Section 1 Introduction to ART Surveillance

Chapter 1

Infertility and ART

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Infertility

Infertility, commonly defined as the inability to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse [1], is a global public health issue affecting millions of women and men worldwide [2]. The absolute prevalence of infertility is difficult to estimate as it varies across populations and can be measured using different methods, depending on the purpose of the measurement. For example, clinical definitions of infertility may include women >35 years of age who attempted pregnancy for 6 months, as these women may benefit from earlier evaluation and treatment [3]. Demographic and epidemiological definitions typically aim to measure infertility among populations using standard definitions but also may vary in their approach. Demographers often define infertility as the absence of a live birth among sexually active women who are not using contraception and use longer intervals, such as 2 or 5 years, to assess infertility prevalence [4, 5, 6]. Epidemiological definitions usually measure an inability to achieve pregnancy among women who are attempting to become pregnant and are 'at risk' for conception. Varying criteria are used to identify at-risk populations, including couple status, use of contraception, frequency of unprotected intercourse, timing of last birth, breastfeeding status and the desire for a child [4, 5, 7]. Infertility can be measured over the course of a lifetime or as a current condition and is often reported separately for nulliparous women (primary infertility) and women with one or more previous live births (secondary infertility) [1].

Recurrent pregnancy loss, distinguished by the spontaneous loss of two or more pregnancies before 22 weeks' gestation, is distinct from infertility as the underlying pathology may differ [1, 3]. By definition, measures of infertility prevalence that use live birth as an outcome include a proportion of women with recurrent pregnancy loss. Impaired fecundity is a term that has been used to describe populations that have difficulty getting pregnant and carrying a pregnancy to term [8]. Although this term is sometimes used interchangeably with infertility, it represents a broader construct that is inclusive of pregnancy loss as well as difficulty getting pregnant.

Globally, it has been estimated that approximately 2% of nulliparous women 20–44 years of age were unable to achieve a live birth after 5 years of trying, and 10% of women 20–44 years of age with at least one previous live birth were unable to have another child over a 5-year period [2]. Estimates of primary infertility were lowest in middle-income countries in Latin America (0.8–1.0%) and highest in countries in Eastern Europe, North Africa/Middle East, Oceania and sub-Saharan Africa (>3.0%). In Canada, the prevalence of current infertility (an inability to achieve pregnancy in the past 12 months among married and cohabiting couples) ranged from 11.5 to 15.7%, depending on how risk of conception was defined (e.g. whether restricted to couples reporting having intercourse in the past 12 months who were trying to become pregnant) [9]. In the United States (US), 6.7% of married women 15–44 years of age in 2011–2015 were infertile (had unprotected intercourse with the same husband for at least 12 consecutive months but did not have a pregnancy) (Table 1.1). Using the broader measure of impaired fecundity that includes pregnancy loss as well as physical difficulties conceiving a pregnancy, the prevalence of impaired fecundity was 15.5% for married women aged 15–44 in 2011–2015 and 12.1% for all women aged 15–44, regardless of marital status. In addition, the prevalence of infertility among nulliparous married women increased with age. Among all women, the prevalence of impaired fecundity increased with age.

Table 1.1 Infertility and impaired fecundity among women aged 15–44 years, by selected characteristics: US, 2011–2015

Characteristic	Infertility among married women[a]	Impaired fecundity among married women[b]	Impaired fecundity among all women[b]
	Percent (standard error)		
Total	6.7 (0.52)	15.5 (0.79)	12.1 (0.41)
Age			
15–24 years	4.6 (2.01)	15.4 (3.04)	7.8 (0.68)*
25–34 years	6.3 (0.78)	14.7 (1.18)	12.6 (0.69)
35–44 years	7.3 (0.87)	16.1 (1.22)	15.7 (0.90)
Parity and age			
No births	14.2 (1.63)**	23.6 (2.59)**	11.2 (0.74)
15–24 years	1.6 (0.98)*	15.1 (4.65)*	7.0 (0.76)*
25–34 years	11.7 (1.83)	16.3 (2.11)	12.3 (1.23)
35–44 years	24.4 (3.90)	39.6 (5.83)	28.7 (3.11)
1 or more births	4.9 (0.56)	13.5 (0.84)	12.8 (0.57)
15–24 years	7.6 (3.74)	15.7 (4.67)	11.9 (1.49)
25–34 years	4.5 (0.84)	14.1 (1.42)	12.8 (0.86)
35–44 years	4.9 (0.77)	12.9 (1.13)	13.0 (0.93)

[a] Married women are classified as infertile if they have been exposed to the risk of pregnancy (had unprotected intercourse) with the same husband for at least 12 consecutive months, but have not had a pregnancy. See reference 8 for further details on this measure.

[b] Impaired fecundity indicates physical difficulties in getting pregnant or carrying a pregnancy to live birth. See reference 8 for further details on this measure.

* Older age among nulliparous women was significantly associated with a higher percentage with the specified fertility problem ($p<0.05$).

** The percentage for women with 1 or more births was significantly higher than that for women with 0 births ($p<0.05$).

Source: CDC/NCHS, 2011–2015 National Survey of Family Growth

Advancing age (typically 35 years or older) is the most important predictor of infertility in women [10, 11]. In many developed countries, maternal age at first birth has been increasing over time as more women delay childbearing to pursue educational or employment opportunities or because of personal circumstances [12, 13, 14]. Because the number and quality of eggs decline as a woman ages, postponement of childbearing can result in couples seeking to start a family at a time when female fecundity is declining [15]. Other risk factors for female infertility include a history of sexually transmitted infections, smoking, illicit drug use, alcohol use, exposure to certain environmental factors and chronic conditions such as diabetes, obesity and cardiovascular disease [15, 16, 17, 18].

Among men, advanced paternal age is associated with decreased semen quality and increasing rates of DNA fragmentation in sperm [19, 20]. Other factors that may affect male fertility are smoking, illicit drug use, alcohol use, exposure to certain environmental factors and obesity [16, 21, 22, 23, 24, 25]. Notably, findings from a recent meta-analysis suggest that sperm counts declined from 1973 to 2011 in North America, Europe, Australia and New Zealand [26]. The reason for the decrease is not known but may be the result of environmental exposures or lifestyle factors.

The History of Assisted Reproductive Technology as a Treatment for Infertility

In the late 1800s, the German researcher Wilhelm August Oscar Hertwig took a position in the Mediterranean studying sea urchins. During this time, he observed the fertilization of an oocyte by a sperm outside of the sea urchin's body. Despite resistance from the scientific community, he published his observations, setting the groundwork for the modern theory of chromosome continuity [27].

The study of fertilization and embryo development continued over the years, and eventually an American biologist, Gregory Pincus, with an interest

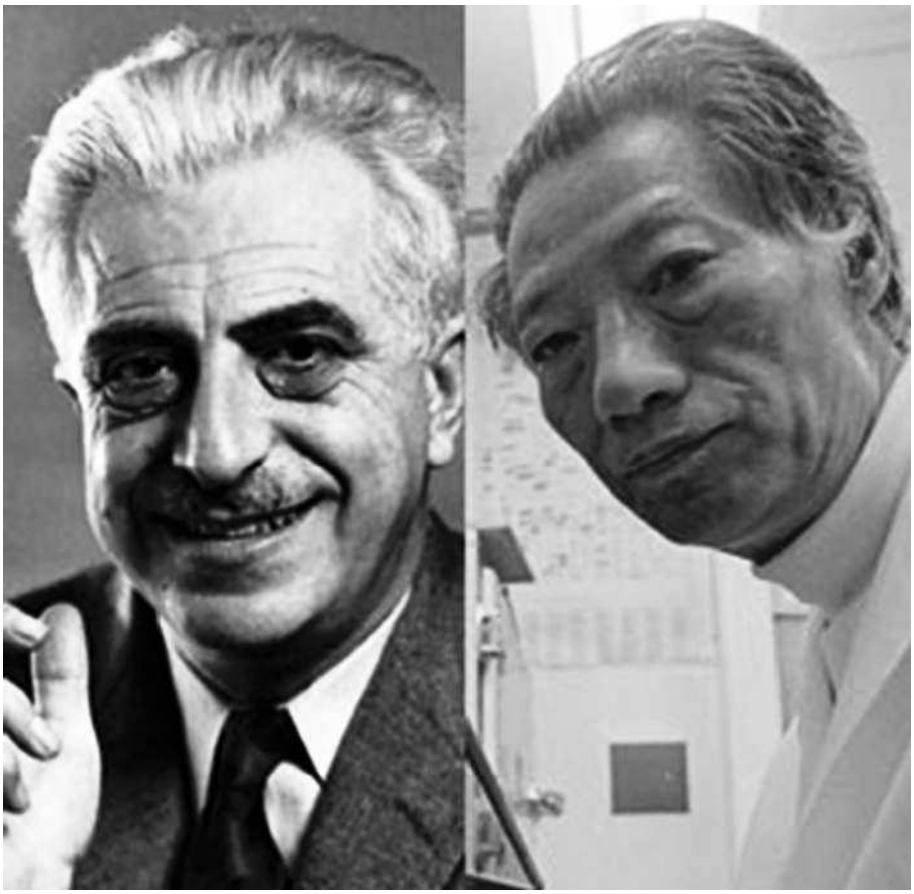

Figure 1.1 Gregory Pincus and Min Chueh Chang, early pioneers in IVF in animal studies.

in the way that hormones affected the reproductive system, began his famous work with rabbits. He removed an oocyte from a mother rabbit and succeeded in fertilizing it outside of the body, so-called Pincogenesis in vitro, and after replacing the embryo in the rabbit he published on the first birth of a mammal by in vitro fertilization (IVF) [28]. Peers had difficulty replicating his experiment until Dr Min Chueh Chang, in 1959, was able to fertilize a black rabbit's eggs with a black rabbit sperm and transfer those embryos into the womb of a white rabbit [29]. Once that rabbit birthed a litter of black rabbits, the potential for use of IVF in humans was visualized by the scientific community. Figure 1.1 contains images of both scientists.

Early use of IVF in animals rapidly caught the public's attention as well. In the classic dystopian science fiction novel *Brave New World*, author Aldous Huxley wrote about a world populated by people grown in artificial wombs through laboratory experiments. His 1932 novel introduced the public to the possibility of a 'test tube baby' [30].

Pincus' and Chang's work with mammals inspired a generation of physician scientists around the world to pursue the fertilization of the human oocyte in vitro. In the 1940s, Menken and Rock harvested oocytes from reproductive-aged women undergoing laparotomy and were the first to publish on the fertilization and cleavage of human embryos in culture [31]. Dr Robert Edwards, an English physiologist, developed the techniques to culture and mature human oocytes in the lab. In a groundbreaking *Lancet* publication, Edwards predicted the potential of IVF to circumvent tubal factor infertility with embryo transfer through the cervix. He even suggested the potential of preimplantation screening of embryos to exhibit control over sex-linked recessive conditions (Fig. 1.2) [32]. The first biochemical

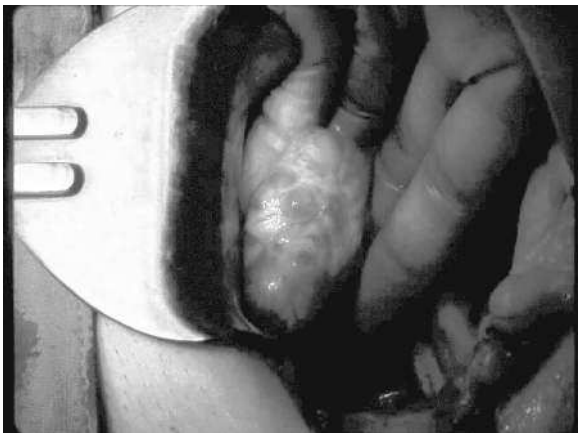

Figure1.2 Stimulated ovaries visible on laparotomy. Photo credit Dr Alan DeCherney.

pregnancy achieved through IVF was accomplished by Carl Wood, John Leeton and Alan Trounson in 1973 at Monash University; however, it resulted in an early miscarriage [33].

A British gynaecologist, Patrick Steptoe, working in the field of laparoscopy in gynaecological procedures, collaborated with Dr Edwards on the development of techniques for IVF. They successfully used hormonal medications to hyperstimulate infertile women's ovaries and used laparoscopy to collect oocytes [34]. Eventually, they used varying techniques to clean and purify sperm samples and fertilized those oocytes in a Petri dish [35]. In 1976, they successfully transplanted an embryo grown in culture into a uterus, resulting in a positive pregnancy test. Although this pregnancy was later identified as ectopic, it proved their technique was feasible [36]. They continued their pioneering work, which eventually resulted in the birth of the world's first IVF baby, Louise Brown, on 25 July 1978 in Oldham General Hospital, Manchester, United Kingdom (UK) [37].

In Australia, the Melbourne team of Wood, Leeton, Trounson and Dr Ian Johnson followed the success of Steptoe and Edwards with the birth of Candice Reed in 1980 [38]. Similar to Edwards and Steptoe, the Melbourne group had focused on natural cycle IVF for their early work.

Husband and wife team Drs Howard and Georgeanna Segar Jones further improved stimulated cycles by incorporating human menopausal gonadotropin. They established the first IVF clinic and lab in the US. Their work at the Eastern Virginia Medical School in Norfolk, Virginia, resulted in the birth of Elizabeth Jordan Carr, the first US-born IVF baby, in 1981 [39].

In France, the work of Dr Rene Frydman and Dr Jacques Testart led to the development of an assay, which could reliably predict the luteinizing hormone (LH) surge in plasma. This breakthrough allowed for improved timing of oocyte retrievals. France celebrated the birth of an IVF baby in 1982 [40].

With the field demonstrating more successes and expanding in popularity, collaboration and technology advanced. In 1976, Dr Yves Menezo developed a culture medium designed to mimic the natural environment the oocyte would be exposed to during fertilization in the fallopian tube [41]. This medium, named B2, was important in the standardization and improvement of embryology labs around the world and is still used today. From 1979–1980, the Melbourne group experimented with various catheter designs for embryo transfer and demonstrated the superiority of the Teflon-lined, open-ended catheter [42]. In 1981, Dr Robert Edwards organized an international meeting at Bourn Hall, the site of his new laboratory near Cambridge (Fig. 1.3). It was at this meeting that the superiority of stimulated cycles using clomiphene was agreed upon, thanks to the increase in oocyte yield and their ability to facilitate the timing of procedures [43]. This desire to increase the success of stimulated cycles stoked the interest of the academic community in expanding their arsenal of injectable gonadotropins.

Prior to the development of injectable gonadotropins, clomiphene was the drug of choice in ovarian stimulation. Although clomiphene was initially synthesized in 1956, it was not approved for marketing until 1967 after it was discovered that anovulatory patients taking clomiphene had higher than expected rates of pregnancy [44].

Human menopausal gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), were first extracted from the urine of postmenopausal women in 1949 and introduced into clinical practice for the management of infertility by Dr Bruno Lunenfeld in 1961 [45]. Dr Lunenfeld developed international standards for gonadotropins as well as established guidelines for classification of infertile patients and ovarian hyperstimulation syndrome resulting from infertility treatment. In 1983,

Figure 1.3 The first international meeting of IVF practitioners, organized by Dr Robert Edwards, at Bourn Hall in 1981.

high-dose human menopausal gonadotropin (hMG) was shown to be a better method for stimulation prior to oocyte retrieval and did not require serum or urinary LH monitoring because of low incidence of spontaneous ovulation [46].

Urinary preparations of LH/FSH were commonly used until more 'pure' methods were discovered using recombinant DNA/RNA technologies. Recombinant FSH and LH have since become the standard of care for use in stimulation cycles [47].

While Steptoe and Edwards had pioneered oocyte retrieval via direct visualization laparoscopy, improvements in ultrasound technology provided for safety and decreased costs incurred during the treatment of infertility. Using abdominal ultrasound, Drs Lenz and Lauritsen were able to harvest eggs percutaneously through the abdominal wall and the bladder [48]. Later, in 1983, Mount Sinai and Rush Medical Center investigators in Chicago, Illinois, demonstrated the possibility of using abdominal ultrasound with a transvaginal approach to collect human oocytes [49]. A Danish group improved on these techniques by installing a guide for the needle on the ultrasound transducer to improve visualization and subsequent yield from the procedure [50]. Dr Pierre Dellenbach, working in Strasbourg, France, was the first to demonstrate a transvaginal approach to oocyte retrieval using an abdominal ultrasound (Fig. 1.4) [51]. Following advancements in transvaginal ultrasonography, Dr David Meldrum proposed that visualization of developing oocytes was superior with the transvaginal approach and advocated for its use in oocyte retrieval [52]. Like the abdominal probes, the transducers for transvaginal ultrasound were eventually fitted with guides to aid in needle aspiration of oocytes. Transvaginal ultrasonography with transvaginal aspiration of oocytes replaced laparoscopy, resulting in decreased need for anaesthesia, decreased operative times, faster recoveries and, eventually, the ability to perform procedures in-office without the need for a traditional operating room.

Working with the Melbourne Group in Australia in 1983, Dr Trounson and his colleagues made major strides in the field of oocyte donation. Using a 42-year-old donor from whom they collected 6 oocytes, they were able to transfer an embryo into a 38-year-old recipient; the embryo implanted successfully. This pregnancy resulted in miscarriage at 10 weeks' gestation [53]; however, the same group, with the help of Dr Lutjen, used similar techniques and reported on the first baby born from oocyte donation in 1984 [54].

While treatment options for patients with absent or non-functioning ovaries were expanding, some women without a uterus began searching for options to have a genetic child of their own. In the treatment of a patient with a history of caesarean hysterectomy, a group out of Mount Sinai Medical Center in Cleveland, Ohio, was able to retrieve her oocytes and fertilize them with her husband's sperm, and later transfer an embryo into the uterus of a friend of the intended mother. The recipient of the embryo became the world's first gestational surrogate [55].

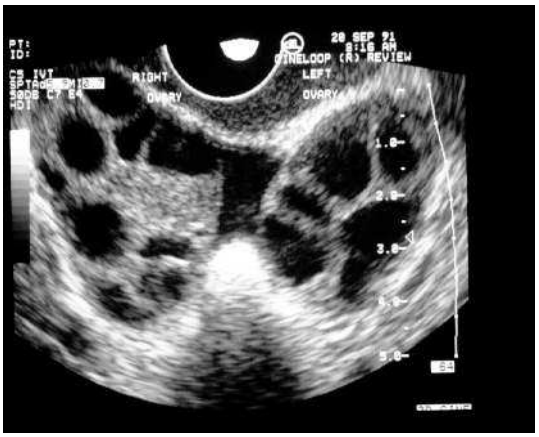

Figure 1.4 Early transvaginal ultrasound of stimulated ovaries. Photo credit Dr Alan DeCherney.

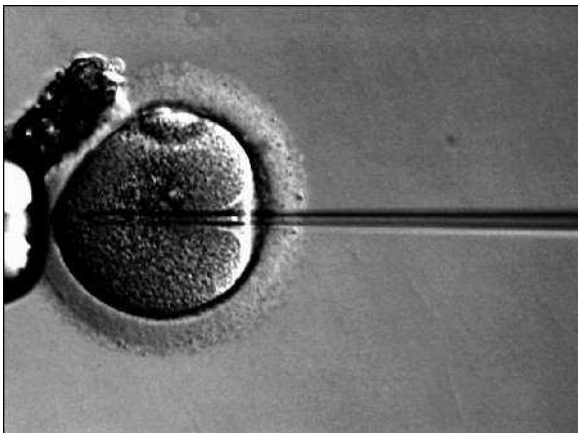

Figure 1.5 Early image of ICSI in progress. Photo credit Dr Alan DeCherney.

As oocyte retrieval procedures improved and more embryos were created in vitro, physician-scientists continued investigations into improving the implantation rate of those embryos. Jacques Cohen, an embryologist working out of Bourn Hall, noted that embryos with a thinner zona pellucida had higher implantation rates. Through this, he postulated that embryos created in the lab may have an impaired ability to hatch from the zona pellucida, an important factor in implantation, and started micromanipulating embryos to assist their ability to hatch. By making artificial defects in the zona pellucida in what would be called 'assisted hatching', they were able to improve their implantation rates from 11% to 23% [56].

As micromanipulation techniques for oocytes, spermatozoa and embryos improved, so did the treatment of male factor infertility. Efforts to bring the sperm closer to the egg, and even into the perivitelline space, under microscopy yielded mixed results. While attempting such a procedure at Vrije University in Brussels, Drs Palermo, Devroey and Van Steirteghem managed to inject spermatozoa directly into an oocyte, which eventually developed into a healthy embryo. They called this method intracytoplasmic sperm injection (ICSI) (Fig. 1.5). They published on their first successful pregnancy with this technique in 1991, which led to a successful delivery in 1992 [57]. ICSI resulted in higher fertilization rates among men with male factor infertility and rapidly became the preferred method of treating male-factor infertility.

As more techniques were developed to increase the number of embryos that were available for transfer, the need for a method of preservation became increasingly important. Using existing models of animal embryo cryopreservation, Trouson and Mohr used slow freezing and thawing techniques of 4- and 8-cell embryos to successfully store and transfer a viable embryo, which resulted in a pregnancy in 1983. The first of these pregnancies resulted in a loss secondary to premature rupture of membranes at 24 weeks' gestational age; however, one year later the group reported a successful term birth after frozen embryo transfer [58]. Vitrification, which involved the use of fast freezing and cryoprotectants to minimize damage to the embryo from ice crystal formation, was developed in 1987 [59].

Oocyte cryopreservation has gained success and popularity using similar vitrification techniques. It can be considered in patients hoping to preserve their future fertility for personal or medical reasons, including plans to undergo gonadotoxic chemotherapies. As of January 2013, the American Society for Reproductive Medicine no longer classifies oocyte cryopreservation as experimental and encourages practitioners to integrate oocyte cryopreservation into their practice [60].

With improvements in cryopreservation and the techniques of embryo micromanipulation, Edwards' theories about IVF allowing for the control over various genetic diseases have become reality. Preimplantation genetic testing (PGT) involves

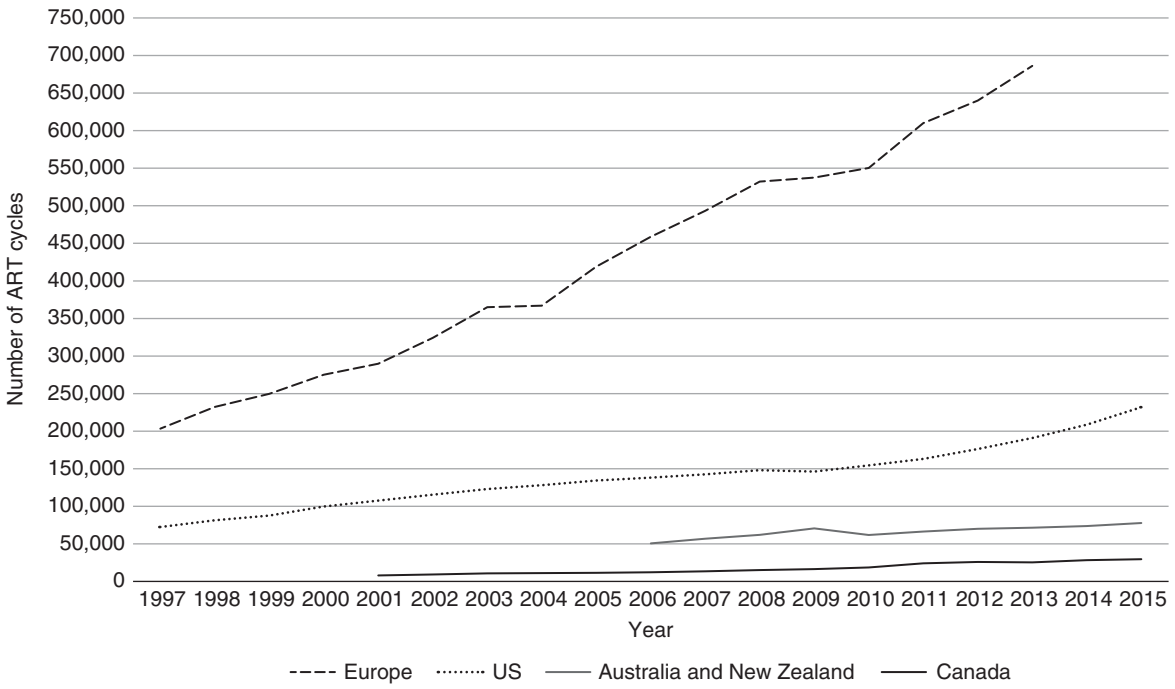

Figure 1.6 Trends in number of ART cycles in Europe, the US, Australia/New Zealand and Canada.
Sources: (1) Calhaz-Jorge C, De Geyter C, Kupka MS, et al. The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. *Hum Reprod*. 2017;**32**(10):1957–73; (2) www.cdc.gov/art/reports/archive.html; (3) https://npesu.unsw.edu.au/surveillance-type/annual-reports; (4) https://cfas.ca/cartr-annual-reports/.

the testing of a sample obtained from a developing embryo before embryo transfer. Techniques for the biopsy of embryos were developed in the 1980s by Wilton (cleavage stage biopsy), Verlinsky (polar body) and Muggleton-Harris (blastocyst biopsy) [53]. In 1989, Handyside et al. published on the first biopsy of a human preimplantation embryo. During their experiment, they removed a single cell from 30 embryos in the 6- to 10-cell cleavage stage and determined embryo sex via polymerase chain reaction [61]. This allowed for embryology labs and doctors treating infertility to effectively screen out sex-linked genetic disorders. They reported on the births of healthy babies from this technique in couples carrying genes for X-linked mental retardation and adrenoleukodystrophy [62]. In 1992, Munne and colleagues used fluorescence in situ hybridization (FISH) to screen for sex and ploidy status of embryos [63]. As newer technologies developed, including whole genome amplifications, microarray and next-generation sequencing, the ability of PGT to properly screen for various genetic disorders has expanded rapidly [64].

Variations in Assisted Reproductive Technology across the Globe

The number of assisted reproductive technology (ART) cycles performed globally has increased over time (Fig. 1.6), with concurrent increases in the number of fertility clinics providing ART [67, 76, 77, 78]. Use of ART varies considerably across regions, countries and states or jurisdictions [67, 76, 77, 79]. Availability of services often depends on factors such as legal restrictions related to relationship status, sex or gender identity [67]. In high- and middle-income countries, the average cost for one fresh IVF procedure is estimated to be $4,950 (USD) and ranges from $1,800 to $13,000 per treatment cycle [80]. Lack of reimbursement of treatment costs is a barrier to accessing ART services [80, 81]; however, there are considerable differences in subsidization of fertility

treatments across countries [67, 80]. In a recent surveillance report from the International Federation of Fertility Societies (IFFS), only 37 of 70 responding countries reported that insurance coverage or government funding was available for fertility treatments [67]. Moreover, funding for treatments is often limited based on fertility status (primary versus secondary), duration of infertility, income and age [67]. Likewise, certain procedures such as ICSI, assisted hatching, preimplantation genetic testing, cryopreservation of eggs or embryos and use of donor eggs or sperm or a gestational carrier may be exempt from reimbursement, depending on the patient's country of residence [67].

In addition to economic barriers to treatment, there may be other obstacles that prevent certain populations from accessing ART or policies that restrict the use of specific procedures. For example, some countries and jurisdictions have regulations or professional guidelines requiring couples to be heterosexual and/or legally married to access ART [67]. Other regulations may apply to use of egg or embryo cryopreservation for non-medical conditions, third-party reproduction (e.g. use of donor gametes, embryos or a gestational carrier), selective reduction, preimplantation genetic testing or fertility preservation [67].

Other differences in the practice of ART across countries have also been noted. For instance, there is some evidence that starting gonadotropin doses are higher in the US than in Europe [82]. In addition, while the rate of single embryo transfer (SET) has been increasing overall, country- or continent-specific SET rates are variable. In 2010, Australia/New Zealand, Europe and Asia had the highest SET rates, while Latin America, sub-Saharan Africa and North America had the lowest rates [77]. Explanations for variations in SET rates may include reimbursement policies, implementation of clinical care guidelines and patient preference [67].

Conclusion

Infertility is an important global public health problem. In the absence of a standard definition of infertility, it is difficult to compare prevalence estimates across populations; however, it is estimated that nearly 50 million couples worldwide are infertile [2]. ART has emerged as a fundamental treatment for infertility, with a century of investigation and collaboration propelling the field of ART towards the success and popularity it currently holds. Globally, access to and utilization of ART are variable and influenced by reimbursement policies, as well as the adoption of legal restrictions and guidelines in the country or jurisdiction where the procedure takes place.

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