

Clinics in Reproductive Medicine and Assisted Reproductive Technology

Volume 4

Volume 4

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Born with a passion of teaching and writing, Prof BN Chakravarty, still at age of 93 years, continues to teach and document information based on his own experience and contemporary scientific publications in his area of interest—Reproductive medicine, infertility and assisted reproductive technology (ART). This volume (Volume 4) of the book bears plenty of such evidences. Apart from technologies like embryo transfer, mitochondrial transfer, vitrification, role of USG scan in reproductive medicine, the other interesting areas are interlinking fertility problems with commonly encountered endocrine, metabolic and some of the treatable oncologic disorders in young victims of reproducing age or even teenage boys and girls. PCOS and unexplained miscarriage are the constant and unavoidable trouble shooting areas for those clinicians who are involved with clinical practice of reproductive medicine. Chapters on these topics have also been included and elaborately discussed in this volume. The material and content of this book provide wide and rich information to the aspiring doctors and students who want to take up postdoctoral degree or specialise in the subspecialties of reproductive medicine and assisted reproductive technology.

BN Chakravarty MO (Cal), FRCOG (Lond), DSc (Hon)

is an eminent Indian obstetrician and gynecologist, and overall a distinguished teacher having the style of teaching the subject from a conceptual point of view, a far cry from the prevailing style of teaching. Many prestigious honors and awards have been bestowed upon him for his magnificent contribution as a teacher. He was awarded the Coates Gold Medal by Calcutta University (1985), Mother Teresa Millennium Award (2006), Eminent Teacher Award (2006), Barclay Medal (2006) and Honorary Fellowship of Asiatic Society (2015). He has been felicitated with honorary membership of the International Federation of Fertility Society at its conference held in New Delhi in 2016. He is the first Indian and second in Asia to have received this honor.



Dr Chakravarty is globally recognized for his pioneering work on reconstructive surgery for cervicovaginal atresia. However, he is best known as an infertility specialist mastering and advancing the art of ART during its infancy stages in India. He played a leading role in shaping the infertility management and reproductive health program in India to its present form. He served as the chairman of the ICMR Committee for Formulation of National Guidelines for Regulation, Supervision and Accreditation of ART Centers in India, and as the convener of Post-doctoral Fellowship Course in Reproductive Medicine under National Board, Ministry of Health and Family Welfare, Government of India.

Dr Chakravarty has to his credit 107 original research papers in peer-reviewed journals. He has contributed many chapters in various textbooks and delivered more than 500 lectures in national and international conferences. This series of volumes of *Clinics in Reproductive Medicine and Assisted Reproductive Technologies* narrates his clinical and research experience interwoven with the traditional textbook knowledge to offer a concise overview of the basics of reproduction together with medical and surgical management of reproductive disorders.

With the concept of bridging the gap between the clinicians and the basic scientists in view, and advance his research work and train new specialists, Dr Chakravarty founded the Institute of Reproductive Medicine (IRM) in Kolkata, West Bengal, in 1986. To keep his ideas and thoughts rolling even after him, Dr Chakravarty has donated IRM to Indian Council of Medical Research (ICMR), Government of India. The only wish that Dr Chakravarty cherishes to dream is that under the aegis of ICMR, IRM should flourish with the innovative research activities in reproductive medicine and fertility management outside the ambit of business.



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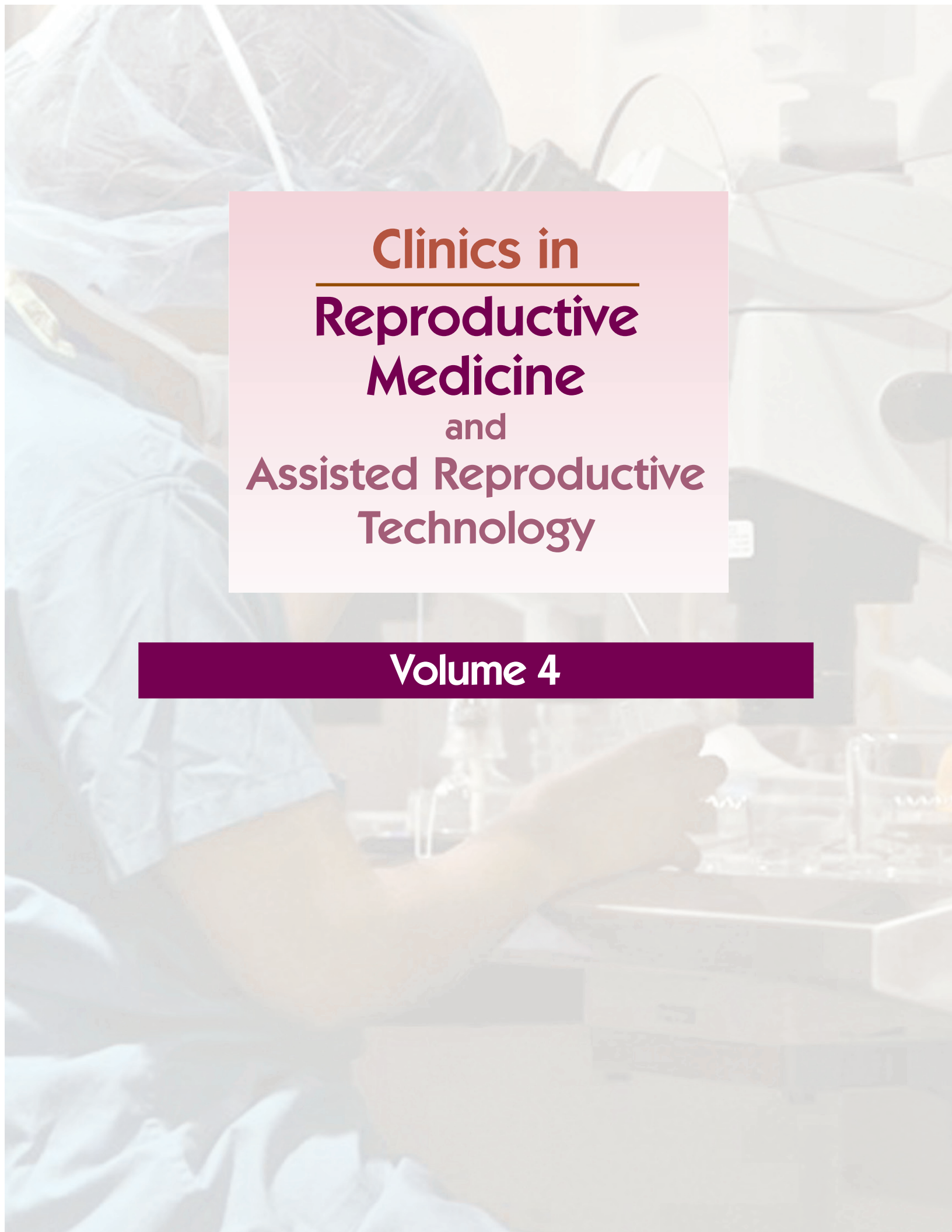


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**Clinics in
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and
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Technology**

Volume 4

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to



Dr Subhas Mukherjee

*Pioneered delivery of first IVF baby in
India and second in world*

and



Dr MN Parikh

*Founder President of ISAR Who by initiating
a solid and stable official organization
brought India to a respectable position in
the world map of IVF*

The author appreciates the services and active support received from his following students during the course of the preparation of the manuscript of this volume.

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Sanghamitra Ghosh

Sunita Sharma

Shovandeb Kalapahar

Sabnam Parvin

Preface to Volume 4

The fourth volume of the book *Clinics in Reproductive Medicine and Assisted Reproductive Technology* is now complete and ready for publication. I am delighted that almost 50% of the chapters are co-authored by those who, once upon a time, were my students and now are considered to be the experts in their respective disciplines. I am also thankful to the guest authors, Prof Hiralal Konar MBBS, MD, DNB, MNAMS, FACS, FRCOG, for Thyroid and Reproduction: Basic and Clinical Aspects; Prof Subhankar Chowdhury DTM&H, MD, DM, MRCP; and Dr Partha Pratim Chakraborty MD, DM, DNB, FACE, for Thyroid and Reproduction: Endocrinological and Clinical Aspects; Prof Sanjay Ghosh MBBS, MD (DERM & VEN) and Dr Saurav Kundu MD (DVL). Their contributions enormously upgraded the prestige of this book. This volume contains many chapters interlinking the disorders related to reproduction with endocrinopathy, metabolic problems, dermatology, developmental errors, oncology, etc. Additionally, obesity and cryopreservation of gamete and gonadal tissue included in this volume are two important topics that hold future areas of research to address many unresolved challenges in reproductive medicine. Besides, the chapters like hirsutism and the associated underlying disorders have remained the topic of combined disciplines like endocrinology, dermatology, gynecology, and oncology. Though complicated, an attempt has been made to simplify the problems of hirsutism in three different chapters: basic (more physiological), clinical aspects and more importantly the cosmetic part of the problem.

With the advent of the new technology of diagnostic modalities and therapeutic approaches, recent workers have taken a renewed interest in the embryogenesis and classification of urogenital anomalies. This topic has been of interest since my younger days, and has been discussed with a new clinical classification based on my own experience.

Customarily it was known that the onset of puberty varies with the geographical location of an individual's habitation. For example, Eskimos have relatively delayed puberty compared to those living near the equator, like South Asians and Africans. With the alteration of nutrition and lifestyle globally, this phenomenon is also now changing. The general onset of puberty has advanced more or less universally. Two chapters; one on precocious puberty and the other on puberty will help clarify some of the mystiques and miracles of this transitional period of a girl between the immaturity of childhood and gradually approaching maturity of adulthood through semi-maturity of adolescence.

Like other disciplines, imaging technologies play an invaluable role in different areas of reproductive medicine including ART, both in diagnostic and therapeutic areas. The related topics have been adequately elaborated in the chapters, namely "Ultrasound Imaging in Female Intertility Management" and "Assessment of Endometrial Receptivity by Ultrasound" by Dr Sunita Sharma MD, FNB, Dr Sanghamitra Ghosh and Dr Kamal Oswal MD.

In near future, cryobiology will be a central pillar in many areas of research and development of the science of reproductive medicine. Dr Shovandeb Kalapahar MS, DNB, FNB one of our students and now a junior colleague has assisted in contributing to the basic chapters "Cryopreservation and vitrification: Laboratory aspects" and "Embryo transfer". Dr Ratna Chattopadhyay MBBS, PhD, has highlighted the importance of *In vitro* Maturation (IVM) in ART.

For writing the sequential volumes of this book, I got the initial incentive from my junior colleague Dr Gita Ganguli Mukherjee MBBS, DGO, MD, FICOG, FRCOG; who keeps on inspiring me for the addition of chapters especially containing my own experiences. Further in this journey, I have received constant encouragement from my colleagues and juniors like Prof BB Hore, DA, MS; Prof BB Sarkar MO; Dr Subhas Halder MD; Dr Biman Kumar Ghosh FRCOG, and many other coworkers to continue my work till the last day of my life. I offer my special thanks to Prof Syed N Kabir PhD; Dr Pratip Chakraborty PhD and Dr Sanghamitra Ghosh MBBS; for their help and assistance in providing me with some constructive criticisms during the compilation of different chapters of this volume. My wife, Dr Manjusree Chakravarty, as usual, inspires and enjoys all my activities.

I thank and appreciate all the assistance from Late Ashis Shit (no more with us), Mr Sushanta Chakraborty, Mr Arup Ranjan Sarkar, Dr Tushar Kanti Das PhD and Dr Sakti Rupa Chakraborty MBBG, DGO, MD, FICOG, for their tireless efforts in compiling by rewriting the manuscript and, thereafter, revising each chapter thoroughly. I will be happy, if the contents of this volume are of benefit to the readers.

BN Chakravarty

Preface

Around 1950s, soon after the Second World War, there were numerous innovations in the vast field of medical science. As a consequence, several superspecialties were identified for the purpose of specialised training and treatment. Most of them have already been recognised for postdoctoral training and specialisation. Examples include cardiology, ophthalmology, otolaryngology, paediatrics, radiology and oncology. On the other hand, recognition of reproductive medicine, a newborn superspecialty in medical curriculum, was relatively late. This discipline, as a superspecialty, was well-established following the advent of assisted reproductive technology (ART). Though science of embryology was documented as early as 1875 by Oscar Hertwig in Germany, it was a difficult subject to study in humans. At that time most knowledge of human reproduction was achieved through animal experiments. Scope of observation and research directly in humans has only been possible following the introduction of assisted reproductive technology in the treatment of infertility. The process of gametogenesis, their maturation, sperm egg interaction, fertilisation and implantation are a few of the major information which have been derived through clinical application of assisted reproduction.

Endocrine background of human reproduction was realised much earlier from late 1920s. Fertility enhancing drugs like gonadotropin, clomiphene and bromocriptine, in addition to fertility preventing drugs like oral contraceptives were discovered and introduced for clinical use around the early 1960s. Knowledge and expertise for clinical use of these hormones expanded further with introduction of gadgets and technologies like ultrasound, laparoscope, RIA and EIA. These technologies have opened up avenues for better understanding of physiology at molecular level of folliculogenesis and ovulation, pathophysiology of PCOS, precocious puberty, premature menopause and many others.

ART has brought about an unprecedented revolution in the treatment of human infertility. The procedure has not only provided help in relieving the distress of childless couples but also has opened up avenues of potential research. One of them is stem cell research which is heading towards another medical discovery through tissue engineering and has already established the foundation stone of a new superspecialty—regenerative medicine. Apart from stem cell research, ART has also provided novel protocols for fertility preservation during and preceding oncotherapy in young cancer victims, both boys and girls.

In 1990s, there has been a breakthrough in the treatment of male infertility through introduction of intracytoplasmic sperm injection (ICSI) procedure. However, till now we do not know the exact treatment of male infertility because in ICSI gametes are treated, but not the individual. Andrology and spermatology are expanding fast and it is expected that many obscure areas in male reproduction will be explored in the near future. Expansion of genetic and immunological knowledge has widened our views on amenorrhoea, recurrent miscarriage and sexual ambiguity.

In spite of all these advances in science and technology, ART still has practical limitations, primarily in four areas which have become a source of concern for the clinician.



These are (a) cost, (b) complexities of treatment, (c) complications and (d) results, at least the prediction of outcome. Clinicians and researchers alike have joined hands to overcome these problems.

Enormous volumes of publications have accumulated over the years discussing ways and procedures for solving these persistent deficiencies of ART through development of good quality embryos, generating effective endometrial receptivity and finding ways for performing smooth and atraumatic embryo replacement. Though to some extent some of the objectives have been achieved, yet many more remained elusive.

Recent publications emphasise more on optimising stimulation protocol, redirecting approaches for mild ovarian stimulation, a move towards single embryo transfer, reducing embryo stress by introducing metabolomics in culture system, time-lapse embryoscope, and attempting to predict endometrial receptivity through non-invasive markers like uterine fluid, follicular fluid components and many others.

From the academic point of view, it is apparent that comprehensive knowledge in reproductive medicine demands a sound background of different branches of basic science and their intelligent application in clinical medicine. Unfortunately, in our medical postgraduate teaching and examinations, these two aspects of the same superspecialty have been segregated. For example, in MD (Obs and Gynae) examination, the emphasis is more on clinical aspect, whereas the PhD course syllabus and training has been oriented more on the basic aspect rather than its clinical application. There is an urgent need for bridging the gap between the two.

However, as far as I am concerned, during my professional career which covers nearly a period of five decades, I had the privilege of being continuously associated with medical teaching, both undergraduate and postgraduate. This uninterrupted commitment has helped me immensely in keeping myself updated with contemporary advances, both basic and clinical aspects of my respective discipline.

I have been teaching reproductive medicine in fellowship and PhD course for the last 20 years. Over the years I have updated and upgraded my teaching slides with contemporary information and novel experiences that I had gathered during my clinical practice. This has provided some opportunities for me to unify both basic and clinical aspects together which I learnt during the last decade of my teaching career. The incentive for writing a book came from my students whom I taught and from my colleagues with whom I have worked from the beginning of my career. Nevertheless, one of my ambitions was not fulfilled owing to my busy schedule during my working years. I could hardly get some time to concentrate and write a book, which I felt was a difficult task for me. The chapters of this book have been written in the way in which I teach my students—meaning thereby that each topic has been discussed from different angles. For example, the topic of PCOS has been covered in 5 different lectures:

- a. Adolescent PCOS—current management strategy
- b. Pubertal metabolic and endocrine changes—their relevance to adolescent PCOS
- c. Overview and management of PCOS
- d. Optimising ovarian stimulation of PCOS patients
- e. Changing concept in PCOS.

Each of these lecture notes has been converted into an individual chapter. To accommodate all these lecture notes, it was not possible to include them in a single publication. Therefore, it has been decided to publish the book in three or four different volumes.

My primary interest in infertility and subsequently in the discipline of reproductive medicine was created by my renowned colleague late Prof Subhas Mukherjee MBBS, DGO, PhD (Edin)

who had pioneered the delivery of first 'test-tube baby' in India in 1978 and the second in the world. My initial experience in ART was gathered through a small team of doctors (all my students) organised by me following the tragic death of Dr Mukherjee in 1981. The team primarily consisted of Dr Sudarshan Ghosh Dastidar, Dr Siddhartha Chatterjee, Dr Arup Kumar Majhi, Dr Sourendra Kanta Goswami, Dr Bani Kumar Mitra, Dr Sanghamitra Ghosh and Dr Ratna Chattopadhyay.

For writing this book I got continuous encouragement from Prof Dr Gita Ganguly Mukherjee MD, FICOG, FRCOG; Prof BB Hore MBBS DA, MS (Cal); Prof Subir Kumar Dutta MBBS, DCP, MD (Cal); Prof BB Sarkar MBBS, DGO, MO (Cal); Dr Biman Kumar Ghosh MBBS, DGO (Cal), DRCOG, EPA, FRCOG; Prof Hiralal Konar MD, DNB, FRCOG, FICOG; Dr Arup Kumar Majhi MBBS; DGO, MD (Cal); and all my students, present and past.

I express my deep appreciation to Dr Ratna Chattopadhyay, Dr Sourendra Kanta Goswami, Dr Sanghamitra Ghosh, Dr Radhika Kandula, Dr Rita Modi, Dr Geetha Rani BS, and Dr Anwesha Ghosh for their meticulous care and painstaking effort and for their assistance in repeated corrections, criticism and revision of my manuscript. I acknowledge and sincerely thank Dr Ratna Chattopadhyay and Dr Pratip Chakraborty for their individual contribution of two chapters on 'Nutraceutical in Male Infertility' and 'Insulin Resistance' respectively in this publication. I also thank and appreciate the efforts and devotion of my computer assistants Mr Ashis Shit, Mr Arup Ranjan Sarker and Ms Ria Chakraborty who have worked continuously and retyped the corrected manuscripts time and again.

Lastly, I have no words to appreciate the silent help offered by my wife Dr Manjusree Chakravarty, who has spared me from my domestic commitments and has continuously encouraged me to express my ideas through writing a book which might help the future generation.

I will be only too happy if the contents of the current and future volumes of this book are of benefit, both for information and for practice of the students and practitioners in reproductive medicine, for whom the book has been compiled.

BN Chakravarty

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