Atlas of
Human Assisted Reproductive Technologies

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Editor

Mangala Telang MBBS DGO MD FACOG

Senior Fellow of American College of Obstetricians and Gynecologists
President of Indian Fertility Society
Director
Fertility Research and IVF Centre
New Delhi

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  Hyderabad 500 095, Phones: +91-40-55610020, +91-40-24758498
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- "KURUVI BUILDING", 1st Floor, Plot/Door No. 41/3098-B &B1, St. Vincent Road
  Kochi 682 018, Ph: +91-0484-4036109, +91-0484-2395739, +91-0484-2395740 e-mail: jaypeekochi@rediffmail.com
- 1A Indian Mirror Street, Wellington Square
  Kolkata 700 013**,** Phones: +91-33-22456075, +91-33-22451926
  Fax: +91-33-22456075 e-mail: jpbcal@dataone.in
- 106 Amit Industrial Estate, 61 Dr SS Rao Road, Near MGM Hospital, Parel
  Mumbai 400 012, Phones: +91-22-24124863, +91-22-24104532, +91-22-30926896
  Fax: +91-22-24160828 e-mail: jpmedpub@bom7.vsnl.net.in
- "KAMALPUSHPA", 38 Reshimbag, Opp. Mohota Science College, Umred Road
  Nagpur 440 009, Phones: +91-712-3945220, +91-712-2704275 e-mail: jpnagpur@rediffmail.com

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To

My parents

Aie, Dada who gave us all they had

and Ananya,

the sparkle in my life and the future

Contributors

Mangala Telang MBBS DGO MD FACOG
Director, Fertility Research and IVF Centre
New Delhi

Ajit Saxena
MS (Delhi), FRCS (Edin), FICS, MNAMS (Urol), Dipl. Urology (London)
Senior Consultant Urologist and Andrologist,
Indraprastha Apollo Hospitals, New Delhi.

Ashok Khurana MBBS MD (Radiology)
Clinical Director, Senior Fetustician and
Consultant in Reproductive Imaging
Institute of Fertility Fulfilment and Research
New Delhi

Rupin Shah MS MCh (Urology)
Consultant Andrologist and Microsurgeon
Lilavati Hospital, Mumbai

Vijay Kulkarni MS
Consultant Andrologist and Microsurgeon
Bhatia Hospital, Mumbai

Narendra Malhotra
MD FICOG FICMCH Ian Donald Diploma
Practising Obstetrician and Gynecologist
Malhotra Test Tube Baby Centre, Agra

Arun Tewari MD
Urologist
Malhotra Test Tube Baby Centre, Agra

Jaideep Malhotra MD
Malhotra Test Tube Baby Centre, Agra

Ashok Sharma
Malhotra Test Tube Baby Centre, Agra

Hrishikesh Pai MD FCPS FICOG
Lilavati Hospital IVF Centre, Mumbai and
Batra Hospital IVF Centre, Delhi

Shilpa Shah MD DNB FCPS
Lilavati Hospital IVF Centre, Mumbai

Rishma Pai MD FCPS DNB FICOG
Lilavati Hospital IVF Centre
Mumbai and Jaslok Hospital
Mumbai

Nandita Palshetkar MD FCPS FICOG
Lilavati Hospital IVF Centre, Mumbai and Batra
Hospital IVF Centre, Delhi

Sushma Ved MD
Southend Rotunda (Centre for Human
Reproduction), Holy Angels Hospital, Vasant Vihar
New Delhi

Sonia Malik MD
Southend Rotunda (Centre for Human
Reproduction), Holy Angels Hospital, Vasant Vihar
New Delhi

Sapna Srinivas MD
Embryologist, Infertility Institute and Research
Centre, Secunderabad, Andhra Pradesh

Alok Teotia MVSc
Consultant Reproductive Biologist, Indraprastha
Apollo Hospitals, New Delhi

Sudesh A Kamat MSc
Consultant Reproductive Biologist, Leelavati Hospital
Mumbai

Vijay Mangoli MSc
Reproductive Biologist, Fertility Clinic and IVF
Centre, Mumbai

Ranjana Mangoli MSc
Reproductive Biologist, Fertility Clinic and IVF
Centre, Mumbai

Col RK Sharma MD
Senior Advisor (Obs., Gynae & ART)
Army Hospital (Research & Referal)
New Delhi

Prochi Madon
Department of Assisted Reproduction and Genetics
Jaslok Hospital and Research Centre
Mumbai

Arundhati Athalye
Department of Assisted Reproduction and Genetics
Jaslok Hospital and Research Centre
Mumbai

Nandkishor Naik
Department of Assisted Reproduction and Genetics
Jaslok Hospital and Research Centre
Mumbai

Firuza Parikh MD
Department of Assisted Reproduction and Genetics
Jaslok Hospital and Research Centre
Mumbai

H Ingolf Nielsen
MediCult a/s, Møllehaven 12, DK-4040 Jyllinge
Denmark, and Essex Fertility Centre
United Kingdom

Anne Lis Mikkelsen
The Fertility Clinic, Herlev University Hospital
DK-2730 Herlev, Denmark

NS Moorthy
Medical Director, Asia Cryo-Cell Private Limited
Chennai

GA Rama Raju
Krishna IVF Clinic, Visakhapatnam

K Murali Krishna
Krishna IVF Clinic, Visakhapatnam

G Jaya Prakash
Krishna IVF Clinic, Visakhapatnam

K Madan
Krishna IVF Clinic, Visakhapatnam

Foreword

The birth of the first human baby conceived *in vitro*, in July 1978, was not an accident. It was preceded by more than 30 years of intense laboratory and animal experimentation by innumerable scientists. From this long list, I believe that it is imperative to highlight: R Moricard, CR Austin, MC Chang, L Dauzier, C Thibault, JM Bedford, R Yanagimachi, P Soupart, BD Bavister and RG Edwards.

Dauzier and Thibault of France were the first to report on "Fertilization *in vitro* of rabbit oocyte" in 1954. Chang and Bedford confirmed their findings in 1959, following which Yanagimachi and Chang reported on "Fertilization of hamster eggs *in vitro*" in 1963. Two years later Edwards reported the "Maturation *in vitro* of mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes." The first clinician, Patrick Steptoe, entered the scene in 1968 when he started to collaborate with Edwards; this association enabled them to perform important studies using human gametes: "Early stages of fertilization *in vitro* of human oocytes matured *in vitro*" (1969), "Fertilization and cleavage *in vitro* of preovulatory human oocytes" (1970), and "Human blastocysts grown in culture" (1971).

The vision and driving force behind the human work was Bob Edwards. The first human pregnancy derived from *in vitro* fertilization (IVF) was a tubal pregnancy in 1976. The first baby conceived *in vitro* was born, by cesarean section, on July 25, 1978, just before midnight. Both events were reported by Steptoe and Edwards in the Lancet; the birth of the first IVF baby was reported immediately and with great fanfare by the world media.

During the first decade that followed this event, the IVF results remained fairly modest. The first international survey carried out in 1984 by Markku Seppala reported a delivery rate per initiated cycle of only 5.4%. This rate remained under 12% until the end of the decade. My team and I, in Vancouver, were fortunate to have the first baby conceived *in vitro* in Canada; he was born on December 25, 1983.

The nineties brought sunshine to IVF; the success rate improved gradually, and by the end of the decade the rate of delivery per initiated cycle, in the USA, reached 25.4%. In 2003, the last reported year, this rate was 28%. It is interesting to note that improvement in outcomes was realized without any change in the cancellation rate, which remained around 13 to 14%.

Intracytoplasmic sperm injection (ICSI) also started with animal experimentation by Gianpiero Palermo and co-workers. Their initial report in 1991 "Enhancement of acrosome reaction and subzonal insemination of a single spermatozoon in mouse eggs" was followed by work on human oocytes that led to a report in 1992 "Induction of acrosome reaction in human spermatozoa used for subzonal insemination". During the same year, Palermo and associates were also able to report on pregnancies in human subjects: "Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte".

The introduction of ICSI has dramatically changed treatment of male infertility. The 2003 USA results clearly confirm the results of previous years, that the delivery per oocyte pick-up (OPU) rates are fairly similar between couples with male factor and those without male factor treated with IVF plus ICSI.

The significant improvement in outcomes was due to the simplification of clinical and especially the simplification and standardization of laboratory techniques; the improvements in cryopreservation of supernumerary embryos, the advent of intracytoplasmic sperm injection (ICSI), and to the industrialization of IVF services. This improvement came about at the expense of a very high rate of multiple pregnancies, especially triplets and higher order of multiples, as a result of replacement (transfer) of multiple embryos.

Multiple pregnancies are associated with a higher incidence of obstetrical complications and neonatal complications and deaths. They incur significant costs to the society, associated with the care of premature and sick infants, and tax the parents financially and emotionally. Fortunately, there is now a growing movement to decrease the number of embryos transferred, and to individualize the number taking into account the woman's age the quality of available embryos and other pertinent parameters.

Assisted Reproductive Technology (ART) which includes IVF has had a tremendous impact in the practice of reproductive medicine. It made IVF possible for a significant proportion of women, who otherwise would not achieve a pregnancy, to bear children. It has permitted the introduction of prenatal genetic diagnosis (PGD), enabling couples who are carriers of genetic disease to have healthy children.

We must be reminded that, despite the impressive progress in outcomes, ART fails to yield an offspring for approximately 50% of couples willing to undergo 3 cycles of treatment. And many do not persist that long. The industrialization of IVF proved to be a two edged sword. On the one hand, it has permitted ready access to this form of treatment globally, while on the other it funnels to IVF many couples who would benefit from simpler forms of treatment. It has caused significant reduction in the use and teaching of reproductive microsurgery. The reestablishment of a balanced approach remains the responsibility of the teaching institutions.

The selection of the initial and subsequent treatment modalities, for a given infertile couple, must be individualized on the basis of the findings obtained from a proper investigation. Reconstructive surgery and ART must not be viewed as competitive techniques; instead, they should be accepted and used as complementary methods to achieve a greater rate of success in patients presenting with complex fertility problems. There is ample evidence in this regard.

IVF has also opened many areas of investigation and progress: stem cell research, gene therapy, therapeutic cloning, etc. It is also opening the Pandora box of human cloning. Such is the destiny of scientific research.

Progress is made by visionaries who are willing to push the envelope; visionaries who have the will to stay the course, and the strength to withstand the abuse from those who fear change.

I am honored to be asked to contribute a foreword to this "Atlas of Human Assisted Reproductive Technologies" edited by Dr. Mangala Telang. This is a concise, practical and richly illustrated book, designed for those involved in the practice of ART, and the personnel working in ART laboratories.

The book is divided into three sections: clinical aspects of ART, laboratory aspects of ART, and new developments. The initial chapter of the first section is authored by Dr. Telang and devoted to the female partner. The chapter commences with a detailed discussion of the evaluation of the female partner, which is so important in selecting the most appropriate treatment. The second part of the chapter covers important clinical aspects of assisted reproduction including controlled ovarian stimulation, ovum pick-up and transfer, etc. The subsequent four chapters that complete the first section ably discuss the evaluation of the male partner, non-surgical and surgical methods of sperm collection, and the role of ultrasound in ART.

The second section commences with a chapter that discusses the laboratory, its equipment, quality control and assurance. The subsequent seven chapters in this section provide a detailed description of the various laboratory

techniques: sperm preparation, culture, ICSI, cryopreservation, PGD, etc. The last section, "new developments" include three chapters devoted to *in vitro* maturation, stem cells, and vitrification.

The balance and clarity of the book reflects the expertise and wisdom of its editor Dr. Mangala Telang who selected its authorship, and crafted and edited its contents. I am certain that it will prove to be a very useful guide to those involved in the practice of ART, personnel working in ART laboratories, and undoubtedly residents in gynecology.

Professor Victor Gomel
Department of Obstetrics and Gynecology
Faculty of Medicine, University of British Columbia
Vancouver BC. Canada

Preface

Assisted Reproductive Technologies (ART) have given a ray of hope to the countless couples who otherwise had no possibility of fulfilling their dream of parenthood. There is hope for women who have lost ovarian function, whose fallopian tubes are blocked, who do not have healthy wombs and even those who develop cancer of the reproductive organs. There is also hope for men who for some reason produce very few sperms or none at all. There is constant addition to the armamentarium needed for ovulation induction and laboratory equipment and techniques.

There was no atlas in the Indian market which would explain pictorially all the facets of clinical and laboratory management of ART. The atlases available from outside India were very expensive for Indian laboratories and this is an attempt to make such a book available for all ART laboratories. All the authors are very renowned and experienced in their own fields of expertise which they have shared in this atlas.

There is a comprehensive section on clinical aspects, which describes in detail the evaluation of an infertile woman and the management of various problems which could affect her fertility.

There are chapters which handle male infertility comprehensively.

Apart from the routine ART, latest advances in cryopreservation, *in vitro* maturation, vitrification have been contributed by very experienced scientists. The latest interest in stem cell research has also been addressed.

I hope this atlas finds a place in every IVF laboratory and is found to be useful both by the clinician and the laboratory personnel.

Mangala Telang

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I am very thankful to Dr Victor Gomel who is a pioneer in the field of endoscopy and ART for being gracious and for writing the foreword for this atlas.

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Contents

Section 1
Clinical Aspects

Section 2
Laboratory Aspects

Section 3
New Developments