ISSN 0377-4910

ICMR BULLETIN

Vol. 30, No. 6-7 June-July, 2000

NEED AND FEASIBILITY OF PROVIDING ASSISTED TECHNOLOGIES FOR INFERTILITY MANAGEMENT IN RESOURCE-POOR SETTINGS

Reproductive health is a state of complete physical, mental and social well-being in all aspects relating to the reproductive system and to its functions and processes. This implies that individuals are able to have a satisfying and safe sex life, and the capacity to reproduce and the freedom to decide if, when and how often to do so. Implicit in this last condition is the right of couples to have babies of their own and the right to access appropriate health-care services that will enable them to reproduce. Infertility, therefore, is a basic component of reproductive health and its prevention and appropriate treatment, where feasible, are essential.

Infertility is a world-wide problem affecting people of all communities, though the cause and magnitude may vary with geographical location and socio-economic status. Approximately 8-10% of couples within the reproductive age group present for medical assessment, generally following two years of failed efforts to reproduce[1,2]. It is estimated that globally between 60-80 million couples suffer from infertility every year[3], of which probably between 15-20 million are in India alone. The magnitude of the problem calls for urgent action, particularly when in the majority of cases the infertility is avoidable.

In the past, medical treatment for infertility, particularly in cases of azoospermia, tubal blockage and other cases where the causes could not be defined, had not been very successful. There was little that a childless couple could do to seek effective help. Over the years with the advancement in knowledge of reproductive physiology and availability of sensitive and specific diagnostic methods, infertility management has improved considerably. A number of clinics specializing in infertility management have come up which offer a wider range of treatment options. The birth of the world's first test tube baby Louise Brown in 1978, where the oocyte was fertilized outside the body and then grown in the womb of the mother, gave new hope to a large number of infertile couples. Since then the assisted reproductive technologies (ARTs) have advanced much farther allowing parenthood to azoospermic men, women with complete tubal blockage or with endometriosis and many others who had at one time lost hope of having a baby of their own. In the United Kingdom alone, there are 76 centres performing more than 30,000 *in vitro* fertilization (IVF) cycles a year[4]. India, in spite of financial constraints, has not remained impervious to the new medical advances in ARTs[5]. India's first scientifically documented test tube baby (Harsha) was born in 1986.

Establishing facilities for assisted technologies for infertility treatment is expensive. Most of the services at present are being provided by the private sector and the benefits of these scientific advances are limited to the wealthier sections of the population. The question that arises is whether in a country of one billion people, of which a third live on or below the United Nations poverty line[6], should State-sponsored infertility management services

through the use of ARTs, be established? Or is it that until the technologies become affordable only the rich should benefit from the scientific advances? In India where a large number of infants and children die each year primarily due to the nonavailability of safe drinking water, sanitary facilities and immunization against infectious diseases how far is it ethical and practical to invest in expensive technologies to treat a condition which is not life threatening and would be required for a limited number of people? To diagnose and manage a large number of infertile cases through ARTs, particularly in a resource-poor setting, is a challenge for the health care providers. This article addresses the usefulness of ARTs, and the need and feasibility of providing such technologies for infertility management in resource-constrained countries.

Need for Treating Infertility

Infertility, whether involuntary or induced, is a distressing condition which prevents reproduction in a couple in the reproductive age. The infertility could be primary when the couple has not conceived even once or secondary when the couple has conceived at least once but is unable to conceive again for two years or more. Only up to 5% of the infertility is due to anatomical, genetic, endocrinological and immunological problems while the rest is due to preventable conditions such as sexually transmitted diseases (STDs), parasitic diseases, harmful health care practices and policies, unsafe abortions, and exposure to potentially toxic substances.

Infertility : An illness

In women, the causes of infertility include tubal disease, ovulatory dysfunction, endometriosis, immunological factors, congenital abnormalities and sexual dysfunction or it could be unexplained. Based on the diagnostic criteria established by the WHO, data from 8,456 couples, from 34 centres in 25 developed and developing countries, diagnosed with infertility problems showed that in women tubal occlusion and other tubal abnormalities contributed the most (almost 41%) to infertility[7], which is often a result of chronic pelvic inflammatory disease caused by different infections including STDs (gonorrhoea, and chlamydia infections), abdominal tuberculosis, post-partum and post-abortion infections. Tubal-factor infertility is the single cause among 85% infertile couples in Africa, 44% in Latin America, 39% in Asia and 36% in developed countries[8].

The endocrine causes such as anovulatory oligomenorrhoea, amenorrhoea with normal or low endogenous gonadal and pituitary hormones, and anovulation and irregular cycles were the second most common cause (38%) of female infertility[7]. In about 35% of women, the cause of infertility was categorised as unexplained. This group with no demonstrable cause could have some women with pelvic adhesions, tubal abnormalities or endometriosis as laparoscopy was not done.

In males, no demonstrable cause is by far the most common diagnosis seen in almost half the infertile men. Some studies have even reported no specific cause in as many as 80% of infertile men[9] and sperm dysfunction in 24 % cases[10]. This probably is a reflection of the lack of knowledge of male reproductive physiology and pathology.

A study carried out under the aegis of the WHO showed that among 6,000 infertile couples surveyed, the male factor infertility was identified in 51.1% couples[11]. Male factor infertility reflects a variety of pathogenetic factors, predominantly defective sperm production, sperm dysfunction and impaired transport[12]. Defective spermatogenesis may be due to pituitary disorders, genetic factors, testicular cancer, germ cell aplasia, varicocele, certain drugs, environmental and therapeutic factors or toxins. Defective sperm morphology and deposition can be related to congenital, immunological, infective, neurogenic or psychological factors.

The underlying causes of infertility are a reflection of the socio-economic status of people, and to some extent these also depend on the geographical location[8]. In the developing countries, the incidence of induced-infertility is relatively high; being higher among the less educated people of low economic status. On the other hand, in developed countries or among individuals of higher socio-economic status, the main causes of infertility are genetical, anatomical, or endocrinological.

Infertility : A distressing condition

Infertility is not fatal but it carries with it an additional burden of social stigma and a sense of personal failure. It deprives the couple of personal happiness, unique relationship with children, the feeling of parenthood and old age security; and inflicts devastating trauma on the individual. The female partner generally feels more responsible and guilty for the problem even when the cause of infertility may be in the male. A large percentage of women feel that infertility is the worst thing that could happen to them. In some individualised societies where blood ties outside the nuclear family are not very important, the issue of infertility is confined to the couple. Having a child

is the couple's decision, without outside interference. However, in most developing countries, infertility is not a personal problem for the couple. The parents, relatives, neighbours and probably the entire community around the infertile couple are anxious and concerned.

Treatment of Infertility

The problem of infertility cannot be solely addressed by justifying and pushing adoption at the infertile couple who is already under immense psychosocial pressure. That the planet is overpopulated does not justify giving less priority to the needs of an infertile couple. The need of parenting a biological child is very intense and it is a basic right of the couple, and no amount of substitution is satisfactory and fulfilling to them.

Importance is given to tubal microsurgery especially when reversal of sterilisation is required due to the death of a child. But tubal microsurgery may be unsuccessful in previously infected tubes more so in women with tuberculosis, making ART the last choice. In male factor infertility even after various medical and surgical lines of treatment there is no marked improvement in the outcome and micromanipulation is the only hope.

These observations clearly underline the importance and need for providing ART to treat an infertile couple. However, a couple would always prefer to have a child through natural heterosexual union and natural childbirth, rather than seeking outside interference. It is therefore essential that the couples are counselled to make them aware of the compelling necessity for resorting to the use of ARTs to overcome the problem of infertility. It is also essential that the government laws ensure that the norms of ethics and safety are followed and the practitioners do not indulge in clandestine practices for commercialization of their services.

Feasibility of Treating Infertility with ARTs

Therapeutic options

With the advancements in reproductive medicine and the experiences gained through the specialised infertility management clinics a wider range of diagnostic and treatment options have become available to the infertile couple. In fact, it is now the issue of affordability which has become a deciding factor for most infertile couples.

Techniques like *in vitro* fertilization and embryo transfer (IVF-ET)[13], zygote intrafallopian transfer (ZIFT)[14], gamete intrafallopian transfer (GIFT)[15], and intracytoplasmic sperm injection (ICSI)[16] have superseded older therapies, and in some cases have provided a backup when all other therapeutic options fail.

ARTs are proving increasingly effective for the management of many types of male infertility. In fact, the technique of ICSI has almost replaced the other treatment modalities. Using this technique, one single spermatozoa recovered from the testes or epididymis, or picked up from the ejaculate of normal or deficient spermatogenesis and regardless of underlying pathophysiology, is adequate to fertilize the egg. The indications for ICSI are (i) normal sperm parameters but either less number of oocytes or oocyte defects, cryopreserved semen; (ii) abnormal sperm parameters such as oligoasthenoteratozoospermia, azoospermia, immotile spermatozoa, cryptozoospermia, oligozoospermia, testicular cancer and following its treatment, genetic defects in males; (iii) ejaculatory dysfunction; and (iv) antisperm antibodies. The obstetric outcome in ICSI pregnancies as a whole is similar to that of conventional IVF-ET pregnancies[17,18]. In male factor infertility, the obstetric outcome of ARTs is encouraging, perhaps because women undergoing ART have normal reproductive tracts.

ARTs have also proved increasingly effective in treating many types of female infertility. IVF-ET was initially applied successfully in patients with fallopian tube block. More recent studies show that GIFT establishes more pregnancies in patients with unexplained infertility than natural intercourse. GIFT is effective in women over the age of 40. It is less valuable with low quality semen. Even in certain conditions where infertility can be treated by specific management *eg*. hormonal and surgical treatments for endometriosis, specific therapies to induce ovulation in anovulatory woman and tubal microsurgery to correct mechanical pelvic disorders, most cases will benefit by ovarian stimulation accompanied by one or other of the gamete manipulation procedures.

Success rate with ARTs : Global status

There is no reliable means to predict whether the use of ARTs will be successful and after how many attempts. The facilities available and the skills of the embryological and clinical staff are the major determining factors in the 'take-home baby rate'. Ovarian stimulation protocols used, the technique of collection and handling of eggs, preparation of spermatozoa prior to fertilization, optimal conditions of embryo growth, endometrial preparation, embryo

replacement, and luteal phase support are a number of factors which determine the pregnancy rate. In addition, the duration of infertility, the age of the mother, quality of the germ cells, number of embryos transferred and the ART procedure followed contribute to the take-home baby rate.

When the IVF-ET is performed in women with tubal infertility the take-home baby rate per cycle varies between 20 to 30%. Analysis of 2,500 couples, aged 25-29 yr, undergoing 4,777 IVF-ET cycles showed a cumulative pregnancy rate of approximately 60% over up to six cycles[19]. This pregnancy rate compares with the chances of pregnancy in a normal couple having unprotected sex two or three times a week in six months. The age of the mother had a profound influence on the pregnancy rate. Analyses of the relationship between maternal age and pregnancy in 767 clinical pregnancies established at Bourn Hall showed a drop in pregnancy rate form 24.4% in women between 30 and 34 yr to 14.7% in women above 40 yr of age[20]. The number of ova retrieved, fertilized and cleaved embryos decreased with increasing age of the women[21]. These observations suggest that lower pregnancy rate and the poorer obstetrics outcomes in older mothers are due to the quality of the gametes rather than endometrial receptivity.

The pregnancy rates following GIFT or ZIFT compare well with that of IVF-ET[22]. Some reports even claim higher take-home baby rate with ZIFT as compared to IVF-ET or GIFT[23]. The association of gametes or embryos in the fallopian tube with some yet unidentified factors has been thought to enhance their fertilizing ability as well as the chances of implantation. However, some reports are contradictory and do not substantiate that ZIFT provides higher pregnancy rate compared to IVF-ET[24]. GIFT is less valuable with semen of low quality.

The European Society of Human Reproduction and Embryology (ESHRE) Task Force analysed the outcome of 13,666 ICSI cycles in 1994 performed by 90 centres in 24 countries. A total of 807 children were born, 763 using ejaculated spermatozoa, 36 using epididymal spermatozoa and 8 using testicular spermatozoa. Sperm morphology did not affect fertilization or implantation rates during ICSI[25]. The results are reassuring that infertility due to various male factors can be treated by using ARTs. The outcome of the children born after ICSI is also a testimony to the immense advances in our knowledge of reproductive medicine.

Safety issues

Since the birth of the first IVF-ET baby in 1978, more than half-a-million babies have already been born all over the world using various ARTs. The children born through the use of assisted technologies are healthy and normal. However, the incidence of preterm deliveries and low birth weight are significantly high[26]. This could be because many ART pregnancies are multiple pregnancies.

The incidence of congenital malformation in IVF pregnancies ranges between 2 to 3% world-wide and is similar to that in babies born following natural conception[27]. There is an increased risk of *de novo* chromosomal abnormalities in ICSI pregnancies[28]. There is no increased risk of congenital anomalies in pregnancies following cryopreservation of embryos[29]. The development of children born through the use of ART is comparable to that of naturally conceived children. The increased incidence of congenital malformation reported in some cases following assisted human conception, could be on account of the fact that the women who become pregnant are usually older than their peers who conceive otherwise. It is therefore essential to counsel the couple of the possibility of higher risk.

Indian Experiences with ARTs

The need for establishing ARTs to restore fertility in tubectomized women, in whom microsurgical reanastomosis of the tube was not successful, was realised as early as 1982 by the Institute for Research in Reproduction (IRR), and the Department of Obstetrics and Gynaecology of the K.E.M. Hospital, Mumbai. In the absence of previous experiences with embryological and surgical procedures, it was not until 1985 that a full-fledged IVF-ET programme could be launched. The first conception under this programme occurred in December 1985, followed by the birth of India's first documented IVF-ET baby in 1986[5]. Soon thereafter, the two institutions also standardised the technique of GIFT, resulting in the birth of India's first GIFT baby in 1988[30]. In addition to these two institutions, a number of private ART Centres started extending services in Mumbai with good success.

The standardization of ARTs in India followed by the birth of babies using such technologies heralded an upsurge of interest in the treatment of infertility and gave new hopes to many infertile couples. The establishment of ART facilities in India also opened up new vistas for research in human reproduction by studying body fluids, cells and tissues which became available by this programme. Unfortunately, the two institutions could not continue with the programme of providing ART services.

Adoption of appropriate strategy for inducing superovulation is most crucial for the ART success. The

drugs used for the purpose should produce sufficient number of high quality ova which could produce healthy embryos, some of which could be transferred and others preserved for possible later use. Over the years, different ovarian stimulation protocols were tried.

During the initial phase (from January 1986 to 1989), controlled ovarian hyperstimulation (COHS) protocol was used. It included administration of clomiphene citrate (CC) from day 3 to 7 of the menstrual cycle, followed by human menopausal gonadotrophin (hMG) from day 5 till optimum stimulation was achieved, followed by a single dose of human chorionic gonadotrophin (hCG) to induce ovulation. Using this protocol, a number of IVF cycles had to be discontinued because of spontaneous premature luteinization of follicles.

In the second phase (during 1990-1995), treatment with human gonadotrophin releasing hormone (GnRH) was introduced with the objective of inducing a state of hypophyseal desensitization to avoid aberrations of endogenous LH activity and premature LH surges. Treatment with GnRH, hMG followed by hCG was used in three different protocols namely short, ultra-short, and the long. The short protocol involved administration of GnRH agonist from day 1 and hMG from day 2 of the menstrual cycle. In the ultra-short protocol the duration of treatment was further reduced, GnRH agonist was administered for the first 3 days and hMG treatment was initiated from day 2 of the menstrual cycle. Treatment with hMG, in both protocols, was continued until the development of optimal follicular size, this was then followed by 10,000 IU of hCG. In the long protocol, GnRH agonist is given from day 23 of the previous cycle and hMG from day 2 or 3 of the menstrual cycle. Longer treatment with GnRH had an additional advantage of ensuring ovarian quiescence and complete suppression of FSH and LH in most of the women (Table).

The results in terms of follicular recruitment, growth, fertilization rate and occurrence of pregnancy were better in patients treated with hMG and GnRH in the long protocol. The incidence of cycle cancellations also diminished significantly.

Another significant change to improve the pregnancy rate was the stage of embryo development at the time of transfer. Until March 1999, 2-8 cell stage embryos were transferred on day 2 or 3 of ovum pick-up. However, since April 1999, blastocysts are being transferred on day 5, 6 or 7 of ovum pick-up, which has resulted in higher pregnancy rates.

IVF-ET, IVF with GIFT and other procedures have been carried out at the Inkus IVF Centre, Mumbai on 5251 cycles during the initial four years (IVF-ET 3622, IVF+GIFT or only GIFT 1005, and ICSI 624). The average take-home baby rate was 24%. The take-home baby rate on the cycles performed during the last two years has been 32%, which is comparable to the best centres in the world.

Table : Ovarian stimulation protocol in relation to ovum pick-up rate (procedures performed at the Inkus IVF Centre, Mumbai)

	Protocol Used			
	CC+hMG+hCG	GnRH+hMG+hCG		
		Short	Ultra-short	Long
Cycles performed	824 (100%)	1,718 (100%)	655 (100%)	2,004 (100%)
Cancellations	24 (2.9%)	18 (1.1%)	15 (2.3%)	3 (0.1%)
Ovum pick-up	800 (97.1%)	1,700 (98.9%)	640 (97.7%)	2,001 (99.9%)

CC : Clomiphine citrate; hMG : Human menopausal gonadotrophin; hCG : Human chorionic gonadotrophin; GnRH : Human gonadotrophin releasing hormone

The authors also have experience with 624 ICSI cycles, performed during January 1997 to June 1999, which include 89% using ejaculatory, 7.7% epididymal and 3.3% testicular spermatozoa. Successful microinjection was performed in 95% of the oocytes selected for ICSI. The fertilization rate (2 pronuclear stage) of the injected oocytes was 70.2%. The clinical pregnancy rate was 43% of which 17.1% ended in first trimester abortion and 3.4% in ectopic pregnancy. There was one still birth due to pregnancy induced hypertension. Major malformation was seen in three (2.1%) children requiring surgical intervention.

Of the total 5251 cycles attempted 1225 babies (591 girls, 634 boys) were born, of which 1029 conception cycles had singletons, 78 twins, 33 triplets and 2 cycles quadruplets.

Although there has not been an increased incidence of foetal malformation following ART per se, there is always a possibility that genetic abnormalities responsible for infertility in a couple could be transmitted to the child born through the use of ARTs. Eleven children out of the 1225 born had some foetal abnormalities, of which 7 had chromosomal abnormalities, 1 each exomphalos, hair-lip palate, meningocele and one haemophilia. It is therefore mandatory to incorporate the facility of prenatal genetic

diagnosis in ART centers. These procedures will prevent unseen congenital abnormalities in a child born following *in vitro* techniques of reproduction.

Economics of ARTs

In the UK, considering the prevalence of infertility among couples of reproductive age and those which require the use of ARTs to treat infertility, it has been estimated that 40 IVF cycles need to be performed per year for a population of 100,000 people[31,32]. Of these 40 cycles, 8.1 cycles per 100,000 population were funded by the State during 1994-95. In the UK provision of IVF is of the order of 80% private to 20% National Health Service. In India, even if the magnitude of infertility management need is equated to that of the UK, it is estimated that for a population of one billion approximately 400,000 IVF cycles will need to be performed annually. This highlights the need for a large number of well equipped ART centres all over the country.

Currently, in India most of the facilities for infertility management, through the application of assisted technologies, are offered through the private sector in some metropolitan cities. It is estimated that the cost per cycle, with a take-home baby rate of just 20-30%, is between Rs.50,000 to Rs.75,000 (US $ 1,200-1,800), which is in addition to the subsequent obstetric costs. These high costs are the consequence of expensive infrastructure, drugs required for inducing multiple ovulations and maintenance expenses. In addition, the infertile couple has to go through stress, agony and loss of time which are difficult to quantitate.

One has to view these expenses in relation to the overall health care costs involved in managing an infertile couple. The pregnancies generated by sub-fertile couples have a higher morbidity, than the general population, with increased early pregnancy wastage (around 30%) and increased late pregnancy complications (in particular multiple pregnancies, pre-term labour, low birth weight infants and complex deliveries). Overall, the perinatal mortality is double that of the general population for singleton births and there is a concomitant increased requirement for neonatal intensive care facilities.

It should be realised that the availability of ART could also reduce the congenital abnormalities and in fecundity preservation within communities, where social changes have led to significant fall in net reproduction rate

Strategies for Making ART Affordable

The usefulness and need for providing ART for fertility management is evident, however, the drawback is the cost factor. Infertility is not a life threatening condition and ART is not a life saving treatment modality. From the ethical point of view, no infertile couple who could have a child through the use of available technologies should be denied the treatment regardless of the cost involved. But one is always reminded of the scarce resources and health-related priorities. Nevertheless, it is essential that the ARTs are easily accessible at affordable costs.

Today the take-home baby rate in the best centres is between 20-30% per cycle and the cumulative pregnancy rate at the end of four attempts is between 60-70%. Although this pregnancy rate compares well with the natural method, the cost to the couple to undergo four attempts is exorbitant.

The private ART setups available today, mainly in the cosmopolitan cities, have the latest state of the art facilities. Interaction between such private clinicians and the government organizations could be worked out in a manner which is complimentary to each other. Exchange of expertise or technologies between these institutions might help to reduce costs. This would also ensure optimum utilization of equipment as well as talent *eg.* a private ART centre may perform an IVF cycle for a patient who cannot afford it, while the government setup may extend services for prenatal genetic diagnosis to the Centre. Another aspect worth considering could be sharing of equipment which would not only help in cutting costs but also ensure optimum utilization.

Most of the equipment and the supplies including drugs used at the ART centres are imported. Development of indigenous technologies, pooling of some of the supplies and waiving of import duties might help in curtailing the expenses.

Setting up of satellite IVF centres is another way of cutting costs. In this approach, the ovum pick-up can be done at small peripheral centres or governmental institutions and the ova transported to a well equipped IVF laboratory at a private or public centre, where further procedures can be performed. This may also lead to optimal utilization of equipment and subsidisation of the costs.

Intravaginal culture of gametes using a cryotube has been evaluated as a cost-effective method of IVF.

However, the pregnancy rate with intravaginal method was less as compared to other ARTs. Nevertheless, transvaginal culture system offers a simplified method of transporting oocytes and sperms to centres where well established ART facilities are available. This approach still needs to be further developed.

Cryopreservation of gametes and fertilized eggs is an additional adjunct to ARTs as it offers the advantage of storage of excess embryos avoiding the need for repetitive hyperstimulation of ovarian functions, egg collection and reducing the incidence of multiple births and their sequelae. Establishing facilities for cryopreservation of embryos should substantially reduce the average cost per cycle.

The high costs involved in ART services could also be reduced by following up the natural cycles rather than stimulated cycles. Stimulated cycles have the advantage of offering a number of eggs which could be cryopreserved for subsequent use. Nevertheless, natural cycle IVF is often credited with being simple and inexpensive as ovarian stimulation as well as cryopreservations are avoided. In addition, natural luteal phase may be superior to that arising after ovarian stimulation. The take-home baby rate with natural cycle has been reported to be between 12 to 22%. The success of the natural cycle IVF would be improved if mature oocytes could be collected from the several growing follicles in addition to the dominant follicle. This method might be suited for patients with polycystic ovarian disease because several follicles can be collected from them. Natural cycle IVF might also be best for highly fertile women below the age of 40 years.

In addition to reducing the costs involved in providing ART to infertile couples, the government institutions should also initiate the provision of services. Such hospitals, can have three or four tier service charges as is routinely done for other services offered at the hospitals. Those who can afford to pay would compensate to some extent for the needy. This can be done in conjunction with some charitable institutions or private sector which are willing to help the needy.

The government centres can also consider incorporating teaching programmes for ART as a form of super specialised course and the fees from the students or trainees can be utilised as corpus fund for the treatment of poor patients. The insurance sector should also recognise infertility management through the use of ART in its schemes and reimburse the medical expenses involved. Better understanding of the reproductive physiology may help increase the success rate per cycle and consequently reduce the average cost per take-home baby. Eventually only those who genuinely cannot afford the costs should be allowed access to the subsidised treatment.

Conclusions

A number of ARTs have been developed which allow parenthood to azoospermic men, women with complete tubal blockage, cases of endometriosis and many others who had at one time lost hope of having a baby of their own. India has not remained impervious to such new medical advances. The first scientifically documented test-tube baby was born in India in 1986 and since then the average take-home baby rate with various techniques ranges between 20-30 % per cycle which is comparable to that of the best ART centres in the world.

Currently, in India, ART services for infertility management are offered through the private sector in some of the metropolitan cities. The high costs involved in offering such services are the consequence of expensive infrastructure, drugs required for inducing multiple ovulations and maintenance expenses. The benefits of these scientific advances are limited to only the wealthier sections of the population. It is therefore essential to reduce the costs involved in offering ART so that all the infertile couples could reap the benefits of newer technologies. It is also essential to make efforts to eliminate the preventable causes of infertility.

References

1. World Health Organization. Recent advances in medically assisted conception. *WHO Tech Rep Ser, 820* : 2, 1992.
2. The ESHRE Capri Workshop. Infertility revisited : The state-of-the-art today and tomorrow. *Hum Reprod 11* : 1779,1996.
3. World Health Organization. *The World Health Report, 1996*, WHO, Geneva, p 12, 1996.
4. Human Fertilisation and Embryology Authority (HFEA). *Annual Report 1997*, HFEA, London, p 1, 1997.
5. Anand Kumar, T.C. *In vitro* fertilization and embryo transfer in India. *ICMR Bull 16* : 41, 1986.
6. *Year Book 1995-96. Family Welfare Programme of India*. Department of Family Welfare, Ministry of Health and Family Welfare, Government of India, p 64, 1997.

7. Rowe, P. J. and Farley, T.M.M. The standardized investigation of the infertile couple. In : *Diagnosis and Treatment of Infertility*. Eds. P.J. Rowe and E.M. Vikhlyaeva. Hans Huber Publishers, Toronto, Stuttgart, p 55, 1988.

8. Farley, T.M.M. and Belsey, F.H. The prevalence and etiology of infertility. In : *Biological Components of Fertility*. Proceedings of the African Population Conference, Dakar, Senegal. International Union for the Scientific Study of Population, 1:2.1.15, 1988.

9. Baker, G.H.W., Burger, H.G., de Kretser, D.M. and Bryan, H. Relative incidence of etiological disorders in male infertility. In : *Male Reproductive Dysfunction*. Eds. R.J. Santen and R.S. Swerdloff, Marcel Dekker, New York, p. 341, 1986.

10. Hull, M.G.R., Glazner, C.M.A., Kelly, N.J., Conway, D.I., Foster, P.A., Hinton, R.A., Coulson, C., Lambert, P.A., Watt, F.M. and Desai, K.M. Population study of causes, treatment and outcome of infertility. *BMJ 291* : 1693, 1985.

11. Comhaire, F.H., Kretser, D., Farley, T.M.M. and Rowe, P.J. Towards more objectivity in diagnosis and management of male infertility. Results of a World Health Organization multicenter study. *Int J Androl 10 (Suppl 7)* : 1, 1987.

12. Dubin, L. and Amelar, R.D. Etiologic factor in 1294 consecutive cases of male infertility. *Fertil Steril 22* : 469, 1971.

13. Steptoe, P.C. and Edwards, R.G. Birth after the re-implantation of a human embryo. *Lancet ii* : 366, 1978.

14. Devroey, P., Braekmans, P. Smitz, J., Waesberghe, L.V., Wisanto, A., Van Steirteghem, A.C., Heytens, L. and Comu, F. Pregnancy after translaparoscopic zygote intrafallopian transfer in a patient with anti-sperm antibodies. *Lancet i* : 1329, 1986.

15. Cha, K.Y., Koo, J.J., Ko, J.J., Choi, D.H., Han, S.Y. and Yoon, T.K. Pregnancy after *in vitro* fertilization of human follicular oocytes collected from non-stimulated cycles, their culture *in vitro* and their transfer in a donor oocyte transfer program. *Fertil Steril 55* : 109, 1991.

16. Palermo, G., Joris, H., Devroey, P. and Van Steirteghem, A.C. Pregnancies after intracytoplasmic injection of a single spermatozoon into an oocyte. *Lancet 340* : 17,1992.

17. Van Steirteghem, A.C., Nagy, Z., Joris, H., Liu, J., Staessen, C., Smitz, J., Wisanto, A., and Devroey, P. High fertilization and implantation rates after intracytoplasmic sperm injection. *Hum Reprod 8* : 1061, 1993.

18. Payne, D., Flaherty, S.P., Jefferey, R., Warnes, G.M. and Mathews, D. Successful treatment of severe male factor infertility in 100 consecutive cycles using intracytoplasmic sperm injection. *Hum Reprod 8* : 2051, 1993.

19. Tan, S.L., Steer, C., Royston, P., Rizk, B., Mason, B.A. and Campbell, S. Conception rates and *in vitro* fertilization (Letter). *Lancet 335* : 299, 1990.

20. Steptoe, P.C., Edwards, R.G. and Walters, D.E. Observations on 767 clinical pregnancies and 500 births after human *in vitro* fertilization. *Hum Reprod 1* : 89, 1986.

21. Sharma, V., Riddle, A., Mason, B.A., Pampiglione, J. and Campbell, S. An analysis of factors influencing the establishment of a clinical pregnancy in an ultrasound based ambulatory *in vitro* fertilization program. *Fertil Steril 49* : 468, 1988.

22. Menezo, Y.J.R. and Janny, L. Is there a rationale for tubal transfer in human ART? *Hum Reprod 11* : 1818, 1996.

23. Yovich, J.L., Yovich, J.M. and Edrisinghe, W.R. The relative chance of pregnancy following tubal or uterine procedures. *Fertil Steril 49* : 858, 1988.

24. Tournaye, H. Tubal embryo transfer. *Hum Reprod 12* : 631, 1997.

25. ESHRE Task Force on Intracytoplasmic Sperm Injection. Assisted reproduction by intracytoplasmic sperm injection : A survey on the clinical experience in 1994 and the children born after ICSI, carried out until 31 December 1993. *Hum Reprod 13* : 1737, 1998.

26. Rizk, B. The outcome of assisted reproductive technology. In: *In Vitro Fertilization and Assisted Reproduction*. Ed. P.R. Brinsden, The Parthenon Publishing Group, New York, p 311, 1999.

27. Gillerot, Y., Jauniaux, E., van Maldergem, L. and Fourneau, C. Pathogenesis of human malformations. In : *The First Twelve Weeks of Gestation*. Eds. E.R. Barnea, J. Hustin and E. Jauniaux. Springer-Verlag, Berlin, p 328, 1992.

28. Abdalla, H.I. and Rizk, B. Intracytoplasmic sperm injection. In : *Assisted Reproductive Technologies*. Eds. H.I. Abdalla and B. Rizk. Oxford Health Press,Abingdon, p. 57, 1999.

29. Bonduelle, M., Wilikens, A., Buysse, A., Assche, E.V., Wisanto, A., Devroey, P., Steirteghem, A.C. and Liebaers, I. Prospective follow up study of 877 children born after intracytoplasmic sperm injection (ICSI), with ejaculated, epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI. *Hum Reprod 11 (Suppl 4)* : 131, 1996.

30. Anand Kumar, T.C., Puri, C.P. Gopalkrishnan, K. and Hinduja, I.N. The *in vitro* fertilization and embryo transfer (IVF-ET) and gamete intrafallopian transfer (GIFT) program. *J IVF-ET 5* : 376, 1988.

31. National Infertility Awareness Campaign. Reports of the Third and Fourth National Surveys of NHS Funding of Infertility Services. College of Health, London, p 1, 1995.

32. Seibel, M.M., Zilbertein, M. and Kearnan, M. *In vitro* fertilization and health care coverage. *Lancet, 345* : 66, 1995.

This article has been contributed by Dr. Chander P. Puri, Deputy Director (Sr. Grade), Institute for Research in Reproduction, Mumbai, Dr. Indira Hinduja and Dr. Kusum Zaveri of the Inkus IVF Centre, Mumbai, India.

Printed and Published by Shri J.N. Mathur for the Indian Council of Medical Research, New Delhi
at the ICMR Offset Press, New Delhi-110 029
R.N. 21813/71