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Assisted Reproductive Technology after the birth of Louise Brown

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Abstract

Background: Public interest in Assisted Reproductive Technology (ART) has remained high since the birth of the world's first *in-vitro* fertilization baby, Louise Brown, in the United Kingdom. ART allows scientists to manipulate the fertilization process in order to bypass some pathological obstacles such as blocked fallopian tubes and non-functioning ovaries in the females, and blocked vas deferens and low sperm count in the males.

Objectives: To provide a historical outline and identify the researches that most contributed to the ART.

Methods: A review of published experimental and clinical studies of assisted reproduction carried out at the University of Bristol library website (MetaLib®). A cross-search of seven different medical databases; (AMED-Allied and Complementary Medicine Database, BIOSIS Previews on Web of Knowledge, Cochrane Library, Embase, and the Medline on Web of Knowledge, OvidSP and PubMed) completed by using the key words to explore the major milestones and progress in the development and implementation of ART.

Results: A speedy advancement in the development of different assisted reproductive techniques makes infertility problem more treatable than it ever had been.

Conclusion: Although no other field in the medicine has integrated new knowledge into the daily practice more quickly than ART yet, there is a need for social research to counterbalance the dominance of biomedical one, in particular the people's actual experiences and expectations of the ART.

Keywords: Infertility management; History/Milestones/ Timelines of Assisted reproductive technology; Louise brown

Introduction

The beginning of *In-Vitro* Fertilization (IVF) was an inspiring event. Lesley Brown and her husband John, from Bristol city in the United Kingdom have failed to conceive naturally throughout nine years of their continuous marriage. Lesley Brown has bilateral tubal blocks. Bilateral salpingostomy has done without success. In 1976, she referred to Dr. Patrick Christopher Steptoe, a gynaecologist in the Oldham general hospital, Manchester city, United Kingdom. He has advised her to try a new experimental technique to bypass her tubal blockage. Accordingly, Lesley underwent a laparoscopic oocyte retrieval during a natural non- stimulated ovulatory cycle. Mr. Robert Geoffrey Edwards, a British physiologist, used her husband's sperms to fertilize the retrieved oocyte in the lab. A few days later, an 8-cell stage embryo placed inside Lesley's uterine cavity. At 11.47 PM on July 25th 1978, Louise Brown was delivered by an elective caesarean section at Oldham hospital by the registrar John Webster at gestational age of 38 weeks and 5 days due to coincidence of maternal pre-eclampsia. Louise was healthy at birth and her weight was 5 pounds and 12 ounces (2700 grams). By the birth of Louise Brown, the world celebrated the start of a new era of assisted human reproductive technology.

Early Attempts

The history of IVF dates back as early as the 1890's when Walter Heape, a professor at the University of Cambridge, UK, reported the first known case of embryo transplantation in rabbits. In 1932, Aldous Huxley described the technique of IVF in his science fiction novel "Brave New World". In 1934, Gregory Pincus mixed rabbit's eggs and sperms in the glass top of his watch and implanted the developing embryo in a surrogate rabbit. Fourteen years later, in 1948, Miriam Menken and John Rock retrieved more than 800 oocytes from women. However, it was not until 1959 that Min Chueh Chang, a young Chinese reproductive investigator, obtained indubitable evidence of *in-vitro* fertilization by achieving for the first time live births from a white rabbit by using eggs and sperms from black ones.

The first human IVF pregnancy was on 1973 reported by Professors Carl Wood and John Leeton in Melbourne, Australia. Unfortunately, it ended in an early embryo death (less than one week) [1]. On 1976, *Patrick Steptoe* and Robert Edwards published a report on an ectopic pregnancy following a transfer of a human embryo at its late morula stage [2].

ART Progress

The birth of Louise Brown on July 25th 1978 was followed by the birth of Courtney Cross on October 16th 1978 and Alastair MacDonald on January 14th 1979, the world's first three IVF babies. Since then, IVF has become a common procedure with a record of more than 5 million births worldwide [3]. The years followed have brought rapid progress that allowed more infertile couples to have their own genetic babies [4].

Back to the year 1978 (Figure 1), Alex Lopata, in Melboure city, Australia described the first ovarian cycles stimulated with clomiphene citrate [5].

On 1979, Alastair MacDonald, the world's third IVF baby (*also considered as the world's first IVF male baby*) born on January 14th. Cohen et al. in France started tracing the growth of the graffian follicles by using pelvic ultrasonography [6]. Their sonographic findings were correlated with the laparoscopic observations. They further indicated that the diameter of the graffian follicles, as measured by ultrasound, is a better predictor of follicular maturation relative to the serum

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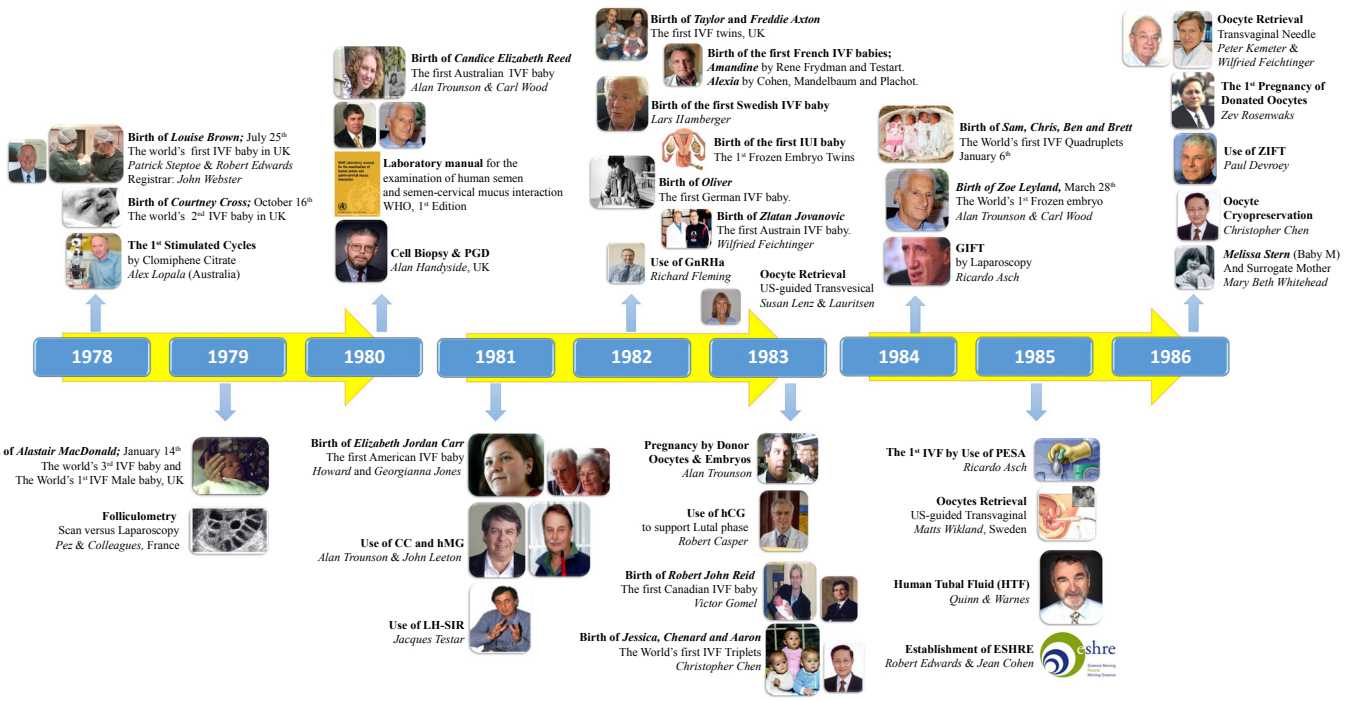

Figure 1: Timeline of Major ART Milestones (Year 1978 - Year 1986).

Oestradiol levels alone (on day 8th of the cycle E_2 level should be ≥ 300 picograms).

On 1980, the Melbourne IVF-team led by Alan Trounson succeeded to get the Australian first IVF baby (*the world's fourth IVF baby*) a female called Candice Elizabeth Reed. On the same year, the first American IVF clinic opened in Virginia, United States [6]. The WHO published the "Laboratory manual for the examination of human semen and semen-cervical mucus interaction" to standardize semen analysis [7]. Alan Handyside, in the United Kingdom, introduced a Pre-implantation Genetic Diagnosis (PGD) to identify genetically abnormal embryos by cell biopsy [7].

On 1981, Howard and Georgianna Jones announced the delivery of the first American IVF baby, Elizabeth Jordan Carr in Virginia after ovarian stimulation by human Menopausal Gonadotrophin (hMG), while Samantha Steel was the first IVF baby born to American parents in England on the same year [6]. Clomiphene Citrate (CC) and human Menopausal Gonadotrophin (hMG) introduced in the IVF treatment protocols by Alan Trounson and John Leeton in Australia [7]. In stimulated ovarian cycles; the number of mature oocytes retrieved increased and by the administration of human Chorionic Gonadotrophin (hCG) identification of the exact timing of ovulation (±36 hours later) and oocyte collection attained. Moreover, Alan Trounson noticed that a delay between oocyte collection and insemination allows the immature oocytes collected to complete its meiotic maturation in the culture media [8,9]. The Clamart's IVF working group in France, led by Jacques Testar, developed a luteinizing hormone-Surge Initiating Rise (LH-SIR) assay that could detect the LH-surge at its initial rise (*not at its peak*) in human plasma for an accurate prediction of ovulation and best timing for oocytes retrieval [6,10].

On 1982, the first IVF twins, Taylor and Freddie Axton, were born at Queen Elizabeth hospital in King's Lynn, United Kingdom. The first French IVF babies were born on the same year as; Amandine, at Clamart in February followed by Alexia at Hopital Sevres in June [6]. The first Swedish IVF birth was born in Gothenburg [11]. The world's first delivery after intrauterine insemination (IUI) and the first frozen embryo twins born in Australia on 1982 [6]. On April 16th at the University Hospital in Erlangen, Oliver, the Germany's first test-tube baby was born by caesarean section; while Zlatan Jovanovic was the first IVF baby born in Vienna's AKH hospital in Austria. Culture media for growing embryos started to be used [12]. Richard Fleming was the first who demonstrated that gonadotrophin releasing hormone (GnRH) agonists could be used to eliminate premature luteinization of the graffian follicles and control the process of ovarian stimulation [13]. Danish gynaecologists, Susan Lenz and Jorgen G Lauritsen, demonstrated how to use the ultrasound as a guide for trans-abdominal trans-vesical oocyte aspiration [14].

On 1983, Alan Trounson's working group in Australia has succeeded to achieve the first pregnancy in a woman with bilateral oophorectomy by using donor oocytes and in infertile woman with primary ovarian failure by using donor embryo [15,16]. The Monash IVF team in Australia has reported a successful pregnancy of the first frozen embryo [17]. On the same year, introduction of *In-Vitro* Maturation (IVM) to fertilize immature oocytes started [18]. Gleicher et al. reported the early use of vaginal route oocytes retrieval via culdocentesis by the aid of transabdominal ultrasonography [19]. Robert Casper et al. were the first to describe the use of low dose Human Chorionic Gonadotrophin (hCG) to support the luteal phase in assisted ovarian cycles [20]. The first report on the Canadian IVF baby, Robert John Saunders Reid, wrote by the working group of Victor Gomel at the University of British Columbia. On the same year, the world's first IVF triplets reported by Christopher Chen.

On 1984, the world's first IVF quadruplets were born on January 6th at the Royal Women's Hospital, in Melbourne, Australia. On March 28th, the birth of the world's first frozen embryo, Zoe Leyland, was a

breakthrough in the ART history. This baby delivered by caesarean section at the Queen Victoria Medical Centre in Melbourne, Australia by Alan Trounson and Carl Wood [6]. During the year 1984, the first legislation to regulate the IVF and human embryo research in the Australia by Government of Victoria; the Infertility (*Medical Procedures*) Act 1984, was produced [6,21]. The first surrogacy embryo transfer was born in California, USA, while the first reported pregnancy following trans-laparoscopic Gamete Intrafallopian Transfer (GIFT) has described by the endocrinologist Ricardo Asch [6,22]. The first pregnancy following IVF and oocyte donation in a women with primary ovarian failure was succeeded [23]. The early trans-vaginal oocyte retrieval introduced by Schulman et al. in Strasbourg, France [24]. The first two pregnancies following the transfer of intact frozen-thawed embryos were successful [25].

On 1985, the first pregnancy achieved by IVF using Percutaneous Epididymal Sperm Aspiration (PESA) was succeeded [26]. It was the year of the first human birth after replacement of hatching blastocyst cryopreserved at an expanded blastocyst stage [27]. A Nordic group, led by the gynaecologist Matts Wikland in Gothenburg, Sweden, described for the first time the possibility of using transvaginal scanning for oocyte retrieval [28]. By this technique, the ovaries visualized well than by the abdominal approach, and the smaller follicles easily punctured. The procedure could done under local anaesthesia and the patient could leave the IVF center after an hour. The first report on the use of abdominal ultrasonography as a guide for embryo transfer published [29]. Dan Szollosi with Jacqueline Mandelbaum described the microstructures of the human oocyte, which become known as 'Oocyte Dysmorphia' [30]. Testart's group in France published impressive results about using propanediol and sucrose as cryoprotectants for embryo freezing, instead of using dimethyl sulphoxide (DMSO) [31]. Quinn and Warnes published a formula entitled Human Tubal Fluid (HTF) that mimics *in-vivo* environment to which the embryo is exposed [32]. The European Society of Human Reproduction and Embryology (ESHRE) established after its first meeting in Bonn, 1985 by the help of Robert Edwards (from UK) and Jean Cohen (from Paris).

On 1986, Lupron® (GnRH agonist) has been used for the first time to prevent premature ovulation. Monash IVF team reported the world's first pregnancy achieved by surgical sperm retrieval from a patient with bilateral vas deferens ducts obstruction [6]. Wilfried Feichtinger and Peter Kemeter used ultrasound-guided trans-vaginal needle aspiration of mature graffian follicles for oocytes retrieval [33]. It was the year of the first successful pregnancy following IVF donated oocytes in a non-ovarian failure woman achieved by Zev Rosenwaks [34]. Navot et al. reported the ability to induce endometrial cycles artificially and to establish pregnancy in absence of functioning ovaries [35]. Devroey et al. reported the first successful pregnancy following laparoscopic Zygote Intrafallopian Transfer (ZIFT) [36]. The introduction of the Direct Intraperitoneal Insemination (DIPI) was on 1986 [6]. Christopher Chen in Australia reported the world's first pregnancy resulting in a birth of twins by using a previously cryopreserved oocyte (slow freezing with dimethylsulfoxide-DMSO/rapid thawing technique) [37]. The first Soviet IVF baby Lena, conceived at Leonov's laboratory in Moscow and born in February. A few months later, another IVF child, Kirill, Lena's brother, was born in Saint Petersburg. Melissa Stern (Baby M) is born on March 27th in the United States. Her surrogate and biological mother, Mary Beth Whitehead (who conceived by artificial insemination) refused to yield custody of Melissa to the couple (William Stern and his wife, Elizabeth Stern) with whom she made the surrogacy contract. The court of New Jersey found it in the best interest of the infant to award custody of Melissa to her biological father William Stern and his wife Elizabeth Stern, rather than to her surrogate mother, Mary Beth Whitehead.

On 1987, the first report on using ultrasound machine during Embryo Transfer (ET) was published (Figure 2). Laws-King et al. reported a new technique called SUZI (sub-zonal injection) that would advance assisted reproductive technology and offers a hope for couples with recurrent failed cycles [38]. The introduction of a new effective method, Ultra-rapid freezing, for cryopreservation of the human embryos was on 1987 [39]. Norway was the first country in the world

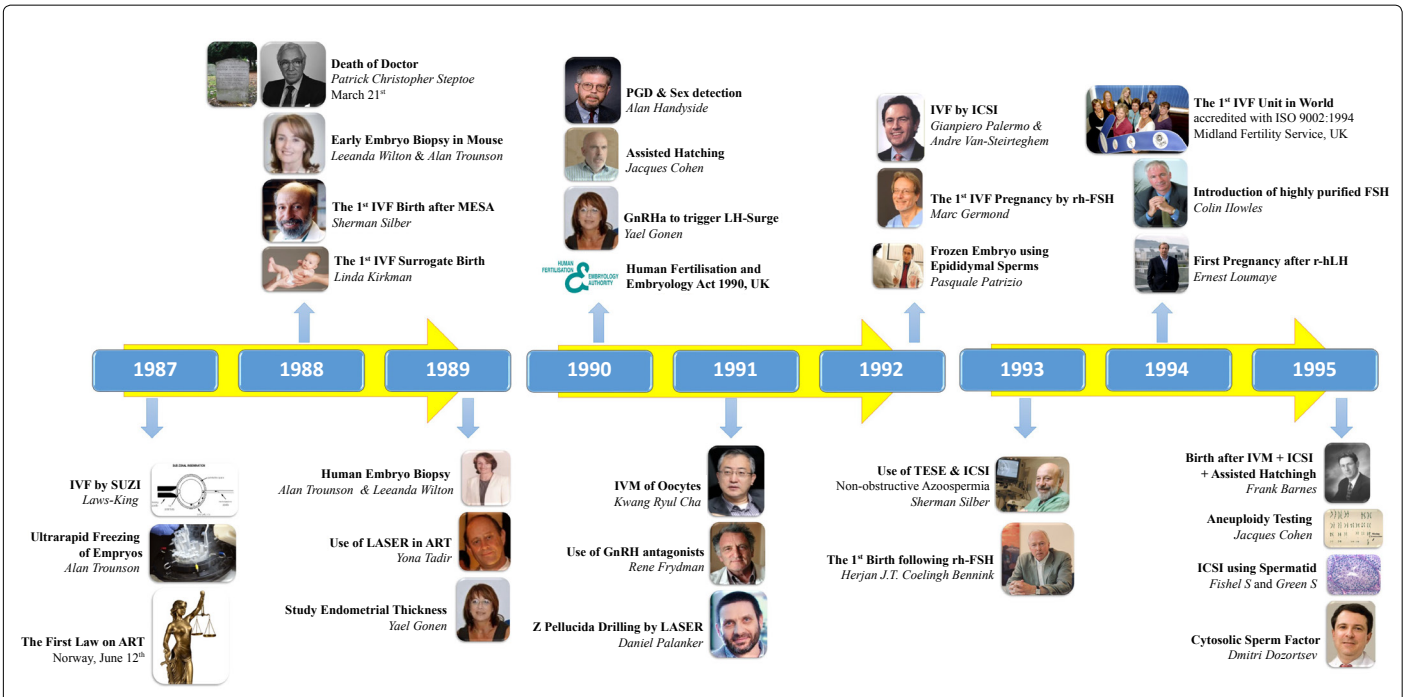

Figure 2: Timeline of Major ART Milestones (Year 1987 - Year 1995).

to pass a law on ART on June 12th, 1987 (Norwegian law on Assisted Reproduction and Genetics). In the Nordic law, treatment is limited to the married or cohabited couples. Same sex couples, lesbian and single women were excluded from the IVF treatment and further surrogacy and embryo donation was not permitted.

On 1988, Patrick Christopher Steptoe died on March 21st. On the same year, the world's first baby after home monitoring of fertility treatment born [6]. Leeanda Wilton and Alan Trounson introduced the early embryo biopsy technique for genetic study [40]. The first reported two babies born after microsurgical epididymal sperm aspiration (MESA) for men with Congenital Bilateral Absence of Vas Deferens (CBAVD) was published on 1988 [41]. In May, Linda Kirkman gave birth to Alice, who has conceived from her mother Maggie's egg, fertilized by sperm from a donor as her husband, Sev, had no sperms. The world's first IVF surrogate birth occurred in Australia [6]. It was the year of the successful pregnancy achieved through sub-zonal sperm injection (SUZI), and after oocyte zona pellucida drilling and mechanical partial zona dissection that facilitated sperm penetration [42,43].

On 1989, the first report on biopsy taking from pre-implanted human embryos and sex detection by DNA amplification was published [44]. It was the same year when laser used for the first time in the field of assisted reproduction [45]. Gonen et al. in Toronto, Canada, have pioneered the use of ultrasound for assessment of endometrial quality in relation to IVF procedures [46].

On 1990, successful deliveries following human embryo vitrification, and after preimplantation biopsy sexed by Y-specific DNA amplification were reported [47,48]. A Dutch embryologist, Jacques Cohen, published the first report on assisted hatching in human embryos [49]. The use of first polar body biopsy for genetic diagnosis done on the same year [50]. Gonen et al. proposed the use of GnRH agonist in the place of hCG to trigger the endogenous LH-surge for IVF cycles [51]. The use of combined oral contraceptive pills for follicular synchronization and cycle scheduling in IVF programme has been suggested [52]. The British Human Fertilization and Embryology Act set out a framework for ART practice and research under license from the Human Fertilization and Embryology Authority (HFEA) [6].

On 1991, *In-vitro* Maturation (IVM) of donor oocytes in a non-stimulated cycle ensued in a successful pregnancy [53]. GnRH antagonist introduced to prevent premature LH-surge in a controlled ovarian hyperstimulation programme [6]. Daniel Palanker used Excimer laser for zona pellucida drilling [54].

On 1992, the first successful pregnancy after Intracytoplasmic Sperm Injection (ICSI) by Gianpiero Palermo and Andre Van-Steirteghem was in Brussels, Belgium [55]. A further successful *in-vitro* fertilization and embryo transfer (IVF-ET) was achieved after treatment with recombinant human FSH (rh-FSH) [56]. It was the year of delivery of the first British SUZI treated baby. Two births recorded by Pasquale Patrizio from frozen embryos produced by epididymal-aspirated sperms [57]. A published scientific report stated that men with Congenital Bilateral Absence of Vas Deferens (CBAVD) have a mild form of cystic fibrosis (CF) [58]. Administration of luteinizing hormone releasing hormone (LHRH) agonist induced ovulation by triggering endogenous LH-surge [59].

On 1993, Silber et al. [57] reported, for the first time, that infertile men with non-obstructive azoospermia become able to father their own babies by the use of Testicular Sperm Extraction (TESE) and ICSI procedures [60]. The genetic cause of Congenital Bilateral Absence of Vas Deferens (CBAVD) among infertile men (cystic fibrosis mutations) could transmitted to their offspring [61,62]. The first live birth was reported following treatment with rh-FSH.

On 1994, a successful *In-Vitro* oocyte Maturation (IVM) and fertilization in non-ovulating women with Polycystic Ovary (PCO) syndrome achieved by Trounson et al. in Australia [63]. It was the year of birth of the first British triplets after maternal surrogacy [6]. The first IVF unit in the world, Midland Fertility Service in United Kingdom accredited with ISO 9002:1994. The first highly purified FSH preparation developed and the first pregnancy after use of r-hLH was recorded [64,65].

On 1995, a successful human birth reported by Frank Barnes after *in-vitro* primary oocyte maturation (IVM), ICSI, and assisted hatching [66]. The first report of aneuploidy testing published by Jacques Cohen, while the first report of spermatids to achieve pregnancy published by Simon Fishel and Green [67,68]. Dozortsev et al. discovered oocyte activation during ICSI procedure triggered by a water-soluble, heat-sensitive, non-species, specific cytosolic sperm factor [69].

On 1996, Gil-Salom et al. reported successful pregnancies employing ICSI after cryopreserved testicular sperms (Figure 3) [70]. The males with severe oligo-astheno-zoospermia discovered to have deletion in their Y-chromosomes [6]. Andrea Jurisicova, a Canadian embryologist, was the first who recognized that preimplantation embryo fragmentation leads to a programmed cell death [71]. Casper et al. at the University of Toronto, Canada used hypo-osmotic swelling test for selection of viable immotile sperms for ICSI procedure in men with complete astheno-zoospermia [72]. Although a successful fertilization of a human oocyte by a late stage spermatid using ICSI first reported by Vanderzwalmen on 1995, it was not before the year 1996 when Jan Tesarik and Simon Fishel announced the delivery of the world's first two successful testicular spermatid babies [6]. This technique introduced the concept of using immature sperms (spermatids) to overcome the problem of males' non-obstructive azoosospermia [73]. On July 5th, Ian Wilmut and Keith Campbell, have succeeded to clone a sheep (Dolly) at Roslin Institute in Scotland by using cells from the mammary glands of an adult sheep and enucleated egg cell.

On 1997, Sun, Jurisicova and Robert Casper described the use of terminal deoxynucleotidyl transferase-mediated dUTP-biotin end labeling (TUNEL) for detection of DNA fragmentation in sperms and its correlation to IVF outcome [74]. They found that sperms with fragmented DNA were less likely to fertilize the oocytes. The first successful birth after the transfer of enucleated donor oocyte cytoplasm into a recipient oocyte (Ooplasm Donation) was on 1997 [75]. The Australia's first twins born after open testicular biopsy. Gamete intra-fallopian transfer (GIFT) has accomplished by Porcu and Dal Prato through trans-cervical falloposcopy [76].

On 1998, Hannatu Kupchi, the first successful IVF baby in Nigeria born. The first case report on a successful pregnancy after controlled ovarian hyperstimulation induced by recombinant FSH and GnRH antagonist (Ganirelix®) published by Joseph Itskovitz-Eldor [77]. David Gardner at Colorado Center for Reproductive Medicine in the USA introduced a serum-free medium for blastocyst transfer and culture [78]. Gianpiero Palermo et al. succeeded to get sperms from men with non-mosaic Klinefelter's syndrome by testicular extraction and achieved pregnancy by using ICSI procedure [79]. A live birth following cryopreservation of immature oocytes, thawing, IVM and then fertilization through ICSI procedure succeeded. The DNA sequence of the human chromosomes (Human Genome Project) broadcasted. In December 1998, the first set of octuplets in the world

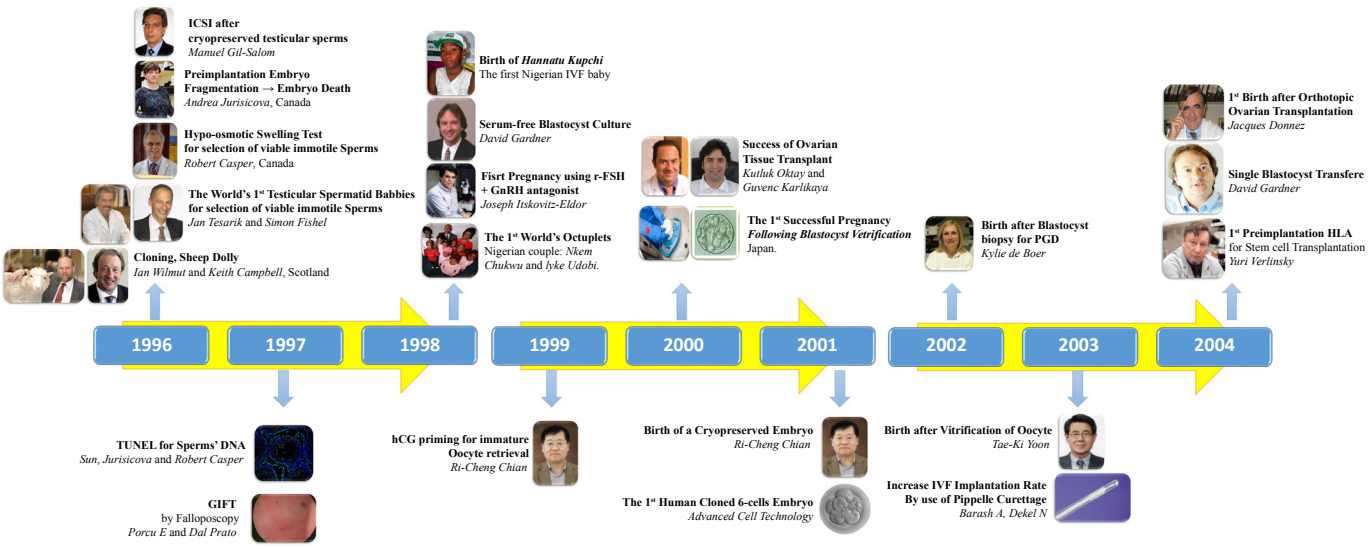

Figure 3: Timeline of Major ART Milestones (Year 1996 - Year 2004).

(8 babies; 6 girls and 2 boys) born at St. Luke's Episcopal Hospital in Houston, Texas, USA, after the use of ovulation induction therapy to a Nigerian-born American couple, Nkem Chukwu and Iyke Louis Udobi. Monash IVF-team in Australia announced the birth of twins by using Cell Robotics Laser Assisted Hatching technique [6].

On 1999, the first unaffected gestation was reported after using preimplantation genetic diagnosis (PGD) for sickle cell anemia [80]. Kuleshova et al. testified a successful birth following vitrification of a human oocyte [81]. Born of the world's first baby for a male after multiple ejaculate re-suspension centrifugation technique. Chian et al. demonstrated that hCG priming prior to immature oocyte retrieval in women with PCO syndrome increases oocyte maturation and pregnancy rate [82]. The world's first baby for a patient with cystic fibrosis was born. It was the world's first successful IVF-ICSI pregnancies after airplane transport of oocytes as reported by McGill Reproductive Centre, Toronto, Canada [83]. Denmark reported the highest number of IVF cycles (1826 cycles) per million inhabitants followed by Finland (1440 cycles) and then Sweden, Iceland and Norway (around 1000 cycles). These exceptionally high numbers of IVF cycles are probably due to a combination of relatively high practice levels in the Nordic countries and a high public recognition of the technique [84].

On 2000, Kutluk Oktay and Guvenc Karlikaya were the first to report on the success of human ovarian tissue transplant after frozen storage [85]. The first successful pregnancy in Japan was achieved through blastocyst vitrification. A completely defined new protein-free embryo culture medium introduced.

On 2001, the implantation rate on the running IVF programmes improved by using trans-vaginal ultrasound guided embryo transfer catheter [86]. Chian et al. reported a successful birth of an infant developed from cryopreserved embryo produced by IVM oocytes that derived from a non-stimulated woman with PCO syndrome [87]. McGill group in Canada reported the first ongoing twin pregnancy after ICSI of PESA retrieved spermatozoa into *in-vitro* matured oocytes [88]. A baby born after sperm retrieval from a moribund man [89]. The British first license awarded for PGD and HLA-tissue typing. Australian scientists succeeded in fertilizing mice eggs without using sperms. This step opened the door for future single-sex procreation. The first human cloned 6-cells embryos have achieved by a private American company, Advanced Cell Technology for purpose of stem cell research.

On 2002, Kylie de Boer and her assistants reported the first live birth after blastocyst biopsy for PGD [90]. A comparative genomic hybridization and polar body testing for PGD of chromosomal aneuploidy applied for the first time [91].

On 2003, Tae-Ki Yoon and his working group reported a live birth after vitrification in a stimulated IVF-ET programme [92]. The first IVF birth after ovarian stimulation by a long-acting human recombinant Follicle Stimulating Hormone (rFSH) agonist was reported [93]. Dr. Barash and Prof. Dekel demonstrated increased IVF implantation rate following endometrial curettage by Pipelle curette as a simple outpatient procedure [94].

On 2004, Jacques Donnez reported the first live birth baby after orthotopic transplantation of cryopreserved ovarian tissue [95]. Fertility preservation programmes for women undergoing cancer treatment using IVM and oocyte vitrification were provided [96]. Publication of the first report on the natural ovulatory cycle in IVF combined with IVM as a potential approach to infertility treatment [97]. Gardner et al. performed the world's first single blastocyst transfer trial to improve pregnancy rate and to reduce the risk of multiple gestation [98]. The British National Health System (NHS) funded PGD programme and preimplantation HLA-tissue typing [99]. The first cloned human blastocyst claimed by a group in Korea. A live baby born following pre-implantation genetic diagnosis for Retinoblastoma [100].

On 2005, Adriana Iliescu was reported as the world's oldest mother to give a birth at the age of 66 years and 320 days in Giulesti Maternity Hospital, Bucharest, Romania (Figure 4). She had an IVF using donated eggs and sperms. Sherman Silber, in USA, testified the first case of successful ovary transplantation between two identical twin sisters discordant for ovarian function. The first birth in Israel from thawed ovarian cortex transplants in a woman with post-chemotherapy ovarian failure has reported [101]. The First baby born alive after trophectoderm biopsy and preimplantation genetic testing of human blastocysts for beta-Thalassaemia [102].

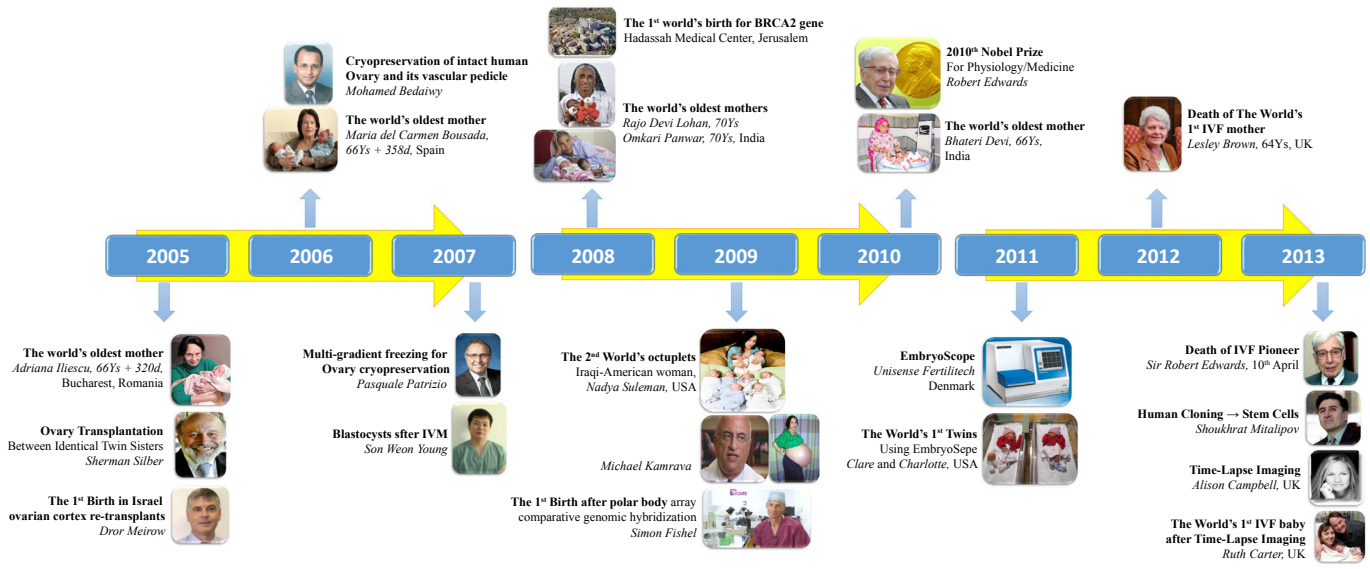

Figure 4: Timeline of Major ART Milestones (Year 2005 - Year 2013).

On 2006, Mohamed Bedaiwy and his group reported a successful cryopreservation of intact human ovary with its vascular pedicle [103]. The first successful pregnancy after PGD for aneuploidy screening in embryos generated from a natural ovulatory cycle reported by McGill Reproductive Centre, Toronto, Canada [104]. Maria del Carmen Bousada became the world's oldest mother to give a birth of twins at the age of 66 years and 358 days in Spain. She conceived by aid of IVF using donated eggs and sperms.

On 2007, the first baby born alive from an egg that had been matured *in-vitro*, frozen, thawed and then fertilized at McGill Reproductive Center, Canada [6]. A report published from the McGill Reproductive Center in Canada and the Maria Infertility Hospital in Korea on successful births after transfer of blastocysts that derived from matured oocytes by IVM [105]. The first European baby born after screening by using Comparative Genomic Hybridisation (CGH) [6]. The concept of mild treatment strategy that substantially reduces the risk of multiple gestation and overall costs was hosted [106]. Pasquale Patrizio introduced a novel multi-gradient freezing technique for cryopreservation of the whole ovary that resulted in preservation of the normal ovarian architecture [107].

On 2008, a viable pregnancy was achieved for the first time at Hadassah Medical Center, Jerusalem, in a 38 years old woman who carries a defective BRCA2 gene. Weon-Young et al. recommended 38 hours interval between hCG injection and oocyte retrieval to increase *in-vivo* and *in-vitro* oocyte maturation rates [108]. On December 2008, the Midland Fertility Services in the UK launched vitrification flash-freezing process. The first report, at Monash Immunology and Stem Cell Laboratories (MISCL), on DNA fingerprinting to identify the blastocyst of origin for live births and that of gene expression profiles of biopsied trophectoderm could discriminate between viable and non-viable blastocysts [109]. The first ever birth of healthy twins after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer [110]. Rajo Devi Lohan and Omkari Panwar became the world's oldest mothers to give birth at the age of 70 years in India.

On 2009, octuplets (8 babies; 6 boys and 2 girls) to Nadya Suleman, a 33 years old Iraqi-American woman in California, USA, were born (The second octuplets in the world). Her treating doctor Michael Kamrava had transferred twelve frozen embryos that left from her previous stimulated IVF cycles, which the medical board of California found it to be a "life-threatening practice" and withdrew his medical license. The first baby boy born from vitrified oocytes in Australia [6]. Cetrorelix acetate (LHRH antagonist) approved by FDA for clinical use in IVF programmes. Simon Fishel and his working group from CARE Fertility, Nottingham, reported a live birth after polar body array comparative genomic hybridization [111,112].

On 2010, the Midland Fertility Services in the UK confirmed the first successful pregnancy from vitrified blastocysts. Several minor changes to the 8th HFEA Code of Practice incorporated into the print version of the Code in April 2010. At Nobel Assembly at Karolinska Institute, Sweden, the year 2010th Nobel Prize for Physiology or Medicine offered to the British physiologist, Robert Edwards for his remarkable work in the field of *in vitro* fertilization. An Indian woman has become the oldest mother in the world to have triplets at the age of 66 years. After she has being childless for 44 years of marriage, Bhateri Devi gave birth to two boys and a girl after IVF.

On 2011, the novel monitoring system for continuous observation of early embryo development around the hour (*EmbryoScope*®) introduced by Unisense Fertilitech, USA. On December, Clare and Charlotte were the world's first twins born to Ed and Caroline Marks by use of the new EmbryoScpe® at Cleveland Reproductive Center, Ohio, USA.

On 2012, the family of Lesley Brown, the first world's IVF mother, confirmed her death at Bristol Royal Infirmary. On the same year, the world's five-millionth IVF baby was born.

On 2013, Professor Sir Robert Edwards, scientist and co-pioneer of IVF, passed away peacefully in his sleep on the morning of April 10th after a long illness. In May, a group of scientists led by Shoukhrat Mitalipov, a reproductive biology specialist at Oregon Health Sciences Universities (OHSU) published a report on a successful human cloning. The approach involved nuclear transfer from human fibroblasts to enucleated oocytes and resulted in viable embryos developing to the blastocyst stage. The researchers planned to obtain embryonic stem cell

from these developed blastocysts for purpose of therapeutic cloning. Alison Campbell, a senior British clinical embryologist in Manchester, introduced the novel Time-lapse imaging for early developing preimplantation embryos for clinical selection of healthy-looking embryo without the need for biopsy and preimplantation genetic screening (PGS) in cases with recurrent IVF failure [112].

On June, Ruth Carter, 42-year-old clinical psychologist, became the world's first mother to give birth a girl at Liverpool's Women Hospital, UK after using the new system Early Embryo Viability Assessment (Eeva) implementing the Time-lapse imaging technique.

ART Expectations

The prospects hold promise for rapid evolution in the ART. Advances in molecular medicine will help in mapping the Y chromosome. Males with testicular failure will be able soon to father their own genetic children. Future researches with oocyte maturation, culture media and endometrial receptiveness may allow immature oocyte retrieval with *in-vitro* maturation to replace the conventional *in-vitro* fertilization. Cryopreservation of human oocytes will provide an alternative to embryo cryopreservation with its ethical repercussions. Advances in Time-lapse imaging technique will increase IVF success rate and avoid the need for invasive and expensive Preimplantation Genetic Diagnosis (PGD) to screen out abnormal embryos. New drugs such as GnRH antagonists hold promise of leading to a better ovarian stimulation, egg quality and implantation rates. The transfer of cytoplasm from younger donor oocytes into older oocytes may improve the viability of developing zygotes and give a better chance for older women to carry their own biological babies.

Conclusion

Advances in the assisted reproductive technology for infertile couples were among the great medical successes of the last century. ART has wide steps and fast progress aiming to find a hope with a suitable treatment option for each infertile couple. Costs and complexity of treatment have reduced to alleviate the stress and social troubles. Problems related to the risk of multiple pregnancy and the use of stimulated cycles are being abridged and new techniques for management of severe male factor infertility and the detection of genetic anomalies in the embryo prior to transfer are being introduced. Further refinements of the techniques and modification of treatments will probably occur with ongoing use and practice.

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Conflict of Interest

I hereby declare that this work carried out in accordance with the requirements of the University of Bristol Regulations and Code of Ethics for Research Programs. It approved by the Research Review Board. Except where indicated by specific reference in the text, this work is my own work. There was no contribution of any other authors. Any views expressed in the study are those of the author. The work was self-funded. I did not receive any financial funding or support from any person or institution. In addition, I state that I have no competing interests.

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