005b;**84**:275–284.
- Franken DR, Barendsen R, Kruger TF. A continuous quality control program for strict sperm morphology. *Fertil Steril* 2000a;**74**:724–724.
- Franken DR, Smith M, Menkveld R, Kruger TF, Sekadde-Kigonde C, Mbizvo M, Akande EO. The development of a continuous quality control programme for strict sperm morphology among sub-Saharan African laboratories. *Hum Reprod* 2000b;**15**:667–671.
- Geelhoed DW, Nayemil D, Asare K, Schagen van Leeuwen JH, Roosmalen J. Infertility in rural Ghana. *Int J Gynaecol Obstet* 2002;**79**:137–142.
- Gerai AS, Rushwan H. Infertility in Africa. *Popul Sci* 1992;**12**:25–46.
- Gerris JM. Single embryo transfer and IVF/ICSI outcome: a balanced appraisal. *Hum Reprod Update* 2005;**11**:105–121.
- Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Van de Meerssche M, Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod* 1999;**14**:2581–2587.
- Gerris J, Van Royen E. Avoiding multiple pregnancies in ART: a plea for single embryo transfer. *Hum Reprod* 2000;**15**:1884–1888.
- Gerris J, De Sutter P, De Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, Vercruyssen M, Kok P, Elseviers M, Annemans L *et al.* A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. *Hum Reprod* 2004;**19**:917–923.
- Gerrits T. Social and cultural aspects of infertility in Mozambique. *Patient Educ Counsel* 1997;**31**:39–48.
- Gilling-Smith C, Nicopoulos JD, Semprini AE, Frodsham LC. HIV and reproductive care – a review of current practice. *BJOG* 2006;**113**:869–878.
- Giwa-Osagie OF. ART in developing countries with particular reference to sub-Saharan Africa. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002a,22–27.
- Giwa-Osagie OF. Social and ethical aspects of assisted conception an Anglophone sub-Saharan Africa. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002b,50–54.
- Giwa-Osagie OF. Management of infertility and ethical issues: current trends in sub-Saharan Africa. In: Sekadde-Kigonde C, Chikamata D, Franken D (eds). *Management of Infertility in AFRO & EMRO Countries*. Geneva, Switzerland: World Health Organization Proceedings of a Workshop, 2002c,117–132.
- Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med* 2000;**343**:2–7.
- Glynn JR, Buvé A, Caraël M, Kahindo M, Macauley IB, Musonda RM, Jungmann E, Tembo F, Zekeng L. Decreased fertility among HIV-1-infected women attending antenatal clinics in three African cities. *J Acquir Immune Defic Syndr* 2000;**25**:345–352.
- Gnoth C, Frank-Herrmann P, Freundl G. Opinion: natural family planning and the management of infertility. *Arch Gynecol Obstet* 2002;**267**:67–71.
- Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod* 2003;**18**:1959–1966.
- Gordts S, Campo R, Rombauts L, Brosens I. Transvaginal hydrolaparoscopy as an outpatient procedure for infertility investigation. *Hum Reprod* 1998;**13**:99–103.
- Gordts S, Campo R, Puttemans P, Verhoeven H, Gianaroli L, Brosens J, Brosens I. Investigation of the infertile couple: a one-stop outpatient endoscopy-based approach. *Hum Reprod* 2002;**17**:1684–1687.
- Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet* 2000;**355**:13–18.
- Grimes DA, Benson J, Singh S, Romero M, Ganatra B, Okonofua FE, Shah IH. Unsafe abortion: the preventable pandemic. *Lancet* 2006;**368**:1908–1919.
- Guilhem D. New reproductive technologies, ethics and legislation in Brazil: a delayed debate. *Bioethics* 2001;**15**:218–230.
- Gunalp S, Onculoglu C, Gurgan T, Kruger TF, Lombard CJL. A study of semen parameters with emphasis on sperm morphology in a fertile population: an attempt to develop clinical thresholds. *Hum Reprod* 2001;**16**:110–114.
- Guzick DS. Ovulation induction management of PCOS. *Clin Obstet Gynecol* 2007;**50**:255–267.
- Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST *et al.* Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network. *N Engl J Med* 1999;**340**:177–183.
- Haile A. Fertility conditions in Gondar, northwestern Ethiopia: an appraisal of current status. *Stud Fam Plann* 1990;**21**:110–118.
- Hamberger L, Janson PO. Global importance of infertility and its treatment: role of fertility technologies. *Int J Gynaecol Obstet* 1997;**58**:149–158.
- Handwerker L. Social and ethical implications of in vitro fertilization in contemporary China. *Camb Q Healthc Ethics* 1995;**4**:355–363.
- Handwerker L. The politics of making modern babies in China. In: horn MC, van Balen F (eds). *Infertility Around the Globe*. London: University of California Press, 2002, 298–314.
- Hauge K, Flo K, Riedhart M, Granberg S. Can ultrasound-based investigations replace laparoscopy and hysteroscopy in infertility? *Eur J Obstet Gynecol Reprod Biol* 2000;**92**:167–170.
- Heijnen EM, Eijkemans MJ, De Klerk C, Polinder S, Beckers NG, Klinkert ER, Broekmans FJ, Passchier J, te velde ER, Macklon NS *et al.* A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial. *Lancet* 2007;**369**:743–749.
- Henshaw SK, Singh S, Haas T. The incidence of abortion worldwide. *Int Fam Plann Persp* 1999;**25**:S30–S38.
- Hohmann FP, Macklon NS, Fauser BC. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. *J Clin Endocrinol Metab* 2003;**88**:166–173.
- Hollos M. Profiles of infertility in southern Nigeria: women's voices from Amakiri. *Afr J Reprod Health* 2003;**7**:46–56.
- Hovatta O, Cooke I. Cost-effective approaches to in vitro fertilization: means to improve access. *Int J Gynaecol Obstet*. 2006;**94**:287–291.
- Huysen C, Loskutoff NM, Singh R, Webber L, Franken DR. Enhanced sperm quality using advanced density gradient technology. *Hum Reprod* 2006;**21**(Suppl. 1):i58.
- Ikechebelu JI, Adinma JI, Orie EF, Ikegwuonu SO. High prevalence of male infertility in southeastern Nigeria. *J Obstet Gynaecol* 2003;**23**:657–659.
- Ingerslev HJ, Hojgaard A, Hindkjaer J, Kesmodel U. A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate. *Hum Reprod* 2001;**16**:696–702.
- Inhorn MC. Global infertility and the globalization of new reproductive technologies: illustrations from Egypt. *Soc Sci Med* 2003;**56**:1837–1851.
- Kafy S, Tulandi T. New advances in ovulation induction. *Curr Opin Obstet Gynecol* 2007;**19**:248–252.
- Kiguli-Malwadde E, Byanyima RK. Structural findings at hysterosalpingography in patients with infertility at two private clinics in Kampala, Uganda. *Afr Health Sc* 2004;**4**:178–181.
- Kahn SM. Rabbis and reproduction – the use of new reproductive technologies among ultraorthodox jews in Israël. In: Inhorn MC, van Balen F (eds). *Infertility Around the Globe*. London: University of California Press, 2002,283–297.
- Kiros K. The prevention and management of infertility – WHO/AFRO strategy. In: Sekadde-Kigonde C, Chikamata D, Franken D (eds). *Management of infertility in AFRO & EMRO countries*. Geneva, Switzerland: World Health Organization Proceedings of a workshop, 2002,92–98.
- Kuku SF, Osegbe ND. Oligo/azoospermia in Nigeria. *Arch Androl* 1989;**22**:233–237.
- Kumar P. Providing the providers – Remediating Africa's shortage of Health Care Workers. *N Engl J Med* 2007;**356**:2564–2567.
- Larsen U. Childlessness, subfertility, and infertility in Tanzania. *Stud Fam Plann* 1996;**27**:18–28.
- Larsen U. Primary and secondary infertility in sub-Saharan Africa. *Int J Epidem* 2000;**29**:285–291.
- Leke RJ. The prevalence of infertility and its preventive measures in Sub-Saharan Africa. In: Sekadde-Kigonde C, Chikamata D, Franken D (eds). *Management of Infertility in AFRO & EMRO Countries*. Geneva, Switzerland: World Health Organization Proceedings of a workshop, 2002,79–91.

- Leke RJ, Oduma JA, Bassol-Mayagoitia S, Bacha AM, Grigor KM. Regional and geographical variations in infertility: effects on environmental, cultural, and socioeconomic factors. *Environ Health Perspect* 1993;**101**(Suppl. 2):73–80.
- Leke RJ, Busingye R, Kiros K, Tozin RR, Oyieke BO, Chikamata D. Prevention of infertility. In: Sekadde-Kigondo C, Chikamata D, Franken D (eds). *Management of Infertility in AFRO & EMRO Countries*. Geneva, Switzerland: World Health Organization Proceedings of a workshop, 2002,43–48.
- Leonard L. “Looking for Children”: the search for fertility among the Sara of southern Chad. *Med Anthropol* 2002;**21**:79–112.
- Loskutoff NM, Huyser C, Singh R, Walker DL, Thornhill AR, Morris L, Webber L. Use of a novel washing method combining multiple density gradients and trypsin for removing human immunodeficiency virus-1 and hepatitis C virus from semen. *Fertil Steril* 2005;**84**:1001–1010.
- Luke B, Keith LG. The contribution of singletons, twins and triplets to low birth weight, infant mortality and handicap in the United States. *J Reprod Med* 1992;**37**:661–666.
- Luna F. Assisted reproductive technology in Latin America: some ethical and sociocultural issues. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,31–40.
- Lyerly AD, Anderson J. Human immunodeficiency virus and assisted reproduction: reconsidering evidence, reframing ethics. *Fertil Steril* 2001;**75**:843–858.
- Makush M, Botega N, Bahamondes L. Physician-patient communication in the prevention of female reproductive tract infections: some limitations. *Cadern S Publ* 2000;**16**:249–253.
- Malpani A, Malpani A. Simplifying assisted conception techniques to make them universally available—a view from India. *Hum Reprod* 1992;**7**:49–50.
- Mascie-Taylor CG. Endemic disease, nutrition and fertility in developing countries. *J Biosoc Sci* 1992;**24**:355–365.
- Massey JB, Ingargiola PE, Tucker MJ, Mitchell-Leef DE, Wright G. Minimal stimulation with simplified monitoring for in vitro fertilization. *J Assist Reprod Genet* 1994;**11**:353–358.
- Mayaud P, Grosskurth H, Chagalucha J, Todd J, West B, Gabone R, Senkoro K, Rusizoka M, Laga M, Hayes R *et al*. Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. *Bull World Health Organ*. 1995;**73**:621–630.
- Meheus A, Reniers J, Colletet M. Determinants of infertility in Africa. *Afr J Sex Transmi Dis* 1986;**2**:31–35.
- Menkveld R, Wong WY, Lombard CJ, Wetzels AMM, Thomas CMG, Merkus HMWM, Steegers-Theunissen PM. Semen parameters, including WHO and strict criteria morphology, in a fertile and subfertile population: an effort towards standardization of in-vivo thresholds. *Hum Reprod* 2001;**16**:1165–1171.
- Myer L, Morroni C, Nachege J, Cooper D. HIV-infected women in ART programmes. *Lancet* 2005;**365**:655–656.
- Nabaitu J, Bachengana C, Seeley J. Marital instability in a rural population in south-west Uganda: implications for the spread of HIV-1 infection. *Africa (Lond)* 1994;**64**:243–251.
- Nachtigall RD. International disparities in access to infertility services. *Fertil Steril* 2006;**85**:871–875.
- Nargund G, Waterstone J, Bland JM, Philips Z, Parsons J, Campbell S. Cumulated conception and live birth rates in natural (unstimulated) IVF cycles. *Hum Reprod* 2001;**16**:259–262.
- Obermeyer CM. The consequences of female circumcision for health and sexuality: an update on the evidence. *Cult Health Sex* 2005;**7**:443–461.
- Okumu CV, Kamau RK, Rogo KO. Past reproductive and sexual characteristics of women with tubal infertility at Kenyatta National Hospital. *East Afr Med J* 1990;**67**:864–872.
- Okonofua FE. The case against new reproductive technologies in developing countries. *Br J Obstet Gynaecol* 1996;**103**:957–962.
- Okonofua FE, Esen UI, Nimalaraj T. Hysterosalpingography versus laparoscopy in tubal infertility: comparison based on findings at laparotomy. *Int J Gynecol Obstet* 1989;**28**:143–147.
- Okonofua FE, Ako-Nai KA, Dighitoghi MD. Lower genital tract infections in infertile Nigerian women compared to controls. *Genitourin Med* 1995;**71**:163–168.
- Olantunji AO, Sule-Odu AO. The pattern of infertility cases at a university hospital. *West Afr J Med* 2003;**22**:205–207.
- Ombelet W, Campo R. Affordable IVF for developing countries. *Reprod Biomed Online* 2007;**15**:267–265.
- Ombelet W, Puttemans P, Brosens I. Intrauterine insemination: a first-step procedure in the algorithm of male subfertility treatment. *Hum Reprod* 1995;**10**(Suppl. 1):90–102.
- Ombelet W, Cox A, Janssen M, Vandeput H, Bosmans E. Artificial insemination: using the husband’s sperm. In: Acosta AA, Kruger TF (eds). *Diagnosis and Therapy of Male Factor In Assisted Reproduction*. New York: Parthenon Publishing, 1996,397–410.
- Ombelet W, Bosmans E, Janssen M, Cox A, Vlasselaer J, Gyselaers W, Vandeput H, Gielen J, Pollet H, Maes M *et al*. Semen parameters in a fertile versus subfertile population: a need for change in the interpretation of semen testing. *Hum Reprod* 1997a;**12**:987–993.
- Ombelet W, Vandeput H, Van de Putte G, Cox A, Janssen M, Jacobs P, Bosmans E, Kruger T. Intrauterine insemination after ovarian stimulation with clomiphene citrate: predictive potential of inseminating motile count and sperm morphology. *Hum Reprod* 1997b;**12**:1458–1463.
- Ombelet W, Pollet H, Cox A, Janssen M, Vandeput H, Bosmans E. Male fertility assessment: Microscopic examination versus biochemical parameters. In: Ombelet W, Stevens K, Vandeput H, Vereecken A, Bosmans E (eds). *Book of Abstracts and Miniposters*. Genk: Andrology in the Nineties, 1998,26.
- Ombelet W, Deblaere K, Bosmans E, Cox A, Jacobs P, Janssen M, Nijs M. Semen quality and intrauterine insemination. *Reprod Biomed Online* 2003;**7**:485–492.
- Ombelet W, De Sutter P, Van der Elst J, Martens G. Multiple gestation and infertility treatment: registration, reflection and reaction: the Belgian project. *Hum Reprod Update* 2005;**11**:3–14.
- Orji EO, Kuti O, Fasubaa OB. Impact of infertility on marital life in Nigeria. *Int J Gynaecol Obstet* 2002;**79**:61–62.
- Oslo Ministerial Declaration—global health: a pressing foreign policy issue of our time. *Lancet* 2007;**369**:1373–1378.
- Otolorin EO, Ojengbede O, Falase AO. Laparoscopic evaluation of the tuboperitoneal factor in infertile Nigerian women. *Int J Gynaecol Obstet* 1987;**25**:47–51.
- Otubu JA, Sagay AS, Dauda S. Hysterosalpingogram, laparoscopy and hysteroscopy in the assessment of the infertile Nigerian women. *East Afr Med J* 1990;**67**:370–374.
- Papreen N, Sharma A, Sabin K, Begum L, Ahsan SK, Baqui AH. Living with infertility: experiences among Urban slum populations in Bangladesh. *Reprod Health Matters* 2000;**8**:33–44.
- Parikh FR, Nadkarni SG, Kamat SA, Naik N, Soonawala SB, Parikh RM. Genital tuberculosis—a major pelvic factor causing infertility in Indian women. *Fertil Steril* 1997;**67**:497–500.
- Pelincck MJ, Hoek A, Simons AH, Heineman MJ. Efficacy of natural cycle IVF: a review of the literature. *Hum Reprod Update* 2002;**8**:129–139.
- Pelincck MJ, Vogel NE, Hoek A, Simons AH, Arts EG, Mochtar MH, Beemsterboer S, Hondelink MN, Heineman MJ. Cumulative pregnancy rates after three cycles of minimal stimulation IVF and results according to subfertility diagnosis: a multicentre cohort study. *Hum Reprod* 2006;**21**:2375–2383.
- Peterson CM, Hatasaka HH, Jones KP, Poulson AM, Jr, Carrell DT, Urry RL. Ovulation induction with gonadotropins and intrauterine insemination compared with in vitro fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. *Fertil Steril* 1994;**62**:535–544.
- Pettersson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *Br Med J* 1993;**307**:1239–1243.
- Pharoah PO, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:174–177.
- Philips SJ, Kadoch IJ. Natural cycle IVF: a question of semantics? *Reprod Biomed Online* 2007;**15**:255–256.
- Philips Z, Barraza-Llorens M, Posnett J. Evaluation of the relative cost-effectiveness of treatments for infertility in the UK. *Hum Reprod* 2000;**15**:95–106.
- Pilcher H. Fertility on a shoestring. *Nature* 2006;**442**:975–977.
- Potts D, Marks S. Fertility in Southern Africa: the quiet revolution. *J South Afr Stud* 2001;**27**:189–205.
- Qiu R-Z. Sociocultural dimensions of infertility and assisted reproduction in the Far East. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,75–80.
- Ranoux C, Seibel MM. New techniques in fertilization: intravaginal culture and microvolume straw. *J In Vitro Fert Embryo Transf* 1990;**7**:6–8.

- Ranoux C, Dubuisson JB, Foulot H, Aubriot FX. Intravaginal culture and embryo transfer. A new method for the fertilization of human oocytes. *Rev Fr Gynecol Obstet* 1987;**82**:741–744.
- Ranoux C, Aubriot FX, Dubuisson JB, Cardone V, Foulot H, Poirot C, Chevallier O. A new in vitro fertilization technique: intravaginal culture. *Fertil Steril* 1988;**49**:654–657.
- Richards SC. "Spoiling the womb": definitions, aetiologies and responses to infertility in north west province, Cameroon. *Afr J Reprod Health* 2002;**6**:84–94.
- Riessman CR. Stigma and everyday resistance practices: childless women in South India. *GenD Soc* 2000;**14**:111–135.
- Rojanasakul A, Choktanasiri W, Suchartwatanachai C, Srisombut C, Chinsomboon S, Chatasingh S. 'Simplified IVF': program for developing countries. *J Med Assoc Thai* 1994;**77**:12–18.
- Sallam HN. Infertility in developing countries: funding the project. *Hum Reprod ESHRE Monograph* 2008;**5**:97–101.
- Saporta L, Yuksel A. Androgenic status in patients with lepromatous leprosy. *Br J Urol* 1994;**74**:221–224.
- Schenker JG. Women's reproductive health: monotheistic religious perspectives. *Int J Gynaecol Obstet* 2000;**70**:77–86.
- Schenker JG. Assisted reproductive practice: religious perspectives. *Reprod Biomed Online* 2005;**10**:310–319.
- Sciarra JJ. Infertility: a global perspective. The role of pelvic infection. *ORGIN* 1994;**3**:12–15.
- Sciarra JJ. Sexually transmitted diseases: global importance. *Int J Gynaecol Obstet* 1997;**58**:107–119.
- Sekadde-Kigonde C, Machoki MJ. Workshop report on management of infertility in Africa and eastern mediterranean regions. In: Sekadde-Kigonde C, Chikamata D, Franken D (eds). *Management of Infertility in AFRO & EMRO Countries*. Geneva, Switzerland: World Health Organization Proceedings of a workshop, 2002,24–26.
- Sekadde-Kigonde C, Chikamata D, Franken D. *Management of Infertility in AFRO & EMRO Countries*. Geneva, Switzerland: World Health Organization Proceedings of a workshop, 2002.
- Serour GI. Ethical considerations of assisted reproductive technologies: a middle eastern perspective. *Middle East Fertil Steril J* 2000;**5**:13–18.
- Serour GI. Attitudes and cultural perspectives on infertility and its alleviation in the middle East area. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,41–49.
- Serour GI. Religious perspectives of ethical issues in ART. In ethical dilemmas. In assisted reproduction. In: Francoise S, Claude S (eds). 3rd edn. UK: Informa Health Care, 2006,99–114.
- Serour GI, Hefnawi FI. Diagnostic laparoscopy for infertile patients as a training program. *Int J Gynaecol Obstet* 1982;**20**:19–22.
- Serour GI, Kandil O, Askalani H, Younis N, Hefnawi F. Laparoscopy on patients with previous lower abdominal surgery: a new technique. *Int J Gynaecol Obstet* 1982;**20**:357–361.
- Serour GI, El Ghar M, Mansour RT. Infertility: a health problem in the Muslim world. *Popul Sci* 1991;**10**:41–58.
- Shaheen R, Subhan F, Tahir F. Epidemiology of genital tuberculosis in infertile population. *J Pak Med Assoc* 2006;**56**:306–309.
- Sovino H, Sir-Petermann T, Devoto L. Clomiphene citrate and ovulation induction. *Reprod Biomed Online* 2002;**4**:303–310.
- Stanton C, Blanc AK, Croft T, Choi Y. Skilled care at birth in the developing world: progress to date and strategies expanding coverage. *B Biosoc Sci* 2007;**39**:109–120.
- Steinkampf MP, Kretzer PA, McElroy E, Conway-Myers BA. A simplified approach to in vitro fertilization. *J Reprod Med* 1992;**37**:199–204.
- Strandell DS, Lindhard A, Eckerlund I. Cost-effectiveness analysis of salpingectomy prior to IVF, based on a randomized controlled trial. *Hum Reprod* 2005;**20**:3284–3292.
- Sundby J. Infertility in the Gambia: traditional and modern health care. *Patient Educ Counsel* 1997;**31**:29–37.
- Sundby J, Mboge R, Sonko S. Infertility in the Gambia: frequency and health care seeking. *Soc Sci Med* 1998;**46**:891–899.
- Tanbo T, Abyholm T. Obstetric and perinatal outcome in pregnancies after assisted reproduction. *Curr Opin Obstet Gynecol* 1996;**8**:193–198.
- Tangwa GB. ART and African sociocultural practices: worldview, belief and value systems with particular reference to francophone Africa. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland: World Health Organization, 2002,55–59.
- Temmerman M. Sexually transmitted diseases and reproductive health. *Sex Transm Dis* 1994;**21**:S55–S58.
- Taymor ML, Ranoux CJ, Gross GI. Natural oocyte retrieval with intravaginal fertilization: a simplified approach to in vitro fertilization. *Obstet Gynecol* 1992;**80**:888–891.
- Tiitinen A, Halttunen M, Härkki P, Vuoristo P, Hyden-Granskog C. Elective single embryo transfer: the value of cryopreservation. *Hum Reprod* 2001;**16**:1140–1144.
- Tiitinen A, Unkila-Kallio L, Halttunen M, Hyden-Granskog C. Impact of elective single embryo transfer on the twin pregnancy rate. *Hum Reprod* 2003;**18**:1449–1453.
- Travis P, Bennett S, Haines A, Pang T, Bhutta Z, Hyder AA, Pielemeier NR *et al.* Overcoming health-systems constraints to achieve the Millennium Development Goals. *Lancet* 2004;**364**:900–906.
- Umezulike AC, Efezie ER. The psychological trauma of infertility in Nigeria. *Int J Gynaecol Obstet* 2004;**84**:178–180.
- Unisa S. Childlessness in Andhra Pradesh, India: treatment-seeking and consequences. *Reprod Health Matters* 1999;**7**:54–64.
- United Nations, Department of Economic and Social Affairs, population Division. World Population Prospects: The 2006 Revision, Highlights, 2007. Working Paper No ESA/P/WP.202.
- Vajta G, Holm P, Greve T, Callesen H. The submarine incubation system, a new tool for in vitro embryo culture: a technique report. *Theriogenology* 1997;**48**:1379–1385.
- Vajta G, Bartels P, Joubert J, de la Rey M, Treadwell R, Callesen H. Production of a healthy calf by somatic cell nuclear transfer without micromanipulators and carbon dioxide incubators using the Handmade Cloning (HMC) and the Submarine Incubation System (SIS). *Theriogenology* 2004;**62**:1465–1472.
- Van Balen F. The psychologization of Infertility. In: Inhorn MC, van Balen F (eds). *Infertility Around the Globe*. London: University of California Press, 2002. 79–98.
- Van Balen F, Gerrits T. Quality of infertility care in poor-resource areas and the introduction of new reproductive technologies. *Hum Reprod* 2001;**16**:215–219.
- Van Royen E, Mangelschots K, De Neubourg D, Valkenburg M, Van de Meerssche M, Ryckaert G, Eestermans W, Gerrits J. Characterization of a top quality embryo, a step towards single-embryo transfer. *Hum Reprod* 1999;**14**:2345–2349.
- Van Voorhis BJ, Syrop CH. Cost-effective Treatment for the couple with infertility. *Clin Obstet Gynecol* 2000;**43**:958–973.
- Van Voorhis BJ, Sparks AET, Allen BD, Stovall DW, Syrop CH, Chapler FK. Cost-effectiveness of infertility treatments: a cohort study. *Fertil Steril* 1997;**67**:830–836.
- van Zandvoort H, de Koning K, Gerrits T. Medical infertility care in low income countries: the case of concern in policy and practice. *Trop Med Int Health* 2001;**6**:563–569.
- Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction. Report of a Meeting*. Geneva, Switzerland: World Health Organization, 2002a,383–385.
- Vayena E, Rowe JP, Peterson HB. Assisted reproductive technology in developing countries: why should we care? *Fertil Steril* 2002b;**78**:13–15.
- Verhulst SM, Cohlen BJ, Hughes E, te Velde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database Syst Rev* 2006;**4**:CD001838.
- Verpoest WM, Kolibianakis E, Papanikolaou E, Smits J, Van Steirteghem A, Devroey P. Aromatase inhibitors in ovarian stimulation for IVF/ICSI: a pilot study. *Reprod Biomed Online* 2006;**13**:166–172.
- Walker U, Hoffer W. Prevalence of Chlamydia trachomatis in pregnant women and infertility cases in Abeokuta, Nigeria. *Trop Med Parasit* 1989;**40**:77–81.
- Widge A. Sociocultural attitudes towards infertility and assisted reproduction in India. In: Vayena E, Rowe PJ, Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*. Geneva, Switzerland World Health Organization, 2002,60–74.
- Wiersema NJ, Drukker AJ, Dung MBT, Nhu GH, Nhu NT, Lambalk B. Consequences of infertility in developing countries: results of a questionnaire and interview survey in the south of Vietnam. *J Transl Med* 2006;**4**:54–61.
- Wolner-Hanssen P, Rydhstroem H. Cost-effectiveness analysis of in-vitro fertilization: estimated costs per successful pregnancy after transfer of one or two embryos. *Hum Reprod* 1998;**13**:88–94.
- World Health Organization. Infections, pregnancies and infertility: perspectives on prevention. *Fertil Steril* 1987;**47**:944–949.

- World Health Organization. *Infertility: A Tabulation of Available Data on Prevalence of Primary and Secondary Infertility*. Geneva: WHO, 1991,WHO/MCH/91.9.
- World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Sperm-cervical Mucus Interaction*. 4th edn. Cambridge, UK: Cambridge University Press, 1999.
- World Health Organization. *Unsafe Abortion: Global and Regional Estimates of the Incidence of Unsafe Abortions and Associated Mortality in 2000*. 4th edn. Geneva, Switzerland: WHO, 2004.
- World Health Organization. *Female Genital Mutilation*. 2005. Fact sheet No 241 (June 2000). <http://www.who.int/mediacenter/factsheets/fs241/en>.
- World Health Organization. *World Health Statistics: 2007*. Geneva, 2007. <http://www.who.int/whosis/whostat2007/en/index.html>.
- Yokoyama Y, Shimizu T, Hayakawa K. Incidence of handicaps in multiple births and associated factors. *Acta Genet Med Gemellol (Roma)* 1995; **44**:81–91.
- Zayed F, Lenton EA, Cooke ID. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild male factor infertility. *Hum Reprod* 1997;**12**: 2408–2413.
- Zegers-Hochschild F, Schwarze J-E, Galdames V. Assisted reproductive technology in Latin America: an example of regional cooperation and development. *Hum Reprod ESHRE Monograph* 2008;**5**:42–47.

Submitted on May 6, 2008; resubmitted on August 5, 2008; accepted on August 13, 2008