

Symposium Highlights

Highlights of the International Symposium on "Recent Advances in the Management of Infertility: Multi-Disciplinary Approach

Alexander E Omu, Majedah K Al-Azemi, Ma'asouma Makhseed,
Eyad Al-Saleh, Hazem Al-Rumaih, Laila Ashkanani, Jehad Al-Harmi

Department of Obstetrics and Gynaecology, Faculty of Medicine, Kuwait University and Maternity Hospital, Kuwait

Kuwait Medical Journal 2002, 34 (2): 161-165

INTRODUCTION

An estimated 10-15 percent of couples worldwide, within the reproductive age group, have infertility problems. Irrespective of differences in culture and traditions, the persistent inability of the couple to have a child poses serious psychological stress to the couple, their marriage and the relationship between the spouses and their close relations. Both spouses can now be thoroughly investigated to highlight the contribution of both male and female factors to infertility. Assisted reproductive technology (ART) is now available in many countries worldwide. Since the first successful performance of artificial insemination with donor (AID) semen in 1884, considerable advances have taken place in the practice of AID worldwide. For religious reasons, only artificial insemination with husband (AIH) sperm is allowed in many Mid-eastern countries. Steptoe and Edwards who performed oocyte collections under direct vision using a laparoscope, initially for tubal blockage, first described the technique of in-vitro fertilization and embryo transfer. This resulted in the birth of Louise Brown in 1978. Since then, there has been a flurry of activities in research in assisted reproductive technology (ART) techniques in the management of infertility. Other indications later included endometriosis and immunological factors, Oligozoospermia and unexplained infertility. Many new therapeutic strategies have been developed with formidable impact on the treatment outcome. Some of these strategies include Gamete intrafallopian transfer (GIFT), Zygote intrafallopian transfer (ZIFT), Pronuclear stage transfer (PROST) and Tubal embryo transfer (TET), and more recently, Intracytoplasmic sperm injection (ICSI). In parallel with the development of

these therapeutic techniques, is the evolution of new techniques of induction of ovulation (superovulation) and retrieval or harvesting of ova in the woman, and testicular and epididymal spermatozoa aspiration or by biopsy.

The cryopreservative effect of glycerol in the preservation of spermatozoa, was discovered by Polge and associates in 1949. In 1953, the first pregnancy obtained using cryopreserved sperm with dry Ice method was reported by Bunge. In 1963, Sherman described the use of liquid nitrogen vapour to freeze sperm with achievement of pregnancies.

As progress in technological knowledge advances in the management of infertility, ethical considerations have inevitably surfaced. There are real concerns about the cost of some of the investigations and techniques, which should be offered as treatments and the outcome of genetic mutations of the offspring of individuals who have been successful with ART. Another area that calls for strict surveillance and monitoring is induction of ovulation. The resultant complications of ovarian hyperstimulation syndrome, high order multiple pregnancy and preterm delivery, are life threatening and consume huge amounts of financial resources. The symposium on "Recent Advances on the Management of Infertility" was, therefore, timely in Kuwait.

The Objective of this review is to discuss the highlights of the international symposium on "Recent Advances on the Management of Infertility: A multi-disciplinary approach" organized by the Department of Obstetrics and Gynaecology, Faculty of Medicine, Kuwait University, Kuwait, between March 8-11, 2002.

Address correspondence to:

Dr. Alexander E. Omu, FRCOG, Professor and Chairman, Department of Obstetrics & Gynecology, Faculty of Medicine Kuwait University, PO Box 24923, Safat-13110, Kuwait. Fax 965 531 8906, e-mail : omu@hsc.kuniv.edu.kw

OPENING CEREMONY

On March 9, 2002, the opening ceremony of the International symposium on "Recent Advances in the Management of Infertility" was held at the Sheraton Hotel, Kuwait. The August occasion was graced with the magnificent presence of His Excellency, The Honourable Minister of Health, Dr. Mohammed Al-Jarallah, the Rector of Kuwait University, Professor Faiza Al-Khorafi and Professor Abdullatif Al-Bader, Dean of the Faculty of Medicine, Kuwait University. This cooperative trilogy underscores the significance of the theme of the symposium. From their respective addresses, it was obvious the authorities are concerned about the problems of infertility management locally and worldwide and exhorted participants at the symposium to evolve strategies of resolving them. Many dignitaries from Kuwait and abroad were also in attendance.

OVERALL PARTICIPATION

Six international guest speakers and experts from Canada, United Kingdom, Belgium, France, Italy, and Egypt and over twenty local speakers from the Faculty of Medicine, Kuwait University and the Ministry of Health presented both clinical and scientific research data during the symposium. On the whole, over three hundred scientists and clinicians from Kuwait and abroad participated in the symposium. There were about forty-seven presentations during the three days of the symposium. The pre-symposium workshop entitled "Investigating Infertility" was held at the premises of Faculty of Medicine in Jabriya, on March 8, 2002. The main objective of the pre-symposium workshop was to lay down a solid base of appreciation of adequate, timely and scientifically sound clinical evaluation of the infertile couple. In addition, like andrological and endocrinological investigations and imaging with ultrasound, computerized tomography scan and magnetic resonance imaging (MRI) and Y chromosome microdeletion assessment should be cost effective. Over two hundred clinicians participated in the didactic and hands-on sessions in techniques of semen analysis, laparoscopy, polymerase chain reaction, Y chromosome microdeletion evaluation, research techniques in reproductive health and ultrasonography.

Scientific sessions of the first day: Aetiology of Infertility

The symposium was a melting point of both reproductive science and reproductive medicine. The tremendous contribution of basic sciences like genetics, molecular and cell biology, developmental biology, neuroendocrinology, and pharmacology to

reproductive medicine was ostensibly evident throughout the three days of the meeting. It was obvious that basic science concepts have now become an integral part of daily clinical activities in reproductive medicine. One such earth breaking advance in clinical application is the initiation and continual advances in In vitro Fertilisation (IVF) and Egg Transfer (ET) and the recent applications like intracytoplasmic injection (ICSI). This has made the specialty one of the most dynamic in modern medicine. It was no surprise therefore, that the keynote address was titled "What have we achieved after two decades of ART?" by the world-renowned expert on assisted reproductive technology (ART), Professor Andre Van Steirteghem of Dutch speaking University of Brussels, Belgium. He charted the historical trail of in-vitro fertilization and egg transfer, from the birth of Louis Brown, through the work of Mr. Steptoe and Professor Edwards to advances such as microinjection, and intracytoplasmic sperm injection (ICSI). The rest of the first day of the meeting focused on causal factors of infertility in general, such as disorders of hypothalamo-pituitary-ovarian axis. Whereas polycystic ovarian syndrome (PCOS), giving rise to anovulation, is a very common cause of infertility accounting for 40.9 percent of infertility in Kuwait, infective tubal factor occurred in 5.9 percent of the patients. The role of inhibin and activin in reproductive medicine, including recurrent pregnancy loss was also discussed. Knowledge begets knowledge. New scientific and clinical frontiers are opening up. Progress has been reported in in-vitro maturation of the female and male germ cells. Better understanding of the role of growth factors, cytokines and the signaling pathways is mandatory. Knowledge is still cloudy about how these factors affect gene expression in germ cell maturation, syngamy and morula and blastocyst differentiation, other preimplantation events and the process of implantation itself. An overview of cytokines as crucial effector molecules and the possible immunological basis of repeated pregnancy loss and pre-eclampsia and the effect of immunoglobulin therapy on women experiencing recurrent pregnancy loss, were timely.

Scientific sessions of the second day: Genetics and endocrinology of Infertility

Since the description of the double helix structure of DNA by Watson and Crick in 1953, there has been an avalanche of discoveries in the molecular function of the normal and abnormal germ and somatic cells. The first session of the second day of the symposium was, therefore, devoted entirely to "Genetics of Infertility". Chromosomal anomaly is one of the major causes

of both male and female infertility. Aneuploidy of X chromosome in females and mosaics for X chromosome is one of the major causes leading to infertility, repeated pregnancy loss and reduced reproductive fitness, as well as an increased risk of aneuploidy in the offspring. A genetic defect could be suspected in all idiopathic cases of azoospermia, oligozoospermia, asthenozoospermia or teratozoospermia. About fourteen Percent of azoospermic men and five percent of severe oligozoospermic men are carriers of chromosomal abnormalities. The incidence of Y chromosome microdeletions is now known to be 10-15 percent in idiopathic azoospermia and 5-7 percent in oligospermic men in the AZFa, AZFb and AZFc regions. Of great concern is the high risk of carriers of genetic anomalies by ICSI candidates affected by severe oligo- or azoospermia and potential risk of transmission to the offspring. Adequate counseling was therefore advocated. Since congenital bilateral absence of vas deferens (CBVD) is responsible for 1-2 percent cases of male infertility, the association with cystic fibrosis, a severe disorder caused by mutations in CFTR gene, was of great interest. The selection of healthy embryos for implantation during ART, in order to avoid offspring with chromosomal anomalies, is therefore important and obviously necessary. Comparative Genomic Hybridization (CGH) is a powerful technique in determining chromosomal copy number in tissues and cell, by simultaneous hybridization of test and reference DNA to normal metaphase chromosomes.

The role of metal ions in fertility and lipid peroxidation was illustrated with the influence of magnesium on the vas deferens and sperm transport. The mechanism by which unilateral testicular torsion of the testis and its treatment by detorsion causes contralateral testicular damage and affect fertility, may involve the generation of toxic reactive oxygen species. Unfortunately, antioxidant prophylaxis has not shown much promise. Similarly the role of nitric oxide (NO), an unstable free radical gas causes muscle and vascular relaxation, is not yet clear.

In the session on reproductive endocrinology, attention was focused on polycystic ovarian syndrome (PCOS), the most common form of anovulatory infertility, associated with menstrual disturbance and insulin resistance. An increasing body of literature has also assessed the non-fertility consequences of PCOS. The consensus is to encourage weight loss and exercise prior to commencement of fertility treatment. Precisely designed endocrine treatment methods during the preconception and pregnancy period are said to be

cornerstone for achieving the expected fertility outcome. The guidelines suggested for management of PCOS, therefore, include (1) Weight loss (2) Correcting hyperandrogenism (3) Induction of ovulation starting with clomiphene citrate (4) Endometrial protection (5) Evaluation and confirmation and treatment of variety of metabolic abnormalities. Clomiphene citrate is the gold standard of induction of ovulation. About 15 percent of women with PCOS do not respond to the maximum dose of clomiphene citrate of 150-200 mg and are therefore branded as being clomiphene resistance. A good number of these women benefit from induction of ovulation with gonadotropins (70-80 percent) and ovarian electro-cautery (80 percent) or gonadotropin releasing hormone (GnRH) analogues. The association between PCOS and obesity was not lost on the participants. Obesity has become an escalating epidemic endocrine disease with an increasing burden of obesity related chronic diseases with insulin resistance and hyperinsulinaemia, hyperandrogenaemia, altered gonadotropin secretion, decreased sex hormone binding globulin and growth hormone. It is of great concern that in Kuwaiti adolescent girls, the body mass index (BMI) exceeds that of the standard in every age. Health education programmes have therefore been advocated to control this syndrome to prevent future risks of infertility and consequences of metabolic disorders. The other endocrinopathy discussed was the disorder of prolactin secretion, which is tenuously linked to impairment of thyroid function. Hyperprolactinaemia accounts for 14 percent of endocrinopathy leading to infertility in Kuwait. In addition to the symptoms of oestrogen deficiency and infertility, visual defects, persistent headaches and personality changes are some of the symptoms that cause concern. Advances in CT scan and enhanced magnetic resonance imaging have greatly contributed to early and precise diagnosis of prolactinomas. The first line therapy is dopamine agonists like bromocriptine and cabergoline with restoration of ovulation in 80 percent of women with hyperprolactinaemia and they are known to be safe even during pregnancy.

Scientific sessions of the third day: ART and the Complications, and controversial issues

In the session on assisted reproductive technology, the drugs used for induction ovulation were reviewed. The role of insulin sensitizers, like glucophage, was emphasized. Conventional in-vitro fertilization (IVF) has been quite successful in the treatment of infertility, especially for female factor or idiopathic

infertility. Intracytoplasmic sperm injection (ICSI) was introduced to treat severe male factor infertility. The question was whether ICSI might be beneficial even in cases where no male factor is involved. In an auto-controlled study conducted in couples with tubal infertility and normozoospermic semen, fertilization, cleavage and implantation rates after IVF and ICSI were comparable, showing that there are no advantages using ICSI in cases of normozoospermia. Two new techniques, namely the use of sequential media has led to growth of human blastocyst and using PGD for aneuploidy screening (PGD-AS) it is now possible to analyze the ploidy status of several chromosomes of invitro-generated embryo before transfer. Aneuploidy increases with maternal age and is correlated with reduced implantation and a higher rate of abortions. An essential preimplantation event is the uterine receptivity. The role of the superfamily of Integrins and natural killer cells (NK) has engaged the fascination of many preimplantation embryologists.

One of the admirable aspects of ART is the unconscious in-built audit. In spite of the tremendous progress being continually made, there are some concerns about outcome issues of ART. Like many therapeutic modalities in medicine, there are side effects and complications associated with ART. Some of these are medical, psychological, socioeconomic and ethical issues. The two main complications of ART are multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). There is irrefutable evidence now that there is increased incidence of multiple pregnancies in association with ART with consequent increased abortion, ectopic pregnancy and preterm delivery rates. Costs of neonatal care are enormous and there are reports of developmental problems. Efforts to reduce their impact or manage them when they do occur will greatly contribute to patient satisfaction. Psychological reaction to infertility generally, to some of the investigations and to failure of ART, especially after huge expenses is rampant. Patients for infertility management particularly with ART need psychological counseling before, during and after ART procedures. Other concerns of ART is the risk of ovarian cancer after induction of ovulation and the inheritance of the genetic defects in the offspring of men with Y chromosome microdeletion after successful ICSI techniques. At the moment, there is not enough reliable data available to substantiate these reports. The benefits of assisted reproductive technology (ART) are also getting out of reach of affordability.

Infertility management is a booming market with escalating costs of ART. Sex preselection is already being practiced and the couple can choose the sex of the child they want to have. The religious and cultural attitude that was initially hostile to this procedure and ART has thawed and it is now generally favourable. Various methods of sex selection are being used. They include sperm separation by flow cytometry, preimplantation genetic diagnosis (PGD) using PCR or fluorescent insitu hybridization (FISH). Post implantation sex selection also uses chorionic villus sampling (CVS), amniocentesis or ultrasonography.

About 40 percent of preterm deliveries are caused by infection and cervical incompetence. The roles of antibiotic treatment of bacterial vaginosis and cervical cerclage and the administration of prenatal corticosteroids to reduce respiratory distress syndrome in multiple pregnancies, in improving perinatal outcome after ART, are not yet clear and therefore await the result of multicenter trials.

Controversies in Infertility Management: Panel discussion

The panel discussion on controversial issues on infertility management by experts was perhaps the highlight of the last day of the Symposium. Topics for discussion included, the need for clinical guidelines in infertility management, timing and prescription of fertility drugs, embryo transfer, cloning and costs of ART. Many doctors in the country (without professional certification and monitoring), carry out infertility management. Some practitioners start induction of ovulation as early as three months after marriage even in women with normal ovulatory cycles. Patients easily get fertility drugs across the counter in private pharmacies without a clinician's prescription. Many practitioners of ART transfer as many as four embryos in the mistaken belief that this would enhance their chances of a successful outcome. In fact, on balance, the opposite is the case. The issue of cost was of great concern. A cycle of ART treatment costs more than three thousand US dollars and some couples may need about three cycles of treatment without success. Cloning or nuclear transfer has understandably been promoted to the forefront as a political issue in many countries. At the end of a very interesting discussion, there was consensus among the experts that:

1. Infertility management should involve a multi-disciplinary team of experts including reproductive medicine physicians, embryologists, pharmacists, endocrinologists,

andrologists, geneticists, neonatologists, nursing personnel and psychologists.

2. Fertility drugs should only be dispensed with prescription duly signed by a certified reproductive medicine physician.
3. Not more than two embryos should be transferred after invitro fertilization.
4. Cloning or nuclear transfer should be encouraged for only therapeutic purposes.
5. To reduce the cost of ART, cryopreservation of oocytes or embryos should be routinely used. Secondly, natural cycles should be used in those with ovulatory cycles. In those with anovulation, Clomiphene citrate should be initially used.
6. Every reproductive medicine physician should document all activities and issues audit report periodically.
7. There should be an independent monitoring board of experts to monitor the certification of practitioners, practice of ART and routine infertility management in the country.

CONCLUDING REMARKS

This international symposium was truly multidisciplinary both in concept and content. While assisted reproductive technology (ART) has made monumental advances in giving hope to many couples with problems of infertility, there are many unanswered questions. Not all the patients have reaped the benefits of the new techniques. Successful outcome is still below 40 percent in many centres. This situation can only improve when there is a deliberate attempt to shorten the journey of scientific discoveries from the laboratory to the bedside. The start-point therefore is appreciation of the epidemiology of fertility disorders and the scientific basis, especially the role of the genetic make-up of the individual and response to internal and external environmental factors and how this may affect gene expression in

the cell. Assisted reproductive technology (ART) is now the hub of infertility management. One of the most important advances in ART is the ability to induce ovulation in anovulatory women and superovulation in controlled cycles. The latter has made cryopreservation of embryos a common practice in many IVF centers in order to reduce costs. On the thorny issue of unethical practices by practitioners and unqualified or uncertificated personnel, this symposium has recommended practice guidelines, which if adopted by the authorities will improve patients' satisfaction and the outcome of infertility management.

ACKNOWLEDGEMENT

The organizing committee thankfully acknowledge the financial support of sponsors of this international symposium; Faculty of Medicine of Kuwait University, Kuwait Institute for Medical Specialization (KIMS) and Kuwait Foundation for Advancement in Sciences (KFAS). We are also grateful to a number of companies in Kuwait, for financial and material support of the symposium. They include Ferring, Tareq Co., Yusuf Ibrahim Al-Ghanin and Co.WLL, Bayer AG and OM Pharma, Pharmacia, Averroes, Organon, Johnson and Johnson Middle East Company, Schering and Solvay and others.

REFERENCES

1. International Symposium: Recent Advances in the Management of Infertility. Book of Abstracts. Editors Omu AE, Al-Azemi MK, AL- Saleh E and Shoumer K. March 9-11, 2002. Publishers - Four Films Co. Kuwait.
2. Omu AE, Al-Qattan F, Ismail AA; Al-Taher SI, Al-Busiri N, Bandar A Causal Factors and Management Options of Infertility in Kuwait. *Med Prin. Pract* 2000; 9:131-138.
3. Al-Qattan F, Omu AE, Makhseed M, Al-Salili M, Al-Busiri N, Al-Taher S. Ismail AA. Effect of post-operative Clomiphene Citrate after Laparoscopic ovarian cautery in Clomiphene Citrate Resistant Polycystic Ovarian Syndrome. *Clinical & Experimental Obstet Gynecol* 2000 [In Press].