Chapter

Introductory Chapter: IVF Technology and Perspectives

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1. Introduction

Assisted reproductive technologies (ART) is the main method of treating infertility, which occurs in 10–15% of people of reproductive age. In recent decades, ART has become one of the most rapidly developing interdisciplinary technologies in medicine. Doctor Patrick Steptoe and biologist Robert Edwards are the pioneers of the *in vitro* method. After 60 unsuccessful attempts, Louise Brown was born on July 25, 1978, the world's first "baby in a test tube."

Currently, almost 10 million children have been born in the world thanks to *in vitro* methods, and during this period of 45 years, the success rate in treatment has increased many times: ranging in the first years from less than 10%, reaching today more than 50% in certain groups of patients. The reason for this rapid increase is the introduction of new medications and stimulation protocols, improvement of embryo culture media, and use of laboratory equipment that all provide better conditions for embryo development. Last but not least, the introduction of modern methods for genetic analysis and new techniques for freezing gametes, embryos, and tissue has improved the diagnostic and therapeutic possibilities of ART.

Regardless of the relatively high success rate of ART, the method has certain limitations. The final result, the birth of a healthy child, depends on many factors, such as the age of the partners, cause of infertility, lifestyle and diet, harmful habits, accompanying diseases, and, last but not least, heredity.

Currently, one out of every three embryos created through *in vitro* fertilization has chromosomal abnormalities that interfere with the development of the pregnancy and the birth of a healthy baby. Advances in genetics and genome sequencing enable the introduction of genetic analysis for each created embryo. This makes it possible to detect genes that correlate with the implantation and normal development of the embryo, as well as genes that correlate with early or late implantation failure. The effects of screening and selection of embryos, as well as improved outcomes, are under debate [1]. However, there has been steady progress on this front. On the other hand, genetic screening methods can better define the underlying genetic diseases and expand screening to cover a larger group of congenital conditions and diseases. Solving this task is complex from both a medical and ethical point of view, but the future convergence of well-defined genomes and very effective embryo testing make the application of genetic screening and selection inevitable [2].

A major criterion for good ART practice is reducing the risk to the patient and the pregnancy and increasing the success rate, which is determined based on live births. Ovarian hyperstimulation syndrome (OHSS) is a major risk for the woman during treatment and is a consequence of gonadotropin stimulation. It is also the most common complication that can end in a fatal outcome. Currently, OHSS occurs relatively rarely and most often in mild or moderate form. This is a consequence of the more frequent application of stimulation protocols: light stimulation and the so-called *in vitro* spontaneous cycle procedure. On the other hand, the use of GnRH-agonists as an ovulation trigger in GnRH-antagonist and progestin priming ovarian stimulation protocols with subsequent embryo freezing makes an OHSS-free clinic a real concept [3].

Reducing the number of transferred embryos leads to a reduction in the percentage of multiple pregnancies, respectively reducing the risk for the fetus and the mother [4]. For this reason, it has become increasingly beneficial in practice to apply a strategy for single embryo transfer (SET), resulting in the birth of one baby. This approach also defends the hypothesis that the embryo is not a group of developing cells, but is a patient like any other who should receive the best possible conditions for development and help, if necessary. Many patients express concern that single embryo transfer (SET) may reduce their already low chances of conceiving. However, recent studies have refuted such a statistically significant relationship, showing that SET has no real impact on pregnancy rates, compared to embryo transfer of two or more embryos [5].

Safety remains a major topic of debate, with some believing that children born after IVF are at greater risk of complications than those born after natural conception. However, a recent study published in *Lancet* [6] showed that the increased risk of pregnancy and birth complications seen in children conceived as a consequence of IVF may be the result of the parent's underlying infertility problems, rather than the technology itself.

Another important question to be answered is how to reduce the cost of ART treatment. It is in the interest of the patient and of society to reduce the direct and indirect costs incurred by infertility treatment. With in vitro treatment, the costs of drugs and procedures are well-known and can be budgeted. Side costs are not few and can be difficult to predict. Direct nonmedical costs, as well as indirect costs, connected to the IVF treatment itself, have been found to vary between 45% and 52% of total costs [7]. This figure includes the costs of travel, food, hotel, and the time a person spends visiting the clinic, which is why they are inclined to take vacations or sick leave. Studies have shown that the time cost alone of performing the entire in vitro procedure averages around 162 hours [8]. Another research article, authored by colleagues from Ireland points out that, depending on the distance to the clinic, patients can lose between 15 and 75 hours in travel, and expenses for local food and accommodation which amount to 104–703 euros [9].

To reduce these costs, new methods are being developed to manage ovarian stimulation during *in vitro* treatment. They are based on the determination of urinary estrone-3-glucuronide levels [10, 11] and salivary hormone oestradiol and progesterone measurements [12]. Currently, two main stimulation approaches have been developed: Self-Operated Endovaginal Telemonitoring (SOET) [13] and Controlled Ovarian Stimulation Monitoring by Self-Determination of Estrone-3-Glucuronide and Single Ultrasound (COSSESU). The implementation of these approaches is carried out with the active participation of patients [14].

Advantages of these two approaches to ovarian stimulation include the reduction of:

1. Costs of regular ultrasound and hormone tests.

2. Stress is incurred by frequent blood sampling to determine serum hormone levels.

3. Time wasted in frequent clinic visits and traveling.

4. Direct nonmedical expenses related to the use of a car, bus, train, hotel accommodation, and food.

5. Risk of infection in situations similar to COVID-19.

The two approaches described above use elements of telemedicine. Although much has been published in terms of telemedicine in the fields of cardiology, diabetes, dermatology, and general practice, little has been reported regarding reproductive medicine. Interest has also increased tremendously due to the recent COVID-19 pandemic. Telemedicine has a place in the treatment of infertility with the use of *in vitro* technologies [15].

Another step in reducing costs and the human factor in IVF treatment is the automation of the laboratory. Technologies and methods from the 80s are currently being used, that is, the embryologist opens the incubator door, removes the petri dish, closes the incubator door, then works on the embryo or medium, opens the incubator door again, puts it back the dish, and closes the incubator door. This series of steps is repeated for each IVF case. The inclusion of Artificial Intelligence for Ovarian Stimulation is also of interest, which is part of the modern trend of introducing artificial intelligence into medicine and, in particular, in vitro technologies. Automation of the IVF lab and other future technological developments will make IVF treatment more efficient and optimized [16].

The trends in assisted reproductive technologies outlined above have found a place in some of the chapters of this book. Readers will be introduced to the modern techniques of seminal analysis and the different methods of sperm processing in various ART techniques. The authors of this book examine some modern technologies, such as egg freezing and the *in vitro* maturation method, as well as the application of artificial intelligence in ovarian stimulation. A current topic will be discussed here, namely ovarian aging and the modern strategy of treating women with this problem. Also, an important place is given to the quality management system in assisted reproductive technologies, which is decisive in modern quality control in ART. This book also addresses the problem of infertility from an immunological perspective, with the authors covering a large number of diagnostic tests and clinical behaviors, including those whose effectiveness continues to be debated in the scientific community.

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