

**Review Article**

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Assisted Reproductive Technology: Where did the Journey Begin, and where are we Today – A 40-year History

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Introduction

Over the last four decades, significant developments have occurred within the field of assisted reproduction, initially sparked by the birth of Louise Brown in 1978, who will be forever be known as the first human baby born through in-vitro fertilization (IVF) treatment in the world. The first IVF cycle was based on a non-stimulated ovulatory cycle, in which the oocyte retrieval procedure was performed laparoscopically. IVF, however, was already being performed experimentally in animals, namely rabbits, as early as the 1980's, with the first IVF human pregnancy reported as early as 1973, but unfortunately resulting in a first trimester loss [1].

Review

The birth of Louise Brown was quickly replicated with two further IVF babies being born within a year of the first human IVF baby; Courtney Cross on the 16th October 1978 and Alastair MacDonald on the 14th January 1979. All three deliveries occurred within the United Kingdom, leading to IVF becoming a viable option for the management of infertile couples' [2].

Clomiphene citrate was concomitantly developed alongside IVF in 1978, by Alex Lopata from Australia [3]. Clomiphene citrate today, is widely used in the management of anovulatory cycles.

In 1980, the World Health Organization (WHO) published its first guidance on human semen analysis to help standardize practices [4] and was the same year as the birth if the fourth IVF baby from an Australian team; Candice Elizabeth Reed [3]. Pre-implantation Genetic Diagnosis (PGD) accounted for another key development within this year; significantly changing the landscape for the prevention of genetic diseases in the newborn through cell biopsy.

Human menopausal gonadotrophin (hMG) was used in the United States for ovarian stimulation, leading to the birth of their first baby through IVF treatment [5]. Following this, human chorionic gonadotrophin (hCG) was utilized for ovulation and oocyte collection, first described by Casper's team, whom reported that hCG would provide the needed luteal support for oocyte maturation in cycles [6]. It is a naturally occurring hormone which is secreted by the placenta syncytiotrophoblast. Richard Fleming illustrated a role for Gonadotrophin releasing hormone (GnRH) agonists in controlling ovarian stimulation and reducing premature luteinisation of follicles [7].

Cycle control gained more favor as the risks of multiple pregnancies and ovarian hyperstimulation syndrome become more apparent. In 1982, the United Kingdom saw the delivery of its first set of IVF twins. This was not surprising, as multiple embryos were replaced to counteract the initial low implantation rates (<5%) [8]. The Human Fertilization and Embryology Authority (HFEA) (United Kingdom), have since made an active attempt to reduce the multiple pregnancy rate, gaining traction following their report 'One child at a time' [9].

The development of cryopreservation of gametes and embryos helped change the landscape of assisted reproductive technology and the management of cycles with ovarian hyperstimulation syndrome. This year also witnessed the delivery of the first set of frozen embryo twins and the delivery of a baby following an intrauterine insemination (IUI) treatment cycle [5].

Alan Trounson and his team (1983), were the first team to achieve a pregnancy from donor oocytes and embryo [10]. Alan

Trounson's team also identified a correlation between delayed insemination following oocyte collection and completion of the oocyte meiotic process [11]. This is the same year that oocyte retrieval was performed using culdocentesis, promoted by Gleicher, initially guided by transabdominal ultrasonography but now largely replaced by transvaginal ultrasonography [12-14].

The first legal framework to regulate the practice of assisted reproductive technologies (ART) was introduced in 1984, in Australia, by the Government of Victoria, Australia; the Infertility Medical Procedures Act 1984 (Victoria Government, 1985). This year also saw the birth of the world's first set of IVF quadruplets, from Australia.

Advancements in the management of male factor infertility occurred in 1985, with surgical sperm retrieval established as a successful method with a pregnancy reported following percutaneous epididymal sperm aspiration (PESA) [15]. PESA has since been widely adopted in the management of obstructive azoospermia, yielding sperm at rates of 80-100% [16]. The world's first pregnancy using autologous sperm from a male suffering from bilateral obstruction of the vas deferens was achieved in 1986, Monash [5].

The European Society of Human Reproduction and Embryology (ESHRE) was also established in 1985; a society that currently hosts over 10 000 delegates annually in a scientific forum.

Ultrasonography in ART cycle management was first documented and performed by Piz, a group from France [5]. It was initially used for follicular tracking and oocyte retrieval procedures, with its use extended to embryo transfer procedures in 1987. Clinical pregnancy rates were seen to improve significantly when embryo transfers were performed under ultrasound guidance compared to the previous touch technique [17].

Couples that had recurrent failed cycles found new light in ART treatment when Laws-King published a technique called SUZI (sub-zonal injection) [18]. It is not long after that, that cryopreservation of embryos was introduced. The ultra-freezing method was initially introduced in 1987 and since then has been further developed to aid ART management. A year later successful pregnancies were reported following SUZI [19].

Continued advancements have led to the usage of 3D ultrasonography and colour doppler to further aid decision making processes [20-23].

Norway, in 1987, made a bold change to the law regarding ART, stating that ART could only be offered to married or cohabiting couples, excluding same sex couples from accessing treatment.

In 1988, a report was published stating the birth of two babies using microscopic epididymal sperm aspiration (MESA).

Live births following the biopsy of pre-implantation embryos and human embryo vitrification were reported two years later [24]. This year also saw the development of assisted hatching [25], as well as the identification of the correlation between bilateral congenital absence of the vas deferens (CBAVD) and a form of cystic fibrosis [26]. This year, however, will mainly be known for the

establishment of the British Human Fertilization and Embryology Act (1990) [5], an independent regulatory body which still governs all practices today.

Although significant advancements in assisted reproduction occurred in the late 70's and early 80's, 1992 saw the first pregnancy following intracytoplasmic sperm injection (ICSI) [27]. A year following this, Silber's team revolutionized the management of male factor infertility, reporting that males suffering with infertility due to non-obstructive azoospermia were able to have their own genetic child using Testicular Sperm Extraction (TESE) and ICSI [28].

In 1994, purified Follicle Stimulating Hormone (FSH) was developed [29]. Cohen published the first report surrounding aneuploidy testing in 1995 [30]. Two years later, the hypo-osmotic swelling test was developed as a method to identify viable sperms for ICSI [31]. This method is widely employed in IVF units across the globe.

Another hallmark discovery in the field of ART occurred when Andrea Jurisicova, recognized and reported details of pre-implantation embryo fragmentation [32]. Following this, Jurisicova further expanded on this in 1997 to describe the detection of DNA fragmentation in sperm and its correlation with IVF outcomes [33].

In 1999, pre-implantation genetic diagnosis for sickle cell anemia resulted in an unaffected pregnancy [34]. Human ovarian tissue transplantation following storage was first reported in 2000, as a successful procedure. Today, this is mainly used for patients undergoing gonadotoxic therapy who wish to preserve their fertility prior to chemotherapy, radiotherapy or radical debulking surgery [35]. It was not until 2004, that the first live birth following orthotopic transplantation of cryopreserved tissue was reported [36].

Time lapse monitoring was introduced in 2011 (EmbryoScope®), allowing continuous monitoring of embryo development with minimal disruption to the embryo, supporting the elective single embryo transfer policy and limiting the multiple pregnancy rate.

Discussion

Over the past 40 years, ART has undergone a major metamorphosis and has provided answers to patients suffering with infertility. It has also seen some steep advancements in procedures performed in ART and the benefit from each of these as the numbers increase. However, the larger question still remains with regards to the outcomes for the children, now adults, born through ART. The prospects of ART and the daily developments further enlighten us as to the exciting opportunities and scope for improvement within this field. Whilst pursuing science to improve patient outcome the ethical dilemma is one that is forever expanding.

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Conflict of interest

No conflict of interest.

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