

# ASSISTED REPRODUCTION TECHNIQUES

CHALLENGES AND  
MANAGEMENT OPTIONS



EDITED BY  
KHALDOUN SHARIF AND  
ARRI COOMARASAMY

 WILEY-BLACKWELL



# Assisted reproduction techniques

## Challenges and management options

To my mother and father, Zena, Omar and Abdallah (KS)

To Dukaydah, Abdea, Tara, Leela, Amma, Appa, Poongo aunti  
and Dharini (AC)

# **Assisted reproduction techniques**

## Challenges and management options

EDITED BY

**Khaldoun Sharif MBBCh, MD, FRCOG, MFFP**

Consultant in Reproductive Medicine and Surgery

Clinical Director

Istishari Fertility Center

Istishari Hospital

Amman

Jordan

**Arri Coomarasamy MBChB, MD, MRCOG**

Professor of Gynaecology

Subspecialist in Reproductive Medicine and Surgery

University of Birmingham and Birmingham Women's Hospital

Birmingham

UK

 **WILEY-BLACKWELL**

A John Wiley & Sons, Ltd., Publication

This edition first published 2012 © 2012 by Blackwell Publishing

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

*Registered office:* John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Editorial offices:* 9600 Garsington Road, Oxford, OX4 2DQ, UK  
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at [www.wiley.com/wiley-blackwell](http://www.wiley.com/wiley-blackwell)

The right of the author to be identified as the author of this work has been asserted in accordance with the UK Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

*Library of Congress Cataloging-in-Publication Data*

Assisted reproduction techniques : challenges and management options / edited by Khaldoun Sharif, Arri Coomasamy.

p. ; cm.

Includes bibliographical references and index.

ISBN-13: 978-1-4443-3555-2 (hardcover : alk. paper)

ISBN-10: 1-4443-3555-3 (hardcover : alk. paper) 1. Human reproductive technology—Case studies. I. Sharif, Khaldoun W.

II. Coomasamy, Arri.

[DNLN: 1. Reproductive Techniques, Assisted—Case Reports. 2. Infertility—complications—Case Reports. 3. Pregnancy—physiology—Case Reports. 4. Reproductive Health Services—manpower—Case Reports. 5. Risk Assessment—Case Reports. WQ 208]

RG133.5.A7857 2012

618.1'7806—dc23

2011017803

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 9/11.5 pt Sabon by Aptara® Inc., New Delhi, India

01 2012

# Contents

Contributors, xi  
Preface, xxii  
How to use this book, xxiii

## Section 1: Counseling and preparation phase

- 1 Risk of cancer from ovarian stimulation, 3  
*Nikos Kanakas, Miltiadis Pitsos and Themis Mantzavinos*
- 2 Risk of early menopause following IVF treatment, 7  
*Sesh Kamal Sunkara*
- 3 The HIV positive female, 9  
*Joshua U. Klein and Mark V. Sauer*
- 4 The HIV positive male, 13  
*Mark V. Sauer and Joshua U. Klein*
- 5 The hepatitis B/C carrier patient, 17  
*Suzanne P.M. Lutgens, I.H.M. Van Loo, E.C.M. Nelissen and G.A.J. Dunselman*
- 6 The patient with cystic fibrosis, 21  
*Tarek El-Toukby*
- 7 The patient on medication, 25  
*Arri Coomarasamy*
- 8 The patient with thrombophilia, 29  
*Ying C. Cheong and N.S. Macklon*
- 9 The patient with autoimmune disorders, 34  
*José Bellver*
- 10 The patient with malignant disease: fertility preservation, 38  
*Arri Coomarasamy*
- 11 The patient with heart disease, 43  
*Natasha Thorogood and Catherine Nelson-Piercy*
- 12 The patient with diabetes, 48  
*Neelam Potdar and Justin C. Konje*
- 13 The patient with thyroid disease, 51  
*Shiao Chan*
- 14 The patient with hyperprolactinemia, 56  
*John Ayuk*

## CONTENTS

- 15 The patient with polycystic ovaries, 61  
*Adam H. Balen*
- 16 The renal transplant patient and IVF, 65  
*Lynne Robinson and Clara Day*
- 17 The patient with previous pelvic irradiation, 69  
*Vishvanath C. Karande*
- 18 Fertility after chemotherapy, 73  
*Nivedita Reddy*
- 19 The patient with abnormal cervical cytology, 77  
*Mahmood I. Shafi*
- 20 The patient with previous borderline ovarian tumor, 80  
*Arri Coomarasamy and Kavita Singh*
- 21 The patient with an endometrioma, 83  
*Luciano G. Nardo and Oybek Rustamov*
- 22 The patient with cervical stenosis, 86  
*Khaldoun Sharif*
- 23 Vaccination and ART, 90  
*Arri Coomarasamy and Dukaydah van der Berg*
- 24 The patient with hydrosalpinx, 95  
*Annika Strandell*
- 25 The patient with poor ovarian reserve, 99  
*Scott M. Nelson*
- 26 The patient with congenital uterine anomalies, 105  
*Sarah Creighton and Lina Michala*
- 27 The patient with congenital cervico-vaginal anomalies, 109  
*Sarah Creighton and Lina Michala*
- 28 The patient with uterine fibroids, 112  
*Haitham Hamoda and Yakoub Khalaf*
- 29 The patient with previous Essure® sterilization, 115  
*T. Justin Clark*
- 30 The patient with previous endometrial ablation, 119  
*T. Justin Clark*
- 31 The couple with recurrent implantation failure, 124  
*Tarek El-Toukhy*
- 32 The patient with previous uterine artery embolization, 128  
*Haitham Hamoda and Yakoub Khalaf*
- 33 Endometrial polyp detected during ART treatment, 131  
*Arri Coomarasamy*
- 34 The obese patient, 135  
*Mostafa Metwally and Bolarinde Ola*



- 35 Asherman syndrome, 139  
*Dan Yu, Enlan Xia and T.C. Li*
- 36 The older patient, 142  
*William Ledger*
- 37 Requests for mild or natural cycle IVF treatment, 146  
*Brad B. Swelstad and Suheil J. Muasher*
- 38 The ART patient with psychosexual problems, 150  
*Sue Elkin*
- 39 The patient needing third-party reproduction, 153  
*Madhurima Rajkhowa*
- 40 Request for “social egg freezing”, 159  
*Valerie L. Peddie and Siladitya Bhattacharya*
- 41 The patient with bariatric surgery, 165  
*Zaher O. Merbi and Harry J. Lieman*

## **Section 2: Pituitary suppression and ovarian stimulation phase**

- 42 Poor response during ovarian stimulation, 171  
*Lynne Robinson and Arri Coomarasamy*
- 43 Ovarian stimulation for IVF in a patient with previous severe ovarian hyperstimulation syndrome, 175  
*Khaldoun Sharif*
- 44 Unable to achieve pituitary down-regulation, 178  
*K. Jayaprakasan and Nick Raine-Fenning*
- 45 The patient discovered pregnant during pituitary down-regulation, 184  
*Mohammed Khairy Mahmoud and Arri Coomarasamy*
- 46 Ovarian cysts following pituitary down-regulation, 188  
*Alison Taylor*
- 47 Poor endometrial development, 192  
*Lynne Robinson and Arri Coomarasamy*
- 48 Missed IVF medications, 201  
*Lynne Robinson and Arri Coomarasamy*
- 49 The patient with a history of estrogen-receptor positive cancer, 205  
*Murat Sönmezer and Kutluk Oktay*
- 50 The patient over-responding to controlled ovarian stimulation during IVF, 208  
*Khaldoun Sharif*

## **Section 3: Oocyte retrieval**

- 51 General anesthesia or sedation for oocyte retrieval?, 215  
*Andrew F. Malins*

## CONTENTS

- 52 Delayed oocyte retrieval, 219  
*Khaldoun Sharif*
- 53 Empty follicle syndrome, 223  
*George Ndukwe*
- 54 Bleeding following oocyte retrieval, 227  
*Annika K. Ludwig and Barbara Sonntag*
- 55 To flush or not to flush follicles at oocyte retrieval?, 232  
*Micah J. Hill and Eric D. Levens*
- 56 Inaccessible ovaries at oocyte retrieval, 236  
*Hazem Al-Rumaih*
- 57 Endometriotic cysts at oocyte retrieval, 239  
*Graciela Kohls and Juan A. García-Velasco*

**Section 4: Embryo transfer**

- 58 Couple splitting while embryos are in storage, 245  
*Masoud Afnan*
- 59 Endometrial cavity fluid identified during IVF treatment, 249  
*Arri Coomarasamy*
- 60 Difficult embryo transfer, 252  
*Khaldoun Sharif*
- 61 Excessive cervical mucus and retained embryo at embryo transfer, 257  
*Hassan N. Sallam, Ahmed F. Galal and Fady S. Moeity*
- 62 Life after embryo transfer, 261  
*Kelton Tremellen*

**Section 5: The luteal phase**

- 63 Vaginal bleeding in the luteal phase after IVF, 267  
*Carol Coughlan and Bolarinde Ola*
- 64 Pelvic infection after IVF, 271  
*Muhammad Faisal Aslam*
- 65 The patient presenting with ovarian hyperstimulation syndrome, 274  
*Khaldoun Sharif*
- 66 Adnexal torsion after IVF, 279  
*Saioa Torrealday and Beth W. Rackow*
- 67 Exposure to infection in the luteal phase of IVF, 283  
*Litha Pepas and Arri Coomarasamy*

**Section 6: The ART laboratory**

- 68 Total failure of fertilization after conventional IVF - rescue ICSI, 291  
*A. Albert Yuzpe*

## CONTENTS

- 69 Couples not wishing to create surplus embryos in IVF, 296  
*Hossam Mohamed*
- 70 Aneuploidy screening for advanced maternal age or repeated IVF failure, 300  
*Haitham Hamoda and Yacoub Khalaf*
- 71 Choosing an embryo for transfer, 304  
*Denny Sakkas*
- 72 Globozoospermia, 308  
*Steven Mansell, Anne Rice, Catherine Beaton and Christopher L.R. Barratt*
- 73 Total failure of fertilization after ICSI, 313  
*Kaoru Yanagida*
- 74 Refreezing of embryos, 317  
*Jerome H. Check*
- 75 Infection in embryo culture medium, 320  
*Peter M.M. Kastrop*
- 76 ICSI or IVF in nonmale-factor infertility?, 324  
*Mohamed Aboulghar*
- 77 The ART program during a natural or human-made disaster, 328  
*Richard P. Dickey and Carla White*
- 78 Using the wrong sperm or embryos in IVF, 331  
*Khaldoun Sharif and Mutaz Al-Ahmad*

**Section 7: The male patient**

- 79 Unexpected inability to produce a semen sample on the day of oocyte retrieval, 337  
*Khaldoun Sharif*
- 80 The azoospermic patient, 340  
*Khaldoun Sharif*
- 81 ART in men with Klinefelter syndrome, 344  
*Ronnie G. Fine and Darius A. Paduch*
- 82 ART in men with 100% immotile sperm, 349  
*Carolina Ortega-Hrepich, Dominique Raïck and Herman Tournaye*
- 83 Request for posthumous fatherhood with perimortem surgical sperm retrieval, 353  
*Zamir P. Patel, Heather E. Ross and Lawrence S. Ross*
- 84 Retrograde ejaculation and anejaculation, 360  
*Asif Muneer and Anthony Hirsh*
- 85 Sperm retrieval in cancerous testes, 364  
*Saad Aldousari and Armand Zini*

## CONTENTS

- 86 Leukocytospermia and ART, 367  
*Giuseppe Ricci*
- 87 The infertile male patient with a genetic cause, 371  
*Katherine L. O'Flynn O'Brien and Ashok Agarwal*
- 88 Y chromosome microdeletions and ART, 376  
*Sherman J. Silber*

**Section 8: The ART pregnancy**

- 89 Unexpected number or gender of babies after IVF, 383  
*Khaldoun Sharif*
- 90 Suspected ectopic pregnancy after IVF, 387  
*Vishvanath C. Karande*
- 91 Cervical ectopic pregnancy after IVF, 391  
*Usha Verma*
- 92 Heterotopic pregnancy after IVF, 396  
*Abdel-Maguid Ramzy*
- 93 Multi-fetal pregnancy reduction after ART, 400  
*R. Katie Morris and Mark D. Kilby*
- 94 Multiple pregnancy after IVF: to cerclage or not to cerclage? 405  
*Harold Gee*
- 95 Hyperreactio luteinalis after IVF, 409  
*Mohammad Ebrahim Parsanezhad, Leila Forooghinia and Maryam Parsa-Nezhad*
- 96 Lactation by a commissioning mother in surrogacy, 412  
*Frank P. Biervliet and Stephen L. Atkin*

**Section 9: General issues**

- 97 Dealing with the emotional distress following failed IVF, 417  
*Linda Hammer Burns*
- 98 IVF when the prognosis is very poor or futile, 421  
*Khaldoun Sharif*
- 99 Unexpected drop in the ART clinic pregnancy rate, 425  
*Bulent Urman and Kayhan Yakin*
- 100 Natural fertility after IVF, 430  
*Frank Nawroth and Annika K. Ludwig*

Index, 433

## Contributors

**Mohamed Aboulghar** MD  
Professor, Faculty of Medicine  
Cairo University;  
Clinical Director, The Egyptian IVF Center  
Maadi, Cairo  
Egypt

**Masoud Afnan** MBBS, FRCOG  
Department Chair  
Department of Obstetrics and Gynecology  
Beijing United Family Hospital  
Beijing  
People's Republic of China

**Ashok Agarwal** PhD  
Professor, Lerner College of Medicine  
Cleveland Clinic  
Cleveland, OH  
USA

**Mutaz Al-Ahmad** BSc  
Director of IVF Laboratory  
Istishari Fertility Center  
Istishari Hospital  
Amman  
Jordan

**Saad Aldousari** MD  
Chief Resident  
Division of Urology  
Department of Surgery  
McGill University  
Montreal, QC  
Canada

**Hazem Al-Rumaih** MRCOG, MD  
Consultant Obstetrician and Gynecologist,  
Reproductive Medicine and Surgery; Director of  
IVF Unit  
Maternity Hospital  
Ministry of Health  
Kuwait

**Muhammad Faisal Aslam** MD, MRCOG  
Attending Physician  
Department of Obstetrics and Gynecology  
Virginia Regional Medical Center  
Virginia, MN  
USA

**Stephen L. Atkin** MBBS, PhD, FRCP  
Head, Academic Endocrinology, Diabetes and  
Metabolism  
Hull York Medical School  
Michael White Diabetes Centre  
Hull  
UK

**John Ayuk** MD, MRCP  
Consultant Endocrinologist  
Department of Endocrinology  
Queen Elizabeth Hospital  
Birmingham  
UK

**Adam H. Balen** MD, DSc, FRCOG  
Professor of Reproductive Medicine and Surgery  
Leeds Teaching Hospitals NHS Trust  
Leeds  
UK

**Christopher L.R. Barratt** PhD  
Professor, Reproductive and Developmental Biology,  
Maternal and Child Health Sciences Laboratories  
Centre for Oncology and Molecular Medicine  
University of Dundee, Ninewells Hospital  
Dundee  
UK

## CONTRIBUTORS

**Catherine Beaton** BSc

MSc Student  
 Reproductive and Developmental Biology, Maternal  
 and Child Health Sciences Laboratories  
 Centre for Oncology and Molecular Medicine  
 University of Dundee, Ninewells Hospital  
 Dundee  
 UK

**José Bellver** MD, PhD

Gynecologist, Department of Human Reproduction  
 Instituto Valenciano de Infertilidad;  
 Associate Professor  
 Department of Pediatrics, Obstetrics and Gynecology  
 Faculty of Medicine  
 University of Valencia  
 Valencia  
 Spain

**Siladitya Bhattacharya** MD, FRCOG

Professor of Reproductive Medicine and Honorary  
 Consultant  
 Division of Applied Health Sciences, School of  
 Medicine and Dentistry  
 University of Aberdeen  
 Aberdeen Maternity Hospital  
 Aberdeen  
 UK

**Frank P. Biervliet** MRCOG

Consultant in Obstetrics and Gynaecology  
 Hull and East Yorkshire Women and Children's  
 Hospital  
 Hull  
 UK

**Linda Hammer Burns** PhD

Associate Professor  
 Department of Obstetrics, Gynecology and  
 Women's Health  
 University of Minnesota Medical School  
 Director of Counseling Services  
 Reproductive Medicine Center  
 Minneapolis, MN  
 USA

**Shiao Chan** PhD, MRCOG

Senior Clinical Lecturer  
 School of Clinical and Experimental Medicine  
 University of Birmingham  
 Birmingham  
 UK

**Jerome H. Check** MD, PhD

Professor, Obstetrics and Gynecology  
 Division Head of Reproductive Endocrinology and  
 Infertility  
 Robert Wood Johnson Medical School at Camden  
 Camden, NJ  
 USA

**Ying C. Cheong** MBChB, BAO, MA, MD, MRCOG

Senior Lecturer and Honorary Consultant in  
 Obstetrics and Gynaecology, Subspecialist in  
 Reproductive Medicine and Surgery  
 Academic Unit of Human Development and Health  
 Faculty of Medicine  
 University of Southampton;  
 Clinical Director  
 Complete Fertility Centre  
 Princess Anne Hospital  
 Southampton  
 UK

**T. Justin Clark** MBChB, MD, MRCOG

Consultant in Obstetrics and Gynaecology  
 Birmingham Women's Hospital  
 Birmingham  
 UK

**Arri Coomarasamy** MBChB, MD, MRCOG

Professor of Gynaecology  
 Subspecialist in Reproductive Medicine and Surgery  
 University of Birmingham and  
 Birmingham Women's Hospital  
 Birmingham  
 UK

## CONTRIBUTORS

**Carol Coughlan** MRCOG, MRCPI  
Subspecialty Trainee in Reproductive Medicine and  
Surgery  
Department of Reproductive Medicine  
Jessop Wing, Royal Hallamshire Hospital  
Sheffield  
UK

**Sarah M. Creighton** MD, FRCOG  
Consultant Gynaecologist  
University College London Hospitals  
London  
UK

**Clara Day** MBChB, MRCP, PhD  
Consultant Nephrologist  
Department of Renal Medicine  
Queen Elizabeth Hospital  
Birmingham  
UK

**Richard P. Dickey** MD, PhD  
Medical Director, Fertility Institute of New Orleans  
Mandeville, LA;  
Chairman, Section of Reproductive Endocrinology  
and Infertility  
Department of Obstetrics and Gynecology  
Louisiana State University School of Medicine  
New Orleans, LA  
USA

**G.A.J. Dunselman** MD, PhD  
Gynecologist  
Department of Obstetrics and Gynecology  
Research Institute Growth and Development  
Maastricht University Medical Center  
Maastricht  
The Netherlands

**Sue Elkin**  
Gynaecology Nurse Counsellor  
Birmingham Women's Hospital  
Birmingham  
UK

**Tarek El-Toukhy** MBChB MSc MD MRCOG  
Consultant in Reproductive Medicine and Surgery  
Assisted Conception Unit and PGD Centre  
Guy's and St Thomas' Hospital NHS Foundation  
Trust  
London  
UK

**Ronnie G. Fine** MD  
Chief Resident  
Department of Urology  
New York Presbyterian Hospital/Weill Cornell  
Medical Center  
New York, NY  
USA

**Leila Forooghnia**  
Assistant Professor  
Department of Obstetrics and Gynecology  
Shiraz University of Medical Sciences  
Shiraz  
Iran

**Ahmed F. Galal** MD  
Senior Lecturer  
Department of Obstetrics and Gynecology  
University of Alexandria  
Alexandria  
Egypt

**Juan A. García-Velasco** MD, PhD  
Associate Professor of Obstetrics and Gynecology  
Department of Human Reproduction  
Rey Juan Carlos University;  
Director, IVI Madrid  
Madrid  
Spain

**Harold Gee** MD, FRCOG  
Former Medical Director  
Birmingham Women's Hospital  
Birmingham  
UK

## CONTRIBUTORS

**Haitham Hamoda MD, MRCOG**  
 Consultant Gynaecologist, Subspecialist in  
 Reproductive Medicine and Surgery  
 The Assisted Conception Unit  
 King's College Hospital  
 London  
 UK

**Micah J. Hill DO**  
 Clinical Fellow, Program in Reproductive and Adult  
 Endocrinology  
 Eunice Kennedy Shriver National Institute of Child  
 Health and Human Development  
 National Institutes of Health  
 Bethesda, MD  
 USA

**Anthony Hirsh MBBS, DRCOG, FRCS**  
 Consultant in Andrology, Whipps Cross University  
 Hospital  
 Hon. Senior Lecturer in Andrology, Guy's and  
 St Thomas' Hospital, and The London  
 Medical Centre  
 London  
 UK

**Kannamannadiar Jayaprakasan MBBS,**  
 MRCOG, PhD  
 Associate Professor and Subspecialist in  
 Reproductive Medicine and Surgery  
 Division of Obstetrics and Gynaecology  
 School of Clinical Sciences  
 Queen's Medical Centre  
 University of Nottingham  
 Nottingham  
 UK

**Nikos Kanakas MD, PhD**  
 Consultant in Obstetrics and Gynecology  
 Embryoland – Center for Assisted Reproduction  
 Athens  
 Greece

**Vishvanath C. Karande MD**  
 President, Medical Director, Director IVF Program  
 Department of Reproductive Endocrinology and  
 Infertility  
 InVia Fertility Specialists  
 Hoffman Estates, IL  
 USA

**Peter M.M. Kastrop PhD**  
 Clinical Embryologist  
 Department of Reproductive Medicine and  
 Gynecology  
 University Medical Center Utrecht  
 Utrecht  
 The Netherlands

**Mark D. Kilby MD, FRCOG**  
 Professor of Fetal Medicine  
 School of Clinical and Experimental Medicine  
 College of Medical and Dental Sciences  
 University of Birmingham  
 Birmingham  
 UK

**Yakoub Khalaf MD, FRCOG**  
 Consultant Gynaecologist, Subspecialist in  
 Reproductive Medicine and Surgery  
 Director, The Assisted Conception Unit and Centre  
 for Preimplantation Genetic Diagnosis  
 Guy's and St Thomas' Hospital  
 London  
 UK

**Joshua U. Klein MD**  
 Fellow, Reproductive Endocrinology and Infertility  
 Department of Obstetrics and Gynecology  
 Columbia University Medical Center  
 New York, NY  
 USA

**Graciela Kohls MD**  
 Gynecologist  
 Department of Human Reproduction  
 IVI Madrid  
 Madrid  
 Spain



## CONTRIBUTORS

**Justin C. Konje** MD, FRCOG  
 Professor of Obstetrics and Gynaecology  
 Reproductive Sciences Section  
 University of Leicester and University Hospitals  
 of Leicester  
 Leicester  
 UK

**William Ledger** MA, DPhil, BM BCh, FRCOG,  
 FRANZCOG  
 Professor and Head of Department of Obstetrics and  
 Gynaecology School of Women's and Children's  
 Health  
 University of New South Wales  
 Randwick, NSW  
 Australia

**Eric D. Levens** MD  
 Attending Physician  
 Program in Reproductive and Adult Endocrinology  
 Eunice Kennedy Shriver National Institute of Child  
 Health and Human Development  
 National Institutes of Health  
 Bethesda, MD;  
 Shady Grove Fertility Reproductive Science Center  
 Rockville, MD  
 USA

**T.C. Li** MD, PhD, FRCOG, FRCP (Glasgow)  
 Consultant in Obstetrics and Gynaecology  
 Honorary Professor of Reproductive Medicine and  
 Surgery  
 Sheffield Teaching Hospitals  
 Sheffield  
 UK

**Harry J. Lieman** MD  
 Associate Professor and Interim Director of the  
 Division of Reproductive Endocrinology and  
 Infertility  
 Albert Einstein College of Medicine;  
 Medical Director Montefiore's Institute for  
 Reproductive Medicine and Health  
 Montefiore Medical Center  
 Bronx, NY  
 USA

**Annika K. Ludwig** MD, PhD  
 Professor of Obstetrics and Gynecology  
 Zentrum für Endokrinologie, Kinderwunsch und  
 Pränatale Medizin  
 Hamburg  
 Germany

**Suzanne P.M. Lutgens** MD, PhD  
 Trainee Medical Microbiologist  
 Department of Medical Microbiology  
 Research Institute Growth and Development  
 Maastricht University Medical Center  
 Maastricht  
 The Netherlands

**N.S. Macklon** MBChB, MD, MNVOG, FRCOG  
 Professor of Obstetrics and Gynaecology  
 Division of Human Development and Health  
 University of Southampton;  
 Director, Complete Fertility Centre Southampton  
 Princess Anne Hospital  
 Southampton  
 UK

**Mohammed Khairy Mahmoud** MD,  
 MRCOG  
 Specialist Registrar in Obstetrics and Gynaecology  
 St John Hospital  
 Livingston  
 UK

**Andrew F. Malins** MBChB, FRCA  
 Consultant Anaesthetist  
 Department of Anaesthetics  
 Birmingham Women's Hospital  
 Birmingham  
 UK

**Steven Mansell** BSc  
 Reproductive and Developmental Biology, Maternal  
 and Child Health Sciences Laboratories  
 Centre for Oncology and Molecular Medicine  
 University of Dundee, Ninewells Hospital  
 Dundee  
 UK

## CONTRIBUTORS

**Themis Mantzavinos** MD, PhD  
 Professor, Obstetrics and Gynecology  
 Embryoland – Center for Assisted Reproduction  
 Aretaicio Hospital  
 Athens  
 Greece

**Zaher O. Merhi** MD  
 Clinical Fellow  
 Department of Obstetrics and Gynecology and  
 Women's Health  
 Division of Reproductive Endocrinology  
 and Infertility  
 Montefiore Medical Center/Albert Einstein College  
 of Medicine  
 Bronx, NY  
 USA

**Mostafa Metwally** MRCOG, MD  
 Consultant Gynaecologist and Subspecialist in  
 Reproductive Medicine and Surgery  
 Ninewells Hospital and Medical School  
 Dundee  
 UK

**Lina Michala** MRCOG  
 Lecturer in Pediatric and Adolescent Gynecology  
 University of Athens  
 Athens  
 Greece

**Fady S. Moeity** MD  
 Senior Lecturer  
 Department of Obstetrics and Gynecology  
 University of Alexandria  
 Alexandria  
 Egypt

**Hossam Mohamed** MBBCh, MD, FRCOG  
 Consultant in Gynaecology and Reproductive  
 Medicine  
 James Cook University Hospital  
 Middlesbrough  
 UK

**R. Katie Morris** PhD, MRCOG  
 NIHR Clinical Lecturer and Subspecialty Trainee in  
 Maternal and Fetal Medicine  
 School of Clinical and Experimental Medicine  
 College of Medical and Dental Sciences  
 University of Birmingham  
 Birmingham  
 UK

**Suheil J. Muasher** MD  
 Associate Professor  
 Department of Gynecology and Obstetrics  
 Division of Reproductive Endocrinology and  
 Infertility  
 Johns Hopkins School of Medicine  
 Baltimore, MD  
 USA

**Asif Muneer** BSc, MBChB, FRCSEd, FRCS(Eng),  
 FRCS(Urol), MD  
 Consultant in Urological Surgery and Andrology  
 University College London Hospital, and The Harley  
 Street Clinic  
 London  
 UK

**Luciano G. Nardo** MD, MRCOG  
 Director, Consultant Gynaecologist and  
 Reproductive Surgeon  
 Department of Gynaecology and Reproductive  
 Medicine  
 GyneHealth  
 Manchester  
 UK

**Frank Nawroth** MD, PhD  
 Professor of Obstetrics and Gynecology  
 Zentrum für Endokrinologie, Kinderwunsch und  
 Pränatale Medizin  
 Hamburg  
 Germany

**George Ndukwe** FWACS, FRCOG  
 Medical Director and Consultant in Reproductive  
 Medicine  
 Zita West Assisted Fertility Clinics  
 London  
 UK

## CONTRIBUTORS

**Ewka C.M. Nelissen MD**  
 Trainee Gynecologist  
 Department of Obstetrics and Gynecology  
 Research Institute Growth and Development  
 Maastricht University Medical Center  
 Maastricht  
 The Netherlands

**Scott M. Nelson BSc, MBChB, PhD, MRCOG**  
 Muirhead Chair in Obstetrics and Gynaecology  
 School of Medicine  
 University of Glasgow  
 Glasgow  
 UK

**Catherine Nelson-Piercy MBBAS, FRCP, FRCOG**  
 Professor of Obstetric Medicine and Consultant  
 Obstetric Physician  
 Department of Women's Health  
 Guy's and St Thomas' Foundation Trust and  
 Imperial College Healthcare Trust  
 London  
 UK

**Katherine L. O'Flynn O'Brien BA**  
 Research Assistant  
 Center for Reproductive Medicine  
 Cleveland Clinic  
 Cleveland, OH  
 USA

**Kutluk Oktay**  
 Director, Division of Reproductive Medicine,  
 Laboratory of Molecular Reproduction and  
 Fertility Preservation  
 Department of Obstetrics and Gynecology  
 Institute for Fertility Preservation and Reproductive  
 Medicine  
 New York Medical College  
 New York, NY  
 USA

**Bolarinde Ola MBBS, FWACS, FRCOG, MD**  
 Consultant and Honorary Senior Lecturer in  
 Obstetrics and Gynaecology  
 Subspecialist and Training Programme Director for  
 Reproductive Medicine and Surgery  
 Sheffield Teaching Hospitals NHS Foundation Trust  
 Sheffield  
 UK

**Carolina Ortega-Hrepich MD**  
 Specialist in Obstetrics and Gynecology  
 Subspecialist in Reproductive Medicine  
 Visiting Clinical Fellow  
 Department of Reproductive Medicine  
 University Hospital  
 Dutch-speaking Brussels Free University  
 Brussels  
 Belgium

**Darius A. Paduch MD, PhD**  
 Assistant Professor of Urology and Reproductive  
 Medicine  
 Department of Urology and Reproductive Medicine  
 New York Presbyterian Hospital/Weill Cornell  
 Medical Center  
 New York, NY  
 USA

**M. Ebrahim Parsanezhad**  
 Professor of Gynecology and Obstetrics  
 Chairman, Department of Gynecology and Obstetrics  
 Medical School  
 Shiraz University of Medical Sciences  
 Shiraz  
 Iran

**Maryam Parsa-Nezhad**  
 Royal College of Surgeons in Ireland – Medical  
 University of Bahrain  
 Kingdom of Bahrain

**Zamip P. Patel MD**  
 Fellow in Reproductive Urology  
 Department of Urology  
 University of Illinois at Chicago  
 Chicago, IL  
 USA

## CONTRIBUTORS

**Valerie L. Peddie** RGN, RM, ADM, BA, MSc  
Clinical Research Midwife and Fertility Specialist  
Obstetrics and Gynaecology, School of Medicine  
and Dentistry  
Division of Applied Health Sciences  
University of Aberdeen  
Aberdeen Maternity Hospital  
Aberdeen  
UK

**Litha Pepas** MBBS, BSc, MRCOG  
Subspeciality Trainee in Reproductive Medicine  
St Bartholomew's Hospital  
London  
UK

**Miltiadis Pitsos** MD, PhD  
Consultant in Obstetrics and Gynecology  
Embryoland – Center for Assisted Reproduction  
Athens  
Greece

**Neelam Potdar** MD, MRCOG  
Clinical Lecturer and Subspecialist Trainee  
Reproductive Medicine  
Reproductive Sciences Section  
University of Leicester and University Hospitals  
of Leicester  
Leicester  
UK

**Beth W. Rackow** MD  
Assistant Professor  
Department of Obstetrics, Gynecology and  
Reproductive Sciences  
Yale University School of Medicine  
New Haven, CT  
USA

**Dominique Raick** PhD  
Head of the ART Laboratory  
Clinic Saint-Vincent  
Rocourt  
Belgium

**Nicholas Raine-Fenning** MBChB MRCOG PhD  
Associate Professor and Reader of Reproductive  
Medicine and Surgery  
Director of Research Nottingham University  
Research and Treatment Unit in Reproduction  
Division of Obstetrics and Gynaecology, School of  
Clinical Sciences  
Queen's Medical Centre  
University of Nottingham  
Nottingham  
UK

**Madhurima Rajkhowa** MD, FRCOG  
Consultant Gynaecologist, Subspecialist in  
Reproductive Medicine  
Department of Obstetrics and Gynaecology  
Birmingham Women's Hospital  
Birmingham  
UK

**Abdel-Maguid Ramzy** MBBCh, MSc, MD  
Professor, Department of Obstetrics and Gynecology  
Kasr Al-Aini Faculty of Medicine  
Cairo University;  
Consultant in Reproductive Medicine and Surgery,  
Director of Research and Training Assisted  
Conception Unit, Cairo University  
Cairo  
Egypt

**Nivedita Reddy** MRCOG  
Associate Specialist, Reproductive Medicine  
Assisted Conception Unit  
Guy's Hospital  
London  
UK

**Anne Rice** BSc  
Reproductive and Developmental Biology, Maternal  
and Child Health Sciences Laboratories  
Centre for Oncology and Molecular Medicine  
University of Dundee, Ninewells Hospital  
Dundee  
UK

## CONTRIBUTORS

**Giuseppe Ricci MD**

Associate Professor of Obstetrics and Gynecology  
 Department of Medical Sciences  
 University of Trieste;  
 Director, Assisted Reproduction Unit  
 Institute for Maternal and Child Health  
 IRCCS Burlo Garofolo  
 Trieste  
 Italy

**Lynne Robinson MBChB, MD, MRCOG**

Subspecialty Registrar in Reproductive Medicine  
 Birmingham Women's Hospital  
 Birmingham  
 UK

**Heather E. Ross JD**

Specialist in Reproductive Law  
 Founding Partner, Ross and Zuckerman, LLP  
 Chicago, IL  
 USA

**Lawrence S. Ross MD**

Past President American Urological Association  
 Clarence C. Saelhof Professor Emeritus  
 Department of Urology  
 University of Illinois at Chicago  
 Chicago, IL  
 USA

**Oybek Rustamov MBBS, MRCOG**

Clinical Research Fellow in Reproductive Medicine  
 St Mary's Hospital  
 Central Manchester University Hospitals NHS  
 Foundation Trust  
 Manchester  
 UK

**Denny Sakkas PhD**

Chief Scientific Officer  
 Molecular Biometrics Inc.  
 Norwood, MA  
 USA

**Hassan N. Sallam MD, FRCOG, PhD**

Professor in Obstetrics and Gynecology  
 University of Alexandria  
 Alexandria  
 Egypt

**Mark V. Sauer MD**

Professor and Vice Chairman, Department of  
 Obstetrics and Gynecology  
 Chief, Division of Reproductive Endocrinology and  
 Infertility  
 Columbia University, College of Physicians and  
 Surgeons  
 Columbia University Medical Center  
 New York, NY  
 USA

**Mahmood I. Shafi, MB BCh, MD, DA, FRCOG**

Consultant Gynaecological Surgeon and Oncologist  
 Department of Gynaecological Oncology  
 Addenbrooke's Hospital  
 Cambridge University Hospitals NHS Foundation  
 Trust  
 Cambridge  
 UK

**Khaldoun Sharif MBBCh, MD, FRCOG, MFFP**

Consultant in Reproductive Medicine and Surgery  
 Clinical Director  
 Istishari Fertility Center  
 Istishari Hospital  
 Amman  
 Jordan

**Sherman J. Silber MD**

Director  
 Infertility Center of St Louis  
 St Luke's Hospital  
 St Louis, MO  
 USA;  
 Professor of Reproductive Medicine  
 University of Amsterdam Faculty of Medicine  
 Amsterdam  
 The Netherlands

**Kavita Singh MD, MRCOG**

Consultant Gynaecologist  
 Pan-Birmingham Women's Gynaecological  
 Cancer Centre  
 City Hospital  
 Birmingham  
 UK

## CONTRIBUTORS

**Murat Sönmezer MD**

Associate Professor  
 Department of Obstetrics and Gynecology and  
 Center for Research on Human Reproduction  
 Ankara University School of Medicine  
 Ankara  
 Turkey

**Barbara Sonntag MD, PhD**

Zentrum für Endokrinologie, Kinderwunsch und  
 Pränatale Medizin  
 Hamburg  
 Germany

**Annika Strandell MD, PhD**

Associate Professor  
 Department of Obstetrics and Gynecology  
 Sahlgrenska Academy  
 University of Gothenburg  
 Gothenburg  
 Sweden

**Sesh Kamal Sunkara MBBS, MRCOG**

Senior Registrar in Obstetrics, Gynaecology and  
 Reproductive Medicine  
 Assisted Conception Unit  
 Department of Women's Health  
 Guy's and St Thomas' NHS  
 Foundation Trust  
 King's College London  
 London  
 UK

**Brad B. Swelstad MD**

Clinical and Research Fellow  
 Department of Gynecology and Obstetrics  
 Division of Reproductive Endocrinology and  
 Infertility  
 Johns Hopkins School of Medicine  
 Baltimore, MD  
 USA

**Alison Taylor MD, MRCOG**

Consultant Gynaecologist and Specialist in  
 Reproductive Medicine  
 The Lister Fertility Clinic  
 London  
 UK

**Natalia Thorogood MBBS, BA**

Consultant  
 Department of Diabetes and Endocrinology  
 Bristol Royal Infirmary  
 University Hospitals Bristol NHS Foundation Trust  
 Bristol  
 UK

**Saioa Torrealday MD**

Clinical Instructor  
 Department of Obstetrics, Gynecology and  
 Reproductive Sciences  
 Yale University School of Medicine  
 New Haven, CT  
 USA

**Herman Tournaye**

Senior Medical Director  
 Center for Reproductive Medicine  
 University Hospital  
 Dutch-speaking Brussels Free University  
 Brussels  
 Belgium

**Kelton Tremellen MBBS, PhD, FRANZCOG, CREI**

Medical Director, Repromed  
 Associate Professor School of Pharmacy and Medical  
 Sciences  
 University of South Australia  
 Adelaide  
 Australia

**Bulent Urman MD**

Associate Professor  
 Department of Obstetrics and Gynecology  
 Koc University Faculty of Medicine  
 Istanbul  
 Turkey

**Dukaydah van der Berg MBChB, DFFP,**

DRCOG  
 General Practitioner  
 Frankley Health Centre  
 Birmingham  
 UK

xx

## CONTRIBUTORS

**Inge H.M. van Loo** MD, PhD  
 Medical Microbiologist  
 Department of Medical Microbiology  
 Research Institute Growth and Development  
 Maastricht University Medical Center  
 Maastricht  
 The Netherlands

**Usha Verma** MD  
 Associate Professor of Obstetrics and Gynecology  
 Director, Gynecological Ultrasound Division  
 University of Miami Miller School of Medicine  
 Miami, FL  
 USA

**Carla White**  
 Administrator  
 Fertility Institute of New Orleans  
 Mandeville, LA  
 USA

**Enlan Xia** MD  
 Professor and Director of Hysteroscopic Center  
 Department of Obstetrics and Gynecology  
 Fuxing Hospital  
 Affiliate of Capital University of Medical Sciences  
 Beijing  
 China

**Kayhan Yakin** MD  
 Associate Professor  
 Assisted Reproduction Unit  
 American Hospital  
 Guzelbahce  
 Istanbul  
 Turkey

**Kaoru Yanagida** MD, PhD  
 Professor and Director, Center for Infertility and IVF  
 International University of Health and  
 Welfare Hospital  
 Tochigi  
 Japan

**Dan Yu** MBBS, MMed  
 Specialist Gynecologist  
 Hysteroscopic Center  
 Fuxing Hospital  
 Affiliate of Capital University of Medical Sciences  
 Beijing  
 China

**A. Albert Yuzpe** MD, MSc, FRCS(C)  
 Emeritus Professor of Obstetrics and Gynecology  
 University of Western Ontario, London, Ontario,  
 Canada;  
 Co-Director, Genesis Fertility Center  
 Vancouver, British Columbia  
 Canada

**Armand Zini** MD, FRCSC  
 Head, Division of Urology  
 Department of Surgery  
 St Mary's Hospital  
 Montreal, QC;  
 Associate Professor of Urology  
 McGill University, Montreal, QC  
 Canada

## Preface

Louise Brown, the world's first baby conceived through *in vitro* fertilization (IVF), was born on July 25, 1978 in Oldham, England. Since then, in a relatively short time in terms of scientific evolution, over 4 million babies have been born world wide from IVF treatment.

IVF and other assisted reproduction techniques (ART) involve counseling, medical, surgical and laboratory steps, all contributing to the eventual potential success of the process. As sure as night follows day, at each step various challenges could be encountered.

The aim of this book is to stimulate resourceful thinking in the ART practitioner when dealing with those challenges, by outlining various management options, the reasoning behind them, and the evidence on which they are based. The practitioner would then be better equipped to choose the most suitable solution that best fits the needs of each particular patient.

*Khaldoun Sharif, Amman, Jordan*  
*Arri Coomarasamy, Birmingham, UK*  
2012



## How to use this book

This is intended to be a highly practical manual, providing viable solutions to real-life ART problems. To this end, the major sections of the book have been written mirroring the patient's journey in the ART process. In addition, each chapter has been written concisely, starting with one or more case histories outlining the problem, followed by a discussion on how the problem occurred, how it could have been prevented, what management options are available, and the reasoning and evidence behind them.

How will you get the most out of this book? We suggest you read the case history, and work out some management solutions yourself before reading the rest of the chapter. Compare and contrast your solutions with the options provided in the book. Discuss with your colleagues – seniors and juniors. If you have a better option than what is outlined in the book, please let us know; if we agree with you, we will acknowledge your contribution in the next edition.



SECTION ONE

**Counseling and  
preparation phase**



## 1

## Risk of cancer from ovarian stimulation

*Nikos Kanakas, Miltiadis Pitsos and Themis Mantzavinos*

Embryoland – Center for Assisted Reproduction, Athens, Greece

**Case History:** A 36-year-old woman had controlled ovarian stimulation as part of IVF treatment, resulting in a term pregnancy 2 years previously. Following that, her mother developed breast cancer at the age of 61 years. Now the patient desires another pregnancy but she is concerned about the risk of cancer due to ovarian stimulation. How should this patient be counseled?

### Background

Women who undergo ovarian stimulation are often concerned about the safety of the drugs and the risk of cancer. One issue to note is that nulliparity itself is a risk factor for developing breast [1], ovarian [2] or endometrial [3] cancers. Furthermore, infertility by itself is associated with cancer risks. Ovarian stimulation drugs have been prescribed only for a few decades now, in different doses and duration, and their long-term effects are not yet well studied.

A population-based cohort study of women who gave birth in 1974–1976 showed that women who received any type of ovulation induction treatment had increased risk of developing cancer overall compared with women who did not receive therapy [4]. However, it is important to note that this study compared women with infertility with women who conceived naturally, and thus any difference observed could be because of the fertility drugs or infertility itself. This ‘comparator problem’ is common in epidemiologic studies of assisted reproduction techniques (ART) and cancer risk.

### Management options

#### Breast cancer

Breast cancer is a hormone-related cancer; many studies have investigated the association between fertility drugs and breast cancer. One Danish cohort study included approximately 54,000 women with infertility from 1963 to 1998 [5]. In this study, the treatment with infertility drugs was not associated with breast cancer risk. Neither was there an association with the number of cycles, length of follow up or histologic type of malignancy. The only association was between gonadotropins and breast cancer in women who remained nulliparous [5]. However, in the Jerusalem Perinatal study, women who underwent ovulation induction had an increased risk for developing breast cancer though the risk disappeared after controlling for other factors, with the increased risk remaining only when ovulation induction was used for over 12 months [4]. Prolonged exposure to gonadotropins for six or more cycles was associated with increased risk of breast cancer compared with the general population in another study [6]. A cohort

## CHAPTER 1

study which included 29,700 patients with a relatively short follow up of 7 years found a transient increase in the incidence of breast cancer the year following IVF but no overall increase in the incidence during the follow-up period [7]. Age at the first IVF cycle might be a factor related with increased risk of breast cancer, with age over 30 years having an increased risk [8], or age over 40 years as shown in another study [9]. In a study that consisted of a small number of patients, fertility medications did not alter the breast cancer risk in women with *BRCA1* or *BRCA2* mutations [10].

### Ovarian cancer

Infertility itself may increase the risk of ovarian cancer in those patients who do not subsequently conceive [11]. There is evidence from an *in vitro* study that follicle-stimulating hormone (FSH) stimulates ovarian cancer cell growth [12]. A large retrospective study which included about 12,000 patients with a median follow up of 18 years showed that infertile patients had a higher risk for developing ovarian cancer than the general population; however, there was no difference between infertile patients who either used or never used infertility drugs [13]. A meta-analysis which included both case-control and cohort studies found that the incidence of exposure to infertility medications was significantly higher in ovarian cancer patients than the general population [14]. However, when the comparison was between fertility drug treated infertile patients and untreated infertile patients there was a trend towards lower ovarian cancer incidence in the treated group [14]. Thus, the increase in ovarian cancer risk appears attributable to infertility itself than ovarian stimulation drugs. This meta-analysis highlighted the importance of an appropriate comparator group (i.e. an untreated infertile group rather than the general population). A study of patients who were treated for infertility in the 1960s and 1970s in Sweden did not show any significant risk for ovarian cancer after follow up for almost 30 years [15]. A case-control study in the USA of more than 3000 women showed that women who used clomiphene citrate for over a year had a higher risk of developing ovarian malignancy than those infertile women who had never used the drug [16]. A pooled analysis of eight case-control

studies showed that among subfertile nulliparous women, ovarian cancer was not associated with fertility drug use nor length of use [17]. There was no increase of ovarian cancer incidence in women treated with IVF compared with the general population in a cohort study with a short follow up of 7 years [7].

### Endometrial cancer

Endometrial cancer is associated with anovulation and with the unopposed effect of estrogens on the endometrium [18]. A cohort study of 2496 infertile women with a mean follow up of 21.4 years showed an increased incidence of endometrial cancer when compared with the general population. However, this risk disappeared when treated infertile women were compared with untreated ones. The increased risk was attributed to the unopposed action of estrogens when researchers studied the hormonal status of women [19]. A recently published cohort study which included 54,362 infertile women reported that the use of gonadotropins increased the risk for uterine cancer after a 10-year follow up. The risk of uterine cancer was also increased with the number of cycles of clomiphene citrate use [20]. In the Jerusalem Perinatal Study, women who were treated with an ovulation induction medication had a higher risk of developing uterine cancer than women who conceived without treatment. The risk was even higher when the treatment was longer than 12 months [4]. As with breast cancer, in the same cohort of women who underwent IVF with a short follow up of 7 years, there was a transient increase in the incidence of uterine cancer the year following IVF without observing overall increase in the incidence of uterine cancer during the follow-up period [7].

Many of the current studies are based on epidemiologic data and follow up at the time when clomiphene citrate was the most common drug and the methods of IVF with superovulation were either not available or were of limited use. Prospective studies will answer the question whether ovarian stimulation increases the risk of cancer. At this time, we know that infertility and nulliparity are risk factors for gynecologic cancers and there is no proof that the medications used in the past decades have had a substantial impact on the cancer risk.