**HISTORY OF MEDICINE**  
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**DEVELOPMENT AND ACHIEVEMENTS OF ASSISTED REPRODUCTIVE TECHNOLOGY**  
**RAZVOJ I DOSTIGNUĆA ASISTIRANE REPRODUKTIVNE TEHNOLOGIJE**

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**Introduction**

Marital infertility has been the subject of interest since the moment the man became aware of the importance of reproduction and procreation. Numerous historical writings, which will be discussed further in the text, testify unambiguously that the issues considering birth have attracted attention of numerous scientists throughout the human history. Some of these scientists were frequently misunderstood and cast off because of their visionary ideas especially in the Middle Ages, when the church hindered the development of scientific thought to a large extent. On the other hand, when reviewing the development of this idea through history, the findings emerge about its course and foundation and who were the giants that enabled its development and progress. At the same time this would represent the incentive for further development [1].

If we take into consideration the facts that even the Ancient Egyptians knew about sterility and that it could occur both in men and in women as well as the fact that the medicine used then was slightly modified through centuries [1], it is quite clear that the road leading to the possibility of the latest methods of assisted reproductive technologies, i.e. medically assisted reproduction, has been very long.

**History of Assisted Reproduction**

The statement that the issue of assisted reproductive technologies is not a modern discovery is testi-
fied by the reports of Professor Walter Heap from the Cambridge University going as far as 1890, who made the first known attempt of an embryo transfer in rabbits. In 1930, Aldous Huxley described the techniques of in vitro fertilization (IVF) in his science fiction novel “Brave New World” [2].

In 1934, Gregory Pincus managed to isolate the egg cells and the sperm of rabbits, and to implant the created embryo into a surrogate rabbit. In 1959, Min Chueh Chang, a young Chinese scientist, who dealt with this issue, came to irrefutable evidence about the possibilities of IVF resulting in births of children alive [2]. The first human IVF was performed in 1973 in Melbourne, as reported by Professors Carl Wood and John Leeton. Sadly, this attempt turned out to be unsuccessful [3]. Three years later, Patric Septoe and Robert Edwards submitted a report on the ectopic pregnancies after IVF [4]. After the birth of the first babies conceived via IVF, Louise Brown (July 25, 1978), Cortney Cross (October 16, 1978) and Alistair McDonald (January 14, 1979), IVF became the procedure widely applied and according to the available data, 5 million babies have been born so far using this method [2]. Assisted reproductive technologies were further developed in the following years, bringing the possibility for many couples confronted with the problem of sterility to realize their dreams of parenthood.

The following moments are important in the development of assisted reproduction methods: in 1987, Alex Lopata, in Melbourne, gave a description of ovarian cycles stimulated by clomiphene citrate [5], while in 1979, Paz with his colleagues in France, started monitoring the follicular growth using ultrasonography and concluded that the ultrasound findings correlated with the laparoscopy findings. Further research suggested that ultrasound monitoring of the follicular diameter represented a more trustworthy indicator of follicular maturation in relation to the level of estradiol in the serum [6]. In 1980, the first baby conceived as the result of IVF technology was born in Australia, the forth one in the world, and according to the available data, 5 million babies have been born so far using this method [2]. Assisted reproductive technologies were further developed in the following years, bringing the possibility for many couples confronted with the problem of sterility to realize their dreams of parenthood.

The first clinic for assisted reproduction in the United States of America (USA) was opened in Virginia in 1980 [6]. The laboratorial examination of semen, cervical mucus, as well as of the interaction between semen and cervical mucus began. Alan Handyside began to study techniques to identify genetic anomalies of embryo in Great Britain [7]. A year later, first babies conceived via IVF were born in the USA, the first one was Elizabeth Jordan Carr after the ovarian stimulation using the human menopausal gonadotropin (HMG) (Howard and Jones), while the other baby, who was also from the US, Samantha Still, was born in England in the same year [6]. Clomiphene citrate and HMG were introduced to IVF by Alan Trounson and John Leeton in Australia [8]. Richard Fleming was the first one who indicated the possibility of using gonadotropin-releasing hormone (GnRH) in ovarian stimulation [9].

The first twins, Taylor and Freddy Axton, were conceived via IVF and born in Great Britain in 1982. In the same year, the first babies conceived via IVF were born in France, Amandine in February and Alexis in October [6]. In Switzerland, the first baby was born after the assisted reproduction in Goteborg [10]. In 1982, the first twins after the transfer of frozen embryo were born in Austria, and the uterine insemination was used for the first time [6]. In Germany the first “test-tube baby” was born on the 16th of April 1982, and Zlatan Jovanovic was the first baby born in Australia after IVF treatment [11].

Danish gynecologists, Susan Lenz and Jorgen Lauristen, were the first ones to indicate the importance and demonstrate the use of ultrasound during the oocyte aspiration [12]. In Australia, the team headed by Alan Trounson succeeded in applying assisted reproductive technology with bilateral oophorectomy of women, with the use of oocyte donor [13], as well as by implanting a donor embryo in the case of a patient with primer ovarian dysfunction [13]. Monash’s team in Australia reported on the first successful pregnancy with the transfer of frozen embryo [14]. In the same year, the procedure of immature oocyte in vitro maturation was introduced [2].

Glaicher et al. gave the first evidence about the early culdocentesis aimed at aspirating egg cells using transabdominal ultrasound [15]. Robert Casper et al. were the first to describe the use of low HCG dosages in the process of ovarian stimulation [16]. On January 6, 1984, the first quadruplets conceived via IVF were born at Women’s Royal Hospital in Melbourne, Australia, and on March 28, 1984, the first baby, Zoe Lyeland, was born with the use of frozen embryo also in Melbourne, which represents an important moment in the application of assisted reproductive technologies [6]. In 1985, the first pregnancy with the application of percutaneous epididymal sperm aspiration (PESA) was described [17]. A Nordic group headed by Monash Wikland in Sweden described the possibility of transvaginal oocyte scanning during their application. In this manner, visualization and access to smaller follicles as well as their traces were made easier than by the previously used transabdominal approach. The procedure would be conducted under local anesthesia and the patient would leave the clinic an hour after the intervention [18].

In 1986, Lupron*(GnRH agonist) was used for the first time to prevent the early ovulation. Monash’s team were the first to report on the pregnancy achieved after the surgical sperm retrieval
from the patient with bilateral obstruction ductus deferens [6]. Wilfred Feichtinger and Peter Kemeter used transvaginal ultrasound guided needle to aspirate the grown follicle [19]. Daniel Navot et al. suggested the possibility of artificial endometrium induction in the absence of ovaries [20]. Paul Devroey et al. were successful in trans-laporoscopy zygote intrafallopian transfer (ZIFT) [21]. Christopher Chan from Australia reported on the first pregnancy successfully carried out with the use of oocyte which had undergone cryopreservation (slow freezing with dimethyl sulfoxide/fast thawing) [22]. In 1987, fast cryopreservation was discussed as a very efficient method for the first time [23]. Lewis-King et al. introduced the method called SUZI (sub-zonal-injection) which was a huge improvement in the field of assisted reproduction, and it has retrieved hope to many couples after the countless trials to become parents [24]. Lynda Wilton and Alan Trounson developed the early embryo biopsy technique to perform genetic analysis [25]. In 1989, embryo biopsy was introduced for the first time before the implantation to determine the gender using the method of deoxyribonucleic acid (DNA) amplification [26]. Laser was introduced to the assisted reproduction technology in the same year [27]. In Toronto, Y. Gonen and her associates were the first to apply ultrasonography to assess the quality of endometrium [28]. A breakthrough in treating the male sterility was made in 1993 when Sherman Spielberg et al. reported on the successful sperm extraction from men with non-obstructive azospermia and the application of intracytoplasmatic sperm injection (ICSI) method [29]. It should be mentioned that in case of congenital bilateral absence of vas deferens (CBAVD) this anomaly could be transmitted on offspring as a cause of male sterility [30]. In 1994, the Australian team headed by Alan Trounson succeeded in in vitro oocyte maturation in women diagnosed to have polycystic ovary (PCO) syndrome [31]. A Canadian embryologist, Andrea Jurisicova, was the first to conclude that embryo pre-implantation fragmentation led to the programmed cell death [32]. In 1998, Sun, Jurisicova and Casper, described the procedure of sperm DNA fragmentation detection and its correlation with IVF. They have concluded that spermatozoids with DNA fragmentation have considerably lowered fragmentation ability [33]). The first baby was born after IVF treatment in Nigeria in 1998, and in the same year a success in controlled ovarian hyper-stimulation was recorded with the use of recombinated follicle-stimulating hormone and GnRH antagonist (Genirelix), and the report was published by Joseph Itskovic-Eldor [34]. G. Palermo et al. succeeded in obtaining the sperm by testicular extraction from the men with non-mosaic Klinefelter syndrome diagnosis, which resulted in successful pregnancy by applying ICSI method [35]. The first octuplets conceived after the application of ovarioc induction were born in December of 1998 in Huston, Texas. A year later the first case of preimplantation genetic diagnosis (PGD) of Sickle-cell disease was recorded [36]. The application of ultrasound-guided transvaginal catheters applied to transfer the embryo largely contributed to the success of IVF treatment (2001) [37]. Kili De Boer and her associates reported on the first baby born alive in 2002 after the blastocysts biopsy applied to make PGD [38]. Comparative genomic hybridization and polar body were used for the first time in the same year to make preimplantation aneuploidy diagnosis [39]. Tea Ki Yoon with her associates reported on the success of applying verification in the process of stimulated IVF protocol in 2003 [40]. Jack Donnez reported on the baby born alive to the patient who had undergone orthotopic transplantation of previously cryopreserved ovarian tissue [41]. In the same year, the Britain’s National Health System made a decision about financing the program of pre-implantation genetic diagnosis and human leukocyte antigen (HLA) standardization [42]. David Garner et al. conducted the first randomized study aimed at determining the extent to which the transfer of one blastocyst would increase the rate of successful pregnancy and reduce the possibility of multiple pregnancies at the same time [43]. A Korean group of scientist produced the first cloned blastocyst, and reported on the first baby born alive with pre-implantation retinoblastoma diagnosis in the same year [44]. In 2005, Adriana Hiescu, from Backrest, gave birth in her 66th year as a result of IVF treatment after changing the egg cells and sperm donation. In the same year, a patient gave birth after the ovarian cortex transplant, done to treat the ovarian dysfunction resulting from chemotherapy [45]. Mohamed Bedaiwy et al. reported on the successful cryopreservation of intact human ovary with vascular pedicle in 2006 [46]. The first successful pregnancy after the application of PGD procedure on aneuploidy from naturally generated ovarian cycle was reported by the Reproductive Center in Toronto in the same year [46]. The concept of the so called “mild” treatment within IVF was developed in 2007 to reduce the expenses and multiple pregnancies rate [48]. Pascal Patrizio introduced a multi-gradient technology of ovaries cryopreservation aimed at preserving its natural architect [49].

In 2008, Son Weon Young and her associates recommended a span of 38 hours between the HCG injection and oocyte aspiration, pointing out that this time period considerably influenced the level of in vivo and in vitro oocyte maturation [50]. Very intensive research in the generic expression and identification field of viable and non-viable IVF blastocysts began in the same year [51]. In 2009, the second octuplets were born (6 boys and 2 girls) in the US. The interesting fact is that in this case 12 transfers of frozen embryos were performed, and the license was taken away from Michael Kamrava, who had performed this intervention [2]. In the same year, Cetrorelix-acetate (luteinizing hormone - releasing hormone antagonist) was approved by the Food and Drug Administration for clinical use in the framework of IVF protocol, and Simon Fishel, from Nottingham, reported on the successful application of multiple genomic hybridization
[2]. In 2010, Bathory Devy, an Indian woman aged 66, gave birth to two boys and a girl conceived via IVF after 44 years of marriage [2]. The year of 2011 was marked by the introduction of continuous early embryo monitoring within an hour with Embryoscope, which was introduced by Unisense Fertilitech, the USA. In December of the same year, the first twins were born with the application of this method [2]. In the following year, 2010, the number of babies conceived by assisted reproductive technologies and born alive reached 5 million.

The following year, 2013, was marked with the use of Kisspeptin (low risk IVF treatment) with the purpose of ovarian stimulation which reduced the risk from hyper-stimulation syndrome. The British also started with the application of this method, their team leader was Professor Dilly in the Royal Hospital in London [2]. In the same year, Alison Campbell from Manchester introduced a new method called time-lapse imaging for early discovery of a damaged embryo without the need for the use of embryo biopsy or the previously mentioned PGD [2].

Professor Robert Edwards, one of the pioneers for IVF technology and a winner of the Noble Price for medicine in 2010, died in April 2013 [2].

Many achievements are to be expected in the field of assisted reproductive which would be made even more efficient and safer.

Conclusion

The review of literature on the development of assisted reproduction has explicitly shown that this process is exceptionally long and complex, which has required hard labor, interdisciplinary approaches and cooperation of many experts from different fields. In support of this fact there are numerous data presented which have unambiguously indicated the time-consuming research, the application of methods whose results have been more or less satisfactory; however, they have initiated further studies and the procurement of better and more efficient solutions.

The data given in this paper represent the most important moments in the development of assisted reproductive technologies, from its very beginning up to the modern achievements. The importance of the development of reproductive technologies can be best illustrated by the information that this method has helped more than five million babies to be conceived and brought to this world and this number is very likely to increase. Many couples were given a chance with this method to accomplish themselves as parents, which classifies the assisted reproduction into one of the most valuable achievements of medicine.

References


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