In-Vitro Fertilization

Third Edition

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CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore,
São Paulo, Delhi, Dubai, Tokyo, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521730723

This edition published by Cambridge University Press 2011
Second edition published by Cambridge University Press 2000
First edition published by Cambridge University Press 1997

Printed in the United Kingdom at the University Press, Cambridge

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data
Elder, Kay, 1946–
In-vitro fertilization / Kay Elder, Brian Dale ; with contributions from Joyce Harper, John Huntriss. – 3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-521-73072-3 (pbk.)
1. Fertilization in vitro, Human. I. Dale, Brian. II. Title.
[DNLM: 1. Fertilization in Vitro–methods. 2. Germ Cells–growth & development. 3. Reproductive Techniques, Assisted. WQ 208]
RG135.D34 2011
618.1′78059–dc22
2010040403

ISBN 978-0-521-73072-3 Paperback

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Cambridge University Press
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Preface

The union of male and female gametes during the process of fertilization marks the creation of a completely new individual, a unique event that ensures genetic immortality by transferring information from one generation to the next. It also creates variation, which introduces the effects of evolutionary forces. During the first half of the nineteenth century, fertilization and the creation of early embryos was studied in a variety of marine, amphibian and mammalian species, and by the early 1960s had been successfully achieved in rabbits (Chang, 1959), the golden hamster (Yanagimachi and Chang, 1964) and mice (Whittingham, 1968). Following a decade of extensive research in mouse, rat and rabbit reproductive biology and genetics, Robert Edwards began to study in-vitro maturation of human oocytes in the early 1960s (Edwards, 1965). On February 15, 1969, the journal *Nature* published a paper authored by R.G. Edwards, B.D. Bavister and P.C. Steptoe: "Early stages of fertilization in vitro of human oocytes matured in vitro" (Edwards *et al.*, 1969). The paper scandalized the international community – reporters and camera crews from all around the world fought to gain entry to the Physiological Laboratory in Cambridge, where Edwards and his team were based. It drew fierce criticism from Nobel Laureates and much of the scientific, medical and religious establishment of the UK and elsewhere, being regarded as tampering with the beginning of a human life: religious, ethical and moral implications were numerous. IVF is now accepted completely as a clinical procedure; in the quest for improvements via new technology we should not be disheartened or surprised by irrational criticism, but draw courage from the pioneering work of Bob Edwards and his colleagues, whose brave perseverance opened up an entirely new field of interdisciplinary study, embracing science, medicine, ethics, the law and social anthropology.

Half a century later, the creation of new life via human IVF continues to attract debate and discussion, prompting many governments to define "the beginning of a human life" in formulating legislation surrounding assisted reproductive technologies (ART). Not surprisingly, these definitions vary from country to country and often reflect the theological beliefs of the nations involved. Scientifically, a number of basic facts regarding fertilization and embryo development must be considered in defining the "Beginning of Life". Both in vivo and in vitro, gametes and preimplantation embryos are produced in great excess, with only a tiny proportion surviving to implant and produce offspring; human gametes are certainly error-prone, and the majority are never destined to begin a new life. Some female gametes may undergo fertilization, but subsequently fail to support further development due to deficiencies in the process of oogenesis. Once gametes are selected, their successful interaction is probably one of the most difficult steps on the way to the formation of a new life. At this stage the two genomes have not yet mixed, and numerous developmental errors can still occur, with failures in oocyte activation, sperm decondensation, or in the patterns of signals that are necessary for the transition to early stages of embryo development. A fertilized ovum is a totipotent cell that initially divides into a few cells that are equally totipotent, but for a brief period of time these cells can give rise to **one** (a normal pregnancy), **none** (a blighted ovum or anembryonic vesicular mole), or even **several** (monozygotic twinning) individuals. Although fertilization is necessary for the life of a being, it is not the only critical event, as preimplantation embryo development can be interrupted at any stage by lethal processes or simple mistakes in the developmental program. A series of elegantly programmed events begins at gametogenesis and continues through to parturition, involving a myriad of synchronized interdependent mechanisms, choreographed such that each must function at the right time during embryogenesis. Combinations of both physiological and chromosomal factors result in a continuous reduction, or "selection" of conception products throughout the stages that lead to the

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potential implantation of an embryo in the uterus. Preimplantation embryogenesis might be described as a type of Darwinian filter where only the fittest embryos survive, and the survival of these is initially determined during gametogenesis.

It may be argued that the task of elaborating and defining the concept of a "new individual" belongs to philosophers and moralists. For some, the beginning of human life coincides with the formation of a diploid body in which the male and female chromosomes are brought together. For others, true human life only occurs after implantation of the embryo in the uterine mucosa. Many believe that a new individual is formed only after differentiation of the neural tube, whilst others believe that life begins when a fetus can live outside the uterus. In its most extreme form, some philosophers consider the acquisition of self-awareness of the newborn to define a new life. Most scientists would probably agree that life is a continuous cyclical process, with the gametes merely bridging the gap between adult stages. Science, one of the bases of human intellect and curiosity, is generally impartial and often embraces international and religious boundaries; ethicists, philosophers and theologians cannot proceed without taking into account the new information and realities that are continuously generated in the fields of biology and embryology. Advances in the expanding range and sensitivity of molecular biology techniques, in particular genomics, epigenomics and proteomics continue to further our understanding of reproductive biology, at the same time adding further levels of complexity to this remarkable process of creating a new life.

In the decade since the previous edition of this book was published, the field of human IVF has undergone significant transformation in many different ways. Further scientific knowledge gained from use of sophisticated technology is one of them; management of patients and treatment cycles has also been influenced by commercial pressures as well as legislative issues. The rapid expansion in both numbers of cycles and range of treatments offered has introduced a need for more rigorous control and discipline in the IVF laboratory routine, and it is especially important that IVF laboratory personnel have a good basic understanding of the science that underpins our attempts to create the potential beginning of a new life.

IVF is practiced in most countries of the world, and the number of babies born is estimated to be in the order of at least 10 million; a vast and comprehensive collection of published literature covers clinical and scientific procedures and protocols, as well as information gained from modern molecular biology techniques. Many books are now available that cover every chapter (and in some cases individual paragraphs) of this edition. Unlike 10 years ago, a wide range and variety of media, equipment and supplies is available specifically for use in human IVF, each with its own instructions and protocols for use. IVF is successfully carried out with numerous adaptations in individual labs, and specific detailed protocols are no longer appropriate. Our aim in preparing this third edition was to try to distill large bodies of information relevant to human IVF into a comprehensive background of physiological, biochemical and physical principles that provide the scientific foundation for well-established protocols in current use.

This book is dedicated to Bob Edwards, who embraces and inspires all who are blessed with the experience of knowing him … we salute and honor his infinite vision and endless optimism:

> *There wasn't any limit, no boundary at all to the future … and it would be so that a man wouldn't have room to store such happiness….*
>
> *(James Dickey, American poet and novelist, 1923–1997)*

Further reading

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Acknowledgements

We are immensely grateful to Helen Picton, David Miller, John Huntriss, Jan Hogg and Allan Pacey for kindly allowing the current course material for the University of Leeds MSc in Clinical Embryology to be adapted for this book. We are also deeply indebted to numerous colleagues who patiently reviewed and revised each emerging chapter; particular thanks to Yves Ménézo, Bryan Woodward, Marc van den Bergh, Darja Kastelic, to Kathy Niakan, Jenny Nicholson and Mila Roode for help with stem cell biology; to Gianfraco Coppola for his help with drawings, and to Oleksii Barash, Marc van den Bergh, Thomas Ebner and Agnese Fiorentino for generously contributing original images of oocytes and embryos.

Special and very sincere thanks to Mike Macnamee and all of the friends and colleagues at Bourn Hall Clinic who continue to offer endless encouragement and support.