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Foreword

> O! for a Muse of fire, that would ascend
> The brightest heaven of invention!
>
> Shakespeare, Henry V

It is only appropriate that, in the foreword of the fifth edition of this book, *Infertility in Practice* begins with the same plea to a muse that the chorus made in the opening scene of *Henry V*. And as in that play where the same muse, that is, Shakespeare, had previously composed *Henry IV*, *Part I* and *Part II*, the plea has been answered here by the same muse who composed the previous four editions of the book: Prof. Adam Balen of Leeds University, UK. The voice of his muse is distinct and illuminating, and he writes in an engaging manner that causes chapters to flow one into another. It is therefore no surprise that previous editions of this book have been translated into many languages, including Greek and Chinese. (These two languages alone should point to the broad reach of this author and this book.)

The ongoing revisions and updates of this book by its dedicated and diligent author have allowed it to become a classic treatise in the diagnosis and treatment of infertility. The foundation upon which this book is built is evidence-based medicine, which in turn is based on a thorough review of relevant scientific studies involving human patients. Practitioners and patients alike turn to data for their decision-making in diagnosis and clinical care. The problem is not the paucity of data but the excess of data, often of dubious origin, conflicting, and ever more available on the internet. The proliferation of data, for example, as are available on national registries of *in vitro* fertilisation (IVF) outcomes, is riven by so many categories (age, type of IVF procedure, source of gametes, etc.) that it requires both a medical degree and a statistical degree to interpret it. Adam Balen's genius in this book is to apply the principles of evidence-based medicine to sift through the profusion of such data and make scientifically sound interpretations and recommendations that are easily comprehensible.

Adam Balen brings to this task a background not only as a skilled and consummate clinician but also as a world-renowned researcher in infertility and a leading medical authority developing infertility treatment guidelines in both the United Kingdom (through the Royal College of Obstetricians and Gynaecologists) and the world (through the World Health Organization). He is a prolific medical author who has composed leading texts for both practitioners and patients.

This new edition of the book is necessary as the world of reproductive medicine is one of the most rapidly evolving fields in medicine. It exists at the crossroads of so many fields, including genomics, pharmacology, medical devices and technology, cancer, and ethics. New chapters have been added to address these areas, including chapters on pre-implantation genetic testing and fertility preservation. The increasing use of cryopreservation has revolutionised assisted reproductive technology. Additionally, declining birth rates in developed countries, deferred childbearing, increased numbers of mothers at high risk, and increased utilisation of fertility treatments by previously marginalised populations, including single parents and LGTBQ+ people, have led to a greater public interest in and scrutiny of the practice of reproductive medicine. These trends are supported by chapters discussing preconception evaluation of patients, ethical and religious principles underlying the practice of reproductive medicine, and counseling of people seeking to start or build a family. This holistic approach is rarely found in textbooks of medicine.

What I find most remarkable are the concluding chapters addressing diminishing returns or failure of treatment in reproductive medicine. These are difficult areas to address in clinical practice, let alone in evidence-based medicine. This often leads to grasping at straws and the overutilisation of medical resources with slim or no hope of success. The chapter on the use of adjuvants and alternative treatments puts many of these practices into their proper, limited perspective. Prof. Balen dissects the causes of recurrent implantation failure and recurrent pregnancy loss. Finally, he provides guidance for the most

difficult decision of all: when to cease treatment. There is no other textbook that provides such a comprehensive summary of infertility treatment than this one.

Let me finish by paraphrasing the muse of *Henry V* to wholeheartedly endorse this book as "your hope, your stay, your guide and the lantern to your feet" in the infertility treatment of your patients.

Richard S. Legro, MD, FACOG, FRCOG, ad eundem
University Professor and Chair, Department of Obstetrics and Gynecology
Penn State College of Medicine
Hershey, PA

Preface

I am pleased to present the fifth edition of *Infertility in Practice*, which has been updated every 5 years or so since it was first published in 1997. Throughout this time, our understanding of infertility and its management has continued to expand rapidly. *Infertility in Practice* has been written as a practical guide and is based on my experience over the last 40 years of daily clinical practice. The aim of the book is to place the modern approach to the management of infertility in the context of sound theory and evidence-based therapy. I have striven to provide the reader with a comprehensive classification of the causes of infertility, their investigation and their management. In this edition, I have thoroughly revised and updated the text and completely rewritten most of the chapters.

In vitro fertilisation (IVF) has been available for almost 45 years, and, in many European countries, 2–5% of babies are the result of IVF therapy. Indeed, approximately 10 million babies have been born worldwide from IVF, half in the last 10 years. A great deal of public attention has naturally been focused on the high-tech advances in assisted conception therapies, yet a fundamental issue is the preconception health of both partners, which is key both to conception, whether natural or assisted, and to the birth of a healthy baby. I introduced preconception health in the very first edition of this book at a time when few were addressing this important topic, and it remains just as relevant now – if not more so. In this edition, I bring in the latest thoughts on nutritional health, periconception care and the exciting new world of the microbiome.

Since the fourth edition of *Infertility in Practice* was published, there have been many advances in the understanding and management of infertility and other updates to practice that are discussed in this new edition – for example, a greater understanding of the pathophysiology of ovarian ageing and ovarian reserve testing, classification of disorders of ovulation and the management of polycystic ovary syndrome, refinement of regimens for superovulation, improved embryo culture systems and the use of artificial intelligence for the selection of embryos, assessments for endometrial receptivity and management of recurrent implantation failure, and pre-implantation genetic testing (PGT) as a therapeutic tool, opening up the possibility for aneuploidy screening. The clinical approach to investigation and therapy also has made great strides to minimise the time taken to reach a diagnosis and direct a couple swiftly to the appropriate treatment.

The field has also seen the publication of a number of evidence-based guidelines for the investigation and management of infertility, produced variously by the British Fertility Society, the Royal College of Obstetricians and Gynaecologists, the UK National Institute for Health and Care Excellence, the European Society for Human Reproduction and Embryology, the American Society for Reproductive Medicine and The World Health Organisation. It is reassuring to see a consolidation of knowledge in an attempt to ensure evidence-based practice which, in the United Kingdom, has been used to state the case for adequate funding of fertility care, although sadly with little effect on the decision makers in government.

When one is determining appropriate treatment for the management of infertility, there may be one clear treatment or several potential options. Furthermore, there are often a variety of drugs to choose between and several potential treatment protocols. It is important to consider not only the efficacy of treatment but also its cost-effectiveness on the basis of a combination of scientific evidence and health economics. There has been a trend for cost-effectiveness analyses to be sponsored by the pharmaceutical industry. Although much research could not take place without industry support, it is important to be cautious when interpreting such data.

The treatments for most causes of infertility provide very satisfactory cumulative chances of conception and of the birth of a healthy child. However, the side effects must be borne in mind, whether it is the immediate risk of ovarian hyperstimulation syndrome and multiple pregnancy or the long-term health

risks, such as the possibility of ovarian cancer (reassuringly not the threat it was once thought to be). In this edition, I also discuss the outcome for children born as a result of assisted reproduction technology.

Improvements in cryopreservation technologies now enable the successful freezing of oocytes, ovarian tissue and even testicular tissue and the prospect of preserving fertility before sterilisation therapy for cancer and other conditions. More controversial is the potential to freeze oocytes as an insurance policy for young women who wish to delay childbearing for social reasons. This also brings with it the need to consider an improvement in fertility education for young people at schools and colleges. In the UK, the average age of first-time mothers is rising, and an increasing proportion of women have never had a child (20%, compared with 10% just one generation ago). This is for a variety of reasons. And, while approximately 15% of the population experiences fertility problems, treatments do not always work, and their success declines with the increasing age of the woman. When people attend fertility clinics, they are often surprised by these facts and wish they had been better informed when they were younger. The need for fertility education arises from changing patterns of family formation in recent times, including starting families at an older age and the changing dynamics of "modern families". Young people feel unprepared for how best to plan their career and family, and whilst they feel they have control over contraception, they have little idea of the various factors that may influence their fertility later in life – whether related to lifestyle, diet, smoking and recreational drugs or the natural biological changes associated with getting older. Studies have found that adolescents do not know much about this, would like to know more and need the information to be conveyed in a way that is engaging and helps them to integrate it at their current life stage. For this reason, I founded the Fertility Education Initiative [1], when I was chair of the British Fertility Society, with the aim of ensuring that people have a greater understanding and awareness about fertility and reproductive health, so that they can make an informed choice about their own fertility journey or that of others upon whom they may have an impact. Educational material for teachers and animations to introduce these important topics to young people have been created [2, 3].

The whole dynamic of modern families has also changed with a greater acceptance of new ways to create families and achieve fertility. The treatment of lesbian couples was provided by very few clinics when I wrote the first edition of this book – an exception being my own; indeed, I have campaigned for and achieved equal funding for same-sex couples in our region. Surrogacy for gay men is much more common these days, as is the use of donor sperm to help single women to conceive. People with gender identity dysphoria are also being assisted to preserve their fertility for potential use in the future.

Throughout *Infertility in Practice*, I comment on emerging technologies, some of which are already being incorporated into daily practice, such as the use of pronuclear transfer for the treatment of inherited mitochondrial disorders, and other developments, such as genome editing, which brings with it significant concerns regarding the potential abuse of such technology.

The topic of "add-ons" is vexed with emotion and concern – not least because of the lack of consensus on what constitutes the definition of an add-on! The term has been applied to a range of procedures, including intracytoplasmic sperm injection (ICSI), time lapse imaging, assisted hatching of embryos, the endoscratch, acupuncture and reflexology. Some may be rooted in science but have not yet been proven by sufficiently sized randomised trials or meta-analyses, whilst others have been proven to be ineffective or even dangerous. People with infertility will go to any length to have a much-wanted baby, and they can be easily enticed by misleading advertising for unproven products. Furthermore, when treatments are often self-funded by the patients themselves, it is essential that they are not exploited by misleading advertising.

This fifth edition of *Infertility in Practice* has been written during the global Covid-19 pandemic, caused by the SARS-CoV-2 coronavirus (discussed in Chapter 1). This is still evolving and there are many unknowns about the long-term effects of the virus, not only on population dynamics but also on fertility and pregnancy. We have all experienced the effects of the pandemic on our health services and also on our ability to provide fertility treatments when clinical resources, and personnel, have been so stretched. A global vaccination programme is the way forward, and I can only hope that we will be through these dark times by the time the sixth edition is being published.

I would like to acknowledge my partner, Grace Dugdale, from whom I have learnt so much about preconception health, about the way in which fertility problems are often a "red flag" for other health conditions and that reproductive health shouldn't be seen in isolation but as part of the whole life course

for women and men. We have recently encapsulated this knowledge in *The Fertility Book* for patients [4]. And lastly, I wish to pay tribute to the tremendous contribution to our field of my mentor and great friend Howard Jacobs, co-author of the first two editions of this book. I hope that wherever you work and whatever your expertise, *Infertility in Practice* will help in the management of couples attending your clinic.

Adam H. Balen
Leeds, 2022

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About the Author

Professor Adam H. Balen MB, BS, MD, DSc, FRCOG is a full time NHS Consultant in Reproductive Medicine at Leeds Teaching Hospitals NHS Trust. Adam is also Chair of the Innovation and Research Board of CARE Fertility and a consultant at CARE Fertility Leeds. In recognition of his research, he was awarded a personal (honorary) chair in 2004 and a DSc in 2010, by the University of Leeds, which is the highest academic degree for clinicians in the United Kingdom. Adam qualified as a doctor in 1983 and spent his first few years of training in obstetrics and gynaecology in London, Oxford and even a spell in Africa. These were the early days of *in vitro* fertilisation (IVF) and he worked with some of its pioneers (Bob Edwards, Howard Jacobs).

He became a consultant in Leeds in 1996, helping to create one of the United Kingdom's largest IVF units – *Leeds Fertility*. For many years, Adam has had a particular interest in the causes and management of polycystic ovary syndrome (PCOS). His research covers the full spectrum of the condition, including its effects during adolescence and adult life on reproductive and metabolic health, fertility, cosmetic effects, quality of life and long-term health. For many years, he has been passionate about preconception health and public education and, together with Grace Dugdale, has written *The Fertility Book – Your Definitive Guide to Achieving a Healthy Pregnancy* (Penguin, Vermilion Press, 2021).

Professor Balen is the only UK gynaecologist to have sat on the international consensus groups on the definition and management of PCOS, which have written major guidelines since 2003. He was Chair of the World Health Organisation (WHO) expert working group on the management of PCOS for the Global Taskforce on Infertility, which produced guidelines that were published in 2016; he continues in the WHO Guideline Development Group and the Global PCOS Alliance which is publishing further guidelines on the management of both infertility and PCOS in 2022/23. Adam also sits on the International Federation of Obstetrics and Gynaecology committee on the classification of disorders of ovulation. Adam has been an advisor to the National Institute for Clinical and Care Excellence and the Human Fertilisation and Embryology Authority. For many years, he chaired the Reproductive Endocrinology section of the European Society for Human Reproduction and Embryology and sat on its international scientific advisory committee. Adam has also been on guideline groups for the American Society of Reproductive Medicine and the National Institutes for Health in the United States.

For many years, Adam was on the Executive Committee of the British Fertility Society (BFS), with many key roles, and was elected Chair in 2015–2018. He now sits on the Board of Trustees of the BFS. He also sits on the Council of the Royal College of Obstetricians and Gynaecologists, for which he is the spokesperson on all matters relating to Reproductive Medicine. He chaired the NHS England working group on funding for IVF and has campaigned to provide equitable funding for assisted conception throughout the UK.

As Chair of the BFS, Adam created The Fertility Education Initiative to improve the provision of education to young people about all aspects of reproductive health, including factors that may influence their future fertility. He continues as Chair of The Fertility Education Initiative, which has influenced the Government in the UK to include fertility education on the national curriculum as part of relationship and sex education in schools.

Adam is the author of more than 260 peer-reviewed papers and 16 books, including his best-selling *Infertility in Practice* (5th edition, 2022). He lectures and speaks nationally and internationally on all matters relating to infertility, PCOS and reproductive medicine. He has also made educational programmes for radio and TV and is regularly in the press commenting on the latest developments in fertility care. In his spare time, Adam is passionate about music and also loves walking and developing his garden in the Yorkshire Dales.

1

Epidemiology of Infertility, 21st-Century Considerations and the Covid-19 Pandemic

1.1 Introduction

Infertility is recognised by the World Health Organization (WHO) as a disease of the reproductive system, and it is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse [1]. Infertility is common, with at least 48.5 million people worldwide not being able to have a live birth over a 5-year period [2]. The overall prevalence of infertility varies around the world: it is estimated at between 4% and 17% in low- and middle-income countries and as high as 30–40% in some regions of sub-Saharan Africa [3]. If we look at the situation in the United Kingdom, infertility is the second most common reason, after requests for contraception, that women of reproductive years see their general practitioner. A recent large, cross-sectional population survey in the UK reported the prevalence of infertility as 12.5% (CI 95% 11.7–13.3) among women and 10.1% (CI 95% 9.2–11.1) among men. Increased prevalence was associated with later cohabitation with a partner, higher socio-economic status and, for those who had a child, becoming parents at older ages. The reported prevalence of seeking help for infertility was 57.3% (CI 95% 53.6–61.0) among women and 53.2% (CI 95% 48.1–58.1) among men [4], and those who sought help were more likely to be better educated and in higher status occupations.

Most accepted definitions of infertility require the number of months (from 12 to 36) before the consultation during which the couple has been exposed to the chance of a pregnancy. When the lifetime experience of a couple's attempt to raise a family is considered, a different picture emerges, with some studies revealing that at least one-quarter of all couples experience unexpected delays in achieving their desired family size, although only one-half of these may seek treatment [5].

In recent years, there has been an increase in publicity about infertility and the success of reproductive medicine technologies that has helped to reduce both the stigma of infertility and the reluctance of couples to seek advice. Indeed, we find that the taboo of infertility in many respects has been replaced by sensitivities in discussing lifestyle factors – such as obesity, which is more of a health concern and yet has become a more sensitive topic for discussion.

It is important at the outset to acknowledge that the single most important determinant of a couple's fertility is the age of the female partner. Green and Vessey [6] showed that, for women up to and including 25 years of age, the cumulative conception rate (CCR) is 60% at 6 months and 85% at 1 year; that is, of 100 couples trying to conceive, 40 couples will not be pregnant after 6 months and 15 couples will still not have conceived after 1 year of trying. For couples where the female partner is aged 35 years or older, the conception rate is 60% at 1 year and 85% at 2 years; that is, fertility has *halved* because of age alone [6]. Some studies have shown a less dramatic effect of age on the cumulative chance of a live birth and have also looked at the influence of male age [7]. One study showed that the proportion of women who had not conceived after 12 cycles ranged from 8% in those aged 19–26, to 13–14% for those aged 27–34 and to 18% for those aged 35–39 [7]. The cumulative conception curve also indicates a continued, albeit gradual, increase in live births over the second year of trying (Figure 1.1). Extrapolating this over 5 years and using monthly fecundity rates ranging from 0.25 (that is 25% of couples per month) at age 25 to 0.15 at 30, 0.1 at 35, 0.05 at 40 and 0.01 at age 45, we can see the dramatic decline in fertility as a women enters her fifth decade of life (Figure 1.2). It is very rare for a woman to conceive naturally in

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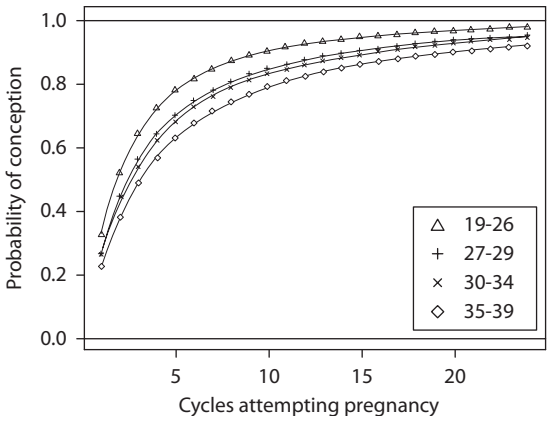

FIGURE 1.1 Cumulative probability of pregnancy assuming a frequency of intercourse of two times a week, according to female age

Source: From reference 6, with permission.

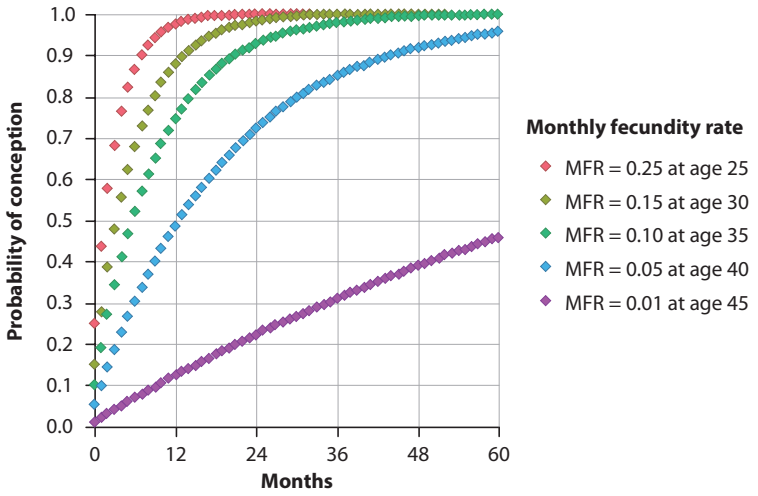

FIGURE 1.2 Five-year extrapolation of monthly fecundity rate in women from age 25 to 45 years.

Source: Richie Cotton, *How long does it take to get pregnant?* www.4dpiecharts.com/2012/06/, under Creative Commons Licence.

the 5 years before her menopause, the average age of which is 51 and is closely related to the age of her mother's menopause. During the 5 years prior to this, that is, 41–46 years for most women, natural fertility is unlikely, and in the preceding 5 years (36–41) fertility is declining more rapidly, in harmony with the decline in oocyte number over time (Figure 1.3).

1.2 Ovarian Ageing

It is worth reflecting on the reason for the strikingly different effects that the passage of years has on the fertility of the two sexes. In men, the supply of sperm is continuous, with the germ cells of the testis dividing all the time, so that the average age of sperm in an ejaculate is measured in months. However, women are born with a finite complement of eggs that do not undergo further cell division until just

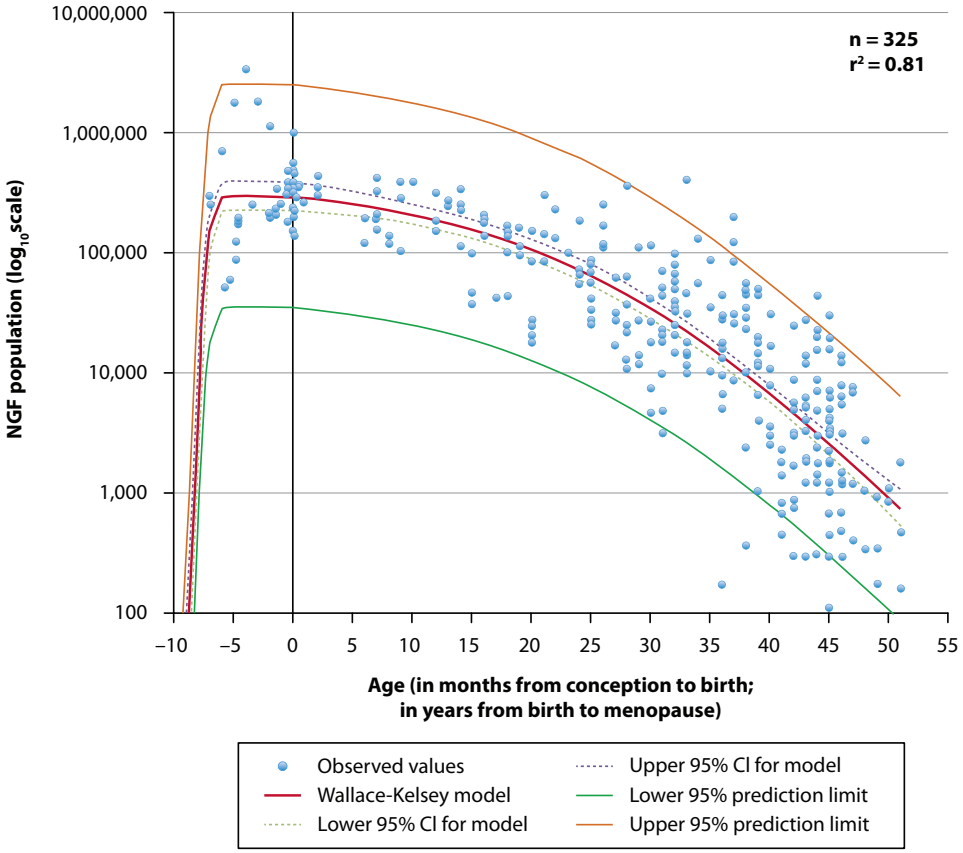

FIGURE 1.3 Depletion of oocytes over time from fetal life through to menopause.

Source: From reference 8, under Creative Commons Attribution License.

after fertilisation. Thus, an oocyte ovulated today is pretty well the same age as the woman from whose ovary it came. Even deoxyribonucleic acid (DNA), the most stable molecule in biology, is not completely invulnerable to the passage of years; this impact of age on oocytes is consistent with its effect on the age-related increased risk of miscarriage and chromosomal abnormalities. Figure 1.3 illustrates the progressive decline in oocytes over time, from fetal life through to menopause. Oocytes are laid down within the ovaries during fetal development and multiply by mitosis, reaching a maximum at about 20 weeks' gestation. Oocytes commence meiosis but are arrested during the first meiotic division until just prior to ovulation, when the pre-ovulatory surge in luteinising hormone (LH) facilitates the completion of meiosis I in preparation for fertilisation. Of the 1–2 million oocytes within both ovaries at birth, only about 450 are destined to ovulate – that is, assuming that ovulation occurs every month for the 38 years or so from menarche at age 13 through to menopause. The remaining oocytes are progressively lost by atresia and apoptosis at a maximum rate of up to 30 per day (1,000 per month) in young women (Figure 1.3, [8]). This loss occurs irrespective of whether a woman is ovulating, pregnant, breastfeeding or taking medication to suppress ovulation, such as the contraceptive pill. Despite extensive research on the processes involved in follicular maturation and recruitment, it has not yet been possible to slow the rate of ovarian ageing – perhaps the "holy grail" of reproductive medicine. The decline in oocyte number can be hastened, however, by poisons such as cigarette smoking or chemotherapy for certain cancers, and it is also determined by chromosomal make-up and genetic factors.

Male fertility also declines with age, but to a lesser degree than for women, and is evidenced by a longer time to conceive, more losses due to miscarriage, a greater need for intracytoplasmic sperm injection

(ICSI) during fertility treatment and a lower chance of success with *in vitro* fertilisation (IVF) for men older than 50 [7]. So whilst men have fathered children into their 90s, there is an increase in the rate of fresh genetic mutations in sperm with increasing paternal age that lead to some inherited congenital defects (such as Marfan's syndrome, Alpert's syndrome, Duchenne muscular dystrophy, haemophilia, bilateral retinoblastoma and achondroplasia) and an increased risk of autism developing in children. Sperm numbers and function do tend to decline with age, although there is no predictable pattern. Whilst the decline is most noticeable after the age of 55, even men older than 35 have been shown to have half the chance of achieving a pregnancy compared with men younger than 25.

1.3 At What Age Should Couples Start Trying for a Family?

The age at which a couple should start trying for a family is a question often asked, yet difficult to answer as it will depend upon a number of factors, not least the number of children that they may desire and whether they might be prepared to use a high-tech fertility treatment such as IVF. Furthermore, differential importance may be attached to first and later children, with many couples who experience secondary infertility (that is, after already having a living child) feeling less concerned than before their first was born. Habbema et al. [9] have produced data from a simulated model, building in whether a couple wants a 50, 75 or 90% chance of realising their desired family size and whether they would be prepared to consider IVF, assuming that the latter is readily available and affordable. For a 90% chance of having a one-child family, a couple should start trying when the woman is 32 if they wish only to try naturally or 35 if they are prepared to consider IVF; for two children the ages are 27 and 31, and for three children 23 and 28, respectively [9]. There is good evidence that most young people are overly optimistic about their chance of conception, and so it is important to provide young people with education about their potential fertility and factors that may influence it.

1.4 Fertility Education

The need for fertility education arises from changing patterns of family formation in recent times, including starting families at an older age and the changing dynamics of "modern families". It has been shown that young people feel unprepared for how best to plan their career and family. While they feel they have control over contraception, they have little idea of the various factors that may influence their fertility later in life – whether related to lifestyle, diet, smoking and recreational drugs or the natural biological changes associated with getting older. Studies have found that adolescents do not know much about this, would like to know more and need the information to be conveyed in a way that is engaging and helps them to integrate it at their current life stage.

In the UK, the average age of first-time mothers is rising, and an increasing proportion of women have never had a child (20%, compared with 10% just one generation ago). This is for a variety of reasons. And, while approximately 15% of the population experiences fertility problems, treatments do not always work and their success declines with the increasing age of the woman. When people attend fertility clinics, they are often surprised by these facts and wish they had been better informed when they were younger.

In 2016, I formed the Fertility Education Initiative (FEI), which comprises a group of healthcare professionals, with the aim of ensuring that people have a greater understanding and awareness about fertility and reproductive health, so that they can make an informed choice about their own fertility journey or that of others upon which they may have an impact. The aims are to provide not only education on male and female reproductive health but also an understanding of societal and cultural variations in family building and knowledge of routes to parenthood for heterosexual, LGBTQ+ and single people with and without fertility issues. This should include information on assisted conception techniques for family building, other routes to parenthood (such as adoption, fostering and stepfamilies) and living a life without children. It is also important to provide an understanding of reproductive technologies, what they can and cannot do and how they might impact on how human beings are made in the future [10–14].

Furthermore, the FEI also responded to the UK government's consultation on Relationship and Sex Education in 2019 and was successful in getting matters relating to fertility and reproductive health onto the national curriculum for schools. The bulk of the guidance naturally deals with general health and well-being, the foundation of healthy relationships and all aspects of physical, emotional, mental, and sexual and reproductive health and well-being. There is also reference to understanding the various forms of sexuality and sexual relationships and "that others' families, either in school or in the wider world, sometimes look different from their family, but that they should respect those differences and know that other children's families are also characterised by love and care". There is an emphasis on age-appropriate information and on when specific topics should be discussed. The inclusion of information on fertility in the guide is a huge step forward for fertility education, which until now has been largely overlooked, poorly taught and not even properly covered in most biology syllabi, let alone PHSE (personal, social, health and economic education) or relationship and sex education (RSE) lessons. There has been a groundswell of interest, with an international group now working to enhance education globally to ensure that young people are empowered with the knowledge they need to make informed decisions about their reproductive choices and that they have a full understanding of all aspects of their reproductive health and what they can do to enhance their chances of having a family when the time is right.

1.5 Measuring Infertility and Response to Treatment

To decide whether a couple should be investigated for treatment, and indeed to formulate a prognosis for the success of that treatment, the clinician needs a definition of normal fertility that is sensitive to the fact that, in nature, the highest rates of fertility do not exceed 25% conception per cycle. Thus, if 100 couples discontinue contraception, at the end of 1 month, 25 women can expect to be pregnant and 75 couples will need to try again next month. At the end of the second month, $75 \times 0.25 = 19$ more women will have conceived, giving a cumulative conception rate (CCR) of 25% + 19% = 44% at 2 months.

If we assume that the monthly rate of conception remains constant, it is easy to see how theoretical CCRs can be calculated for any infertility diagnosis and for any duration of treatment. In practice, monthly rates of conception do not remain constant because the more fertile couples conceive in the earlier months, and when we turn from theoretical examples to real clinical situations, follow-up is usually incomplete. The question then arises as to how to deal with the results of couples who leave a study before they have conceived or before their programme of treatment has been completed. Moreover, couples leave treatment after different periods of time according to their own needs and circumstances, for example, because of emotional stress, financial constraints or the advice given to them by their specialists.

By convention, in the calculation of CCR, the outcome for those leaving a programme for reasons other than pregnancy is assumed to be the same as for those who remain in treatment. This assumption is the basis for the construction of CCR based on life table analysis, a method that was originally devised to describe survival from malignant disease, but in the case of fertility, is inverted to show increasing conception rather than declining survival.

CCRs calculated from life tables have been used extensively to express fertility rates in relation to age and disease and to compare the results of treatment in different centres. An important extension of the CCR is the cumulative live birth rate (CLBR). Because the rates of miscarriage and several obstetric complications are closely influenced by maternal age, and indeed other maternal factors that influence reproductive potential, the fall-off with age of the CLBR is even more severe than that of the CCR. However, it is the CLBR that patients want to know in response to the question, "What are our chances of having a baby?"

Thus, it behoves us to acknowledge certain limitations in CLBR's interpretation. The first limitation is that it has been shown that, as the number of dropouts increases, the *calculated* conception or birth rate increases. This finding means that the less careful clinics are in obtaining follow-up information, the more this method of describing results exaggerates their success. The second important point to note is that dropouts from treatment are not random; people leave a programme largely because of their experience with it. One may safely assume that the outcome of the whole group would have been worse if those

who had dropped out because of their, or the staff's, lack of confidence had stayed in, and their results would have contributed directly to the determination of the group's response to treatment. Because of the free-market approach to infertility treatment, patients may enter a given clinic's statistical record after already having had treatment elsewhere. Thus, what may be recorded as a first cycle may actually only be the first in that clinic for the couple concerned, and so they would be starting with a lower prospect of success than if they were only just beginning treatment. This situation is the case particularly in countries, such as England, in which the majority of patients have been forced to fund their own treatment and many travel between clinics.

1.6 Definition of Infertility

The live birth rate (or the "take-home baby rate") clearly depends on both the rate of conception and the survival of the pregnancy, and in infertility practice this rate is largely determined by the miscarriage rate. By convention, when a patient is referred to as being infertile, it means a slow rate of conception – infertility is rarely absolute. Indeed, I prefer the expression subfertility. As already mentioned, in most people, age is the most important determinant of the conception rate. All other things being equal, a couple in which the female partner is 25 years old or younger stands a 5 out of 6 chance of conceiving in the year after discontinuing contraception. If, despite a regular menstrual cycle and a normal sex life, pregnancy has not occurred by then, most authorities would accept that a couple has a fertility problem and would offer investigation and treatment. If there is a history of menstrual disturbance, assessment of the patient's fertility could take into account how long it will take her to accumulate the 12 or 13 ovulations that a woman with a normal cycle has in 1 year. Clearly, if a woman ovulates only four times a year, it will take her three times as long as a woman with a regular cycle to have the same chance of getting pregnant. In that situation, however, it makes no sense to defer investigation for a year, let alone 3 years. Similarly, if there is a history of pelvic inflammatory disease or a severe attack of appendicitis (particularly if there has been peritonitis), or if the male partner has had an attack of orchitis or a history of cryptorchidism, investigation should begin sooner rather than later.

A more difficult problem is defining infertility in the couple with an older female partner. In one way, one might consider delaying investigation because it takes longer for a woman of 35 years or older to achieve a particular conception rate. Conversely, the slope of the line relating the risk of childlessness to age gets much steeper as a woman approaches 40 years of age. Furthermore, the prospects of achieving a pregnancy with treatment are parallel to this curve. There is therefore little time to lose for such couples, and in my practice, I am more active in advising investigation and treatment as the female partner passes her 35th birthday. There seems little point in waiting beyond 1 year, and for many women, particularly those with some diagnostic clue in their history, I recommend initiating investigation after 6 months of unprotected intercourse. In practice, it is reasonable to perform some basic fertility investigations in any couple who seeks advice, irrespective of their age or duration of trying, if only for reassurance.

1.7 Is Infertility Becoming More Common?

According to the UK Government Statistical Services, there is a steadily rising proportion of women who have never had a child. In the latest cohort to be published in 2020, women in England and Wales born in 1974 who completed their childbearing in 2019 (aged 45 years) had, on average, 1.92 children [15]. Nearly half (49%) of women born in 1989 remained childless by their 30th birthday, compared with 38% for their mothers' generation and just over one-fifth for their grandmothers' generation (born in 1961 and 1934, respectively). The most common age at childbirth for women born in 1974 was 31 years, compared with 23 years for their mothers' generation. The fertility patterns of women born more recently indicate this trend is likely to continue, with women born in 1995 showing lower levels of fertility in their 20s compared with previous cohorts [15].

Figure 1.5 demonstrates the percentage of women remaining childless at 45 and 30 and shows that, despite an increasing trend in childlessness by age 30 in recent years, the percentage of women who are

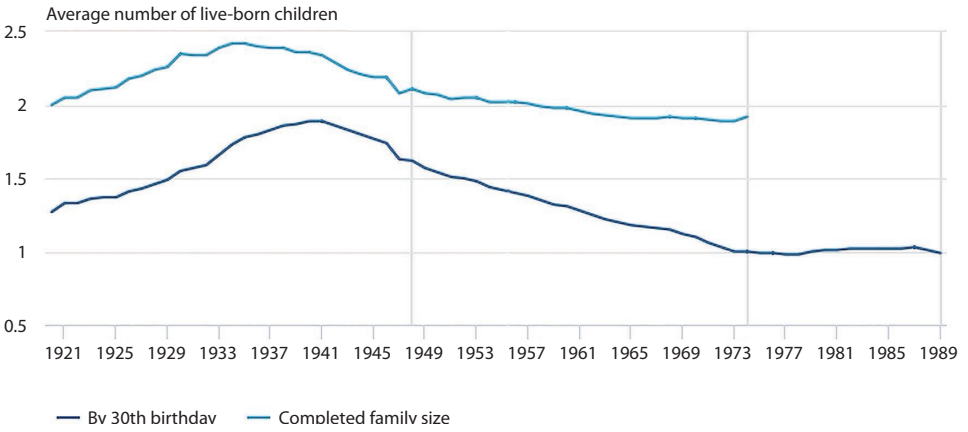

FIGURE 1.4 Average number of live-born children by age 30 years and completed family size by year of birth of the woman, 1920 to 1989, in England and Wales.

Source: From reference 15, under Open Government Licence.

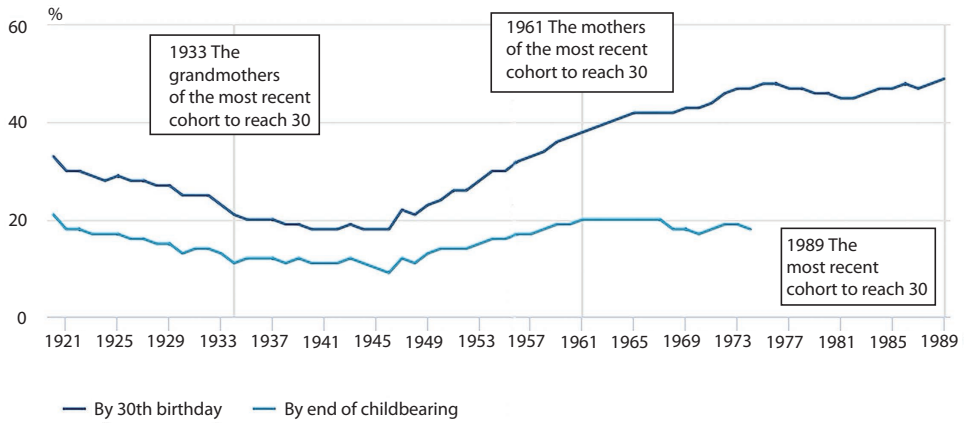

FIGURE 1.5 Percentage of women remaining childless at age 45 years and at age 30 years, 1920 to 1989, in England and Wales.

Source: From reference 15, under Open Government Licence.

childless by the end of their childbearing years has remained fairly consistent at around 20% for women born since the late 1950s, although this is still double that of their mothers' generation, of whom about 10% were childless. This suggests that women are delaying childbearing rather than not having children. Furthermore, it does not necessarily indicate an increase in infertility, as many women choose not to have children for a variety of reasons.

Women are deferring childbearing for a number of reasons. More women are entering higher education, wanting to have a longer working career before starting a family and also delaying long-term partnerships and/or marriage. There are also clear economic disadvantages for a woman to start her family in her 20s because of the lack of support for young mothers in the workplace, the need to establish a career in a competitive environment and also the need to have the financial stability to live independently from her parents. There is also a lack of commitment by young men to settle down and start a family.

Figure 1.6 illustrates the progressive fall in fertility rates in women aged 20 since their peak in 1946, known as the post–World War II "baby boom". There was a second "baby boom" in the 1960s. Later