Assisted reproduction techniques have led to the birth of 4 million babies worldwide.

Assisted reproduction techniques (ART), in particular in-vitro fertilization and intra-cytoplasmic sperm injection, are the most advanced forms of infertility treatment. They involve numerous counseling, medical, surgical and laboratory-based steps. At each step various problems and complications could be encountered that challenge even the most experienced ART practitioners. Moreover, patients with complex medical disorders may require ART, presenting further challenges.

Assisted Reproduction Techniques will stimulate resourceful thinking in the ART practitioner when faced with these challenges. It outlines various management options, the reasoning behind them, and the evidence on which they are based to enable the practitioner to choose the most suitable solution for the needs of each patient.

Written by 122 internationally renowned experts, Assisted Reproduction Techniques follows the patient’s journey throughout the whole ART process, with chapters on:

- Counseling and preparation
- Ovarian stimulation
- Oocyte retrieval
- Embryo transfer
- The luteal phase
- The ART laboratory
- The male patient
- The ART pregnancy

Each of the 100 concise chapters includes clinical cases, background, evidence-based practical management options, preventive measures and key-point summaries of the important details.

Assisted Reproduction Techniques gives a wide-ranging practical guide to all those wishing to support couples who cannot conceive naturally.
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

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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 worldwide 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*
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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

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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.