Contents

CHAPTER

1

History and epidemiology of human fertility

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The history of fertility is the history of mankind. Since the dawn of humanity, fertility has played a major role in human thought, culture, and activities, and the mystery of reproduction was one of the earliest dilemmas facing the human race. In fact, for a good part of their early history, humans did not understand how a woman became pregnant, and the discovery of the relation between sexual intercourse and pregnancy must have been one of the earliest concepts achieved by the human brain.

Fertility in the ancient world

In the ancient world, humans related fertility to superpowers and many fertility deities were worshiped in various parts of the world to seek their help in understanding the mystery of fertility. Most of these deities were female goddesses, as the fertility myth was perceived to reside mainly in the females who bring the offspring to this world. In ancient Egypt, Isis was the goddess of fertility, while Hathor was the goddess that protected women in labor (Fig. 1.1). In ancient Greece, Aphrodite was the goddess of fertility. She was also the mother of Eros, the god of love, while in Roman mythology, Venus was the goddess of love, sex, beauty, and fertility. In African culture, the goddess was Ashanti, and in the Inca culture, she was Mama Oclio. In China, she was Jiutian Xuanwu, while in India, she was Banka-Mundi. In Sumerian and Babylonian cultures, she was Ishtar, and in Ireland, she was Brigit. Each goddess had powers that were also helped by certain rituals and flowers that attracted fertility, mainly the rose, the lotus, and the orchid [1].

On occasions, attempts were made to develop more mundane solutions for infertility, but these were not successful due to the absence of the basic tools and the scientific method. For example, ancient Egyptians developed a primitive pregnancy test: women were asked to urinate on barley or wheat seeds and sprouting

FIGURE 1.1 Headless sculpture of Isis, goddess of fertility in ancient Egypt made from basalt showing the characteristic knot on her chest from the Graeco-Roman Period (332 BCE–395 CE) found in Alexandria (Bibliotheca Alexandrina collection).

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seeds indicated pregnancy. While this may sound like pseudoscience, Ghalioungui et al. reported that it correctly identified 70%–85% of pregnancies [2].

In ancient Greece, attempts at explaining fertility and infertility were made but offer little to help in our current understanding of the fertility process. The Hippocratic Corpus contains three texts related to fertility, "Diseases of Women" (*Gynaikeia*) 1 and 2 and "On Infertile Women" (*Peri Aphorôn*) with various empirical treatments and recipes. Even Aristotle (384–322 BCE), the most enlightened of the Greek philosophers, believed that only male semen was incorporated into the fetus and that the female played no role in the generative material. However, Soranus of Ephesus, one of the leading scientists of the old Alexandria Medical School, and who was the first to describe the human uterus, contradicted Aristotle, and wrote in his book "Gynecology" that both the male and female produce "seeds" necessary for conception [3]. He also noted that masculine-appearing females and those exercising excessively failed to menstruate and commented on contraception, noting that blockade of the cervical os was an effective means of preventing conception [4].

Galen (129–200 AD) was a leading Roman physician who also trained in Alexandria before traveling to Rome to become the personal physician of the Emperor Marcus Aurelius and his son Commodus. He described the "female testes," which he thought corresponded to the male testes, and thought that menstruation was a form of auto-phlebotomy and represented a means to eliminate unfavorable circulating humors, a concept that remained alive well into the Middle Ages [5]. However, few advances were made during the Middle Ages, and even during the Arab/Islamic golden age in Andalucia, no notable discoveries were made in the field apart from the primitive obstetrics forceps described by Abulcassis of Cordoba [6].

Fertility in the post-Renaissance era

It is only after the Renaissance and subsequent age of enlightenment that various discoveries started to shed light on our current understanding of the processes of human reproduction. In 1506, Leonardo da Vinci (1452–1519) began his anatomical drawings in Milan and later collaborated with the physician-anatomist Marcantonio della Torre in Pavia and made an accurate sketch of the fetus in utero [7]. Subsequently, Gabriele Falloppio (1523–62) professor of anatomy in Padua described the Fallopian tube, which bears his name to this day. However, the real breakthrough came with the invention of the microscope when Antonie van Leeuwenhoek (1632–1723) a Dutch scientist and businessman living in Delft was the first to observe and describe the spermatozoa using his primitive instrument and called them "animalicules" [8].

It was also the Dutch physician and anatomist Regnier de Graaf (1641–73) also working in Delft who summarized the work of his predecessors and made key discoveries in reproductive biology. He described the testicular tubules, the efferent ducts, and corpora lutea and was probably the first to understand the reproductive function of the Fallopian tube, but his most important discovery is probably the description of the ovarian follicles (later called after him: Graafian follicles), which he thought were the oocytes [9]. Subsequently, the Italian priest and physiologist Lazzaro Spallanzani (1729–99) working in Pavia was the first to show that fertilization requires physical contact between the sperm and the ovum and used this information to perform successful artificial insemination in dogs in 1770 [10]. Ten years later, the Scottish surgeon John Hunter (1728–93) working in London performed the first successful artificial insemination in humans [10]. However, it was the Baltic-German scientist Karl Ernst von Baer (1792–1876) who eventually discovered the human oocyte in 1827 while working at Königsberg University in Kaliningrad and showed that it resided inside the follicle [9]. Finally, it was Oscar Hertwig (1849–1922) working in Berlin who, by studying sea urchins, proved in 1870 that fertilization occurs due to the fusion of a sperm and an egg cell [11].

At the same time, the concept of hormones was introduced by Arnold Berthold (1803–1861) in 1846 while working in the University of Göttingen by finding that castrated cock chickens lost their aggressive male behavior and characteristics, but it was Ernest Starling and William Bayliss of University College London who introduced the term "hormone" in 1905 [12] (Fig. 1.2).

Fertility in modern times

With the dawning of the 20th century and the understanding of the basic principles of fertility, major discoveries were made in a remarkably short time. These included the understanding of the hypothalamic-pituitary-ovarian axis, the discovery of gonadotrophins and the isolation of gonadal steroids, the understanding of the hormonal changes involved in the control of the menstrual cycle, culminating in the success of in-vitro fertilization and its allied techniques.

The hypothalamic-pituitary-ovarian axis

In 1910, Samuel Crowe, working at Johns Hopkins, showed that partial pituitary ablation resulted in

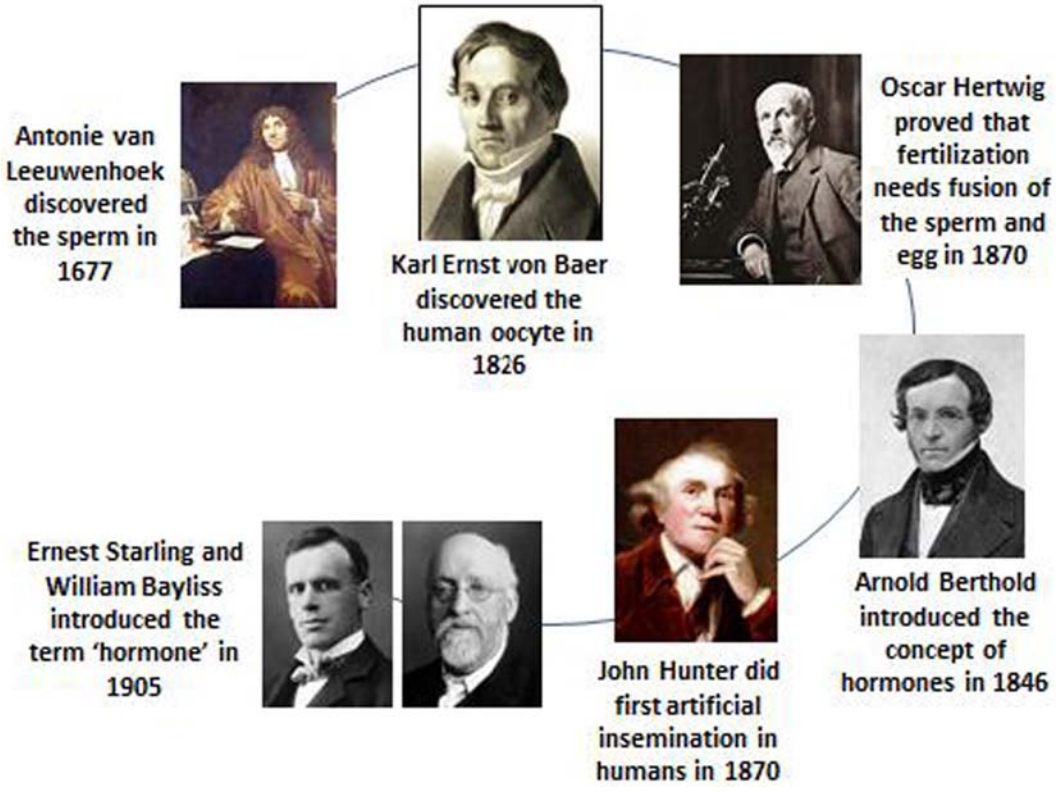

FIGURE 1.2 The fathers of human reproduction in the post-Renaissance era. *Adapted from Lunenfeld B. Gonadotropin stimulation: past, present and future. Reprod Med Biol. 2012;11(1):11–25.*

atrophy of the genital organs in adult dogs [13], and in 1912, the Austrian physician Bernhard Aschner (1883–1960) working in Vienna observed that men and women with diseases, tumors, or injuries of the hypophysis and pituitary stalk suffered the same fate [14]. Subsequently, in 1926 Philip Smith (1884–1970) working in Berkeley and later in Columbia showed that daily implants of fresh anterior pituitary gland tissue into immature male and female mice and rats induced precocious sexual maturity [15].

At the same time (in 1926), Bernhard Zondek (1891–1966) working in the Charité Hospital in Berlin implanted anterior pituitary glands from adult cows, bulls, and humans into immature animals and showed that this led to rapid development of sexual puberty [16]. It was also Zondek who proposed in 1929 the idea that the pituitary secretes two hormones that stimulate the gonads—Prolan A and Prolan B—and in 1930, he showed that the blood and urine of postmenopausal women contained gonadotropins. He proposed that Prolan A stimulated follicular growth and the secretion of "foliculin" (estradiol) and that Prolan B induced ovulation, formation of the corpus luteum, and secretion of "lutein" (progesterone) [16]. He also suggested in 1930 that the synchronization of Prolan A and Prolan B secretion by the anterior pituitary was responsible for the rhythmic activity of the ovary and the cyclic preparation of the endometrium [17]. However, it was in 1931 that Fevold working in Wisconsin actually extracted the two hormones from the pituitary and called them follicle-stimulating (FSH) and luteinizing (LH) hormones [18].

Simultaneously, in 1927, Selmar Ascheim (1878–1965), working again with Bernhard Zondek at the Charité Hospital in Berlin, showed that the blood and urine of pregnant women contained a substance that stimulated the gonads. They also showed that injecting this substance into intact immature female mice produced follicular maturation and luteinization, which was to become the Ascheim Zondek pregnancy test [19]. However, Ascheim and Zondek believed that this substance was produced by the anterior pituitary, and it was in 1943 that Georgeanna Seegar-Jones (1912–2005) working at Johns Hopkins showed that this gonadotropin was produced by the placenta and not the pituitary gland and called it human chorionic gonadotrophin (HCG) [20].

The gonadotrophins

With the understanding of the role of gonadotrophins, attempts at using them for treating infertile women started. Pregnant mare serum gonadotrophins (PMSG) were the first to be used, and in 1945, Hamblen et al. of Duke University in North Carolina introduced the two-step protocol for women with hypofunctioning ovaries: administration of PMSG during the follicular phase followed by HCG 12–18 days later [21]. In parallel, and in the same year of 1945, HMG was purified and isolated from urine of menopausal women and the first pregnancy was reported by Lunenfeld et al. in 1962 [22].

On the other hand, in 1958, Carl Gemzell, working in Uppsala, Sweden, extracted gonadotropins from human pituitary glands and used them to treat anovulation. However, in 1990, four cases of Creutzfeldt–Jakob disease (CJD or mad-cow disease) were discovered in Australia, France, and the United Kingdom, and the production of these human pituitary gonadotrophins was stopped [16]. HMG therefore became the drug of choice, with each ampoule containing 75 IU of FSH and 75 IU of LH.

With the use of HMG, it became clear that the patients' response to stimulation varied. Patients with polycystic ovarian syndrome who already had a high LH/FSH ratio were particularly liable to ovarian hyperstimulation syndrome. Work on the purification of HMG using polyclonal antibodies to remove LH by immunechromatography started, and in 1982, purified HMG (urofollitropin) was available on the market, with each ampoule containing 75 IU of FSH and 25 IU of LH. Highly purified HMG (urofolllitropin-HP) was introduced next using monoclonal antibodies with each ampoule containing 75 IU of FSH and less than 1 IU of LH [16]. With increased demand and the proliferation of IVF units, recombinant FSH was introduced by incorporating the FSH gene into the nuclear DNA of Chinese hamster ovary cells. Follitropin-α was produced in 1988 and Follitropin-β in 1996 (Table 1.1).

TABLE 1.1 Comparison of HMG and FSH preparations.

Product	Purity (%)	Specific activity
HMG (menotropins)	5	Variable
Purified FSH (urifollitropin)	5	100–150 IU/mg
Highly purified FSH (urifollitropin-HP)	95	10.000 IU/mg
Recombinant FSH (follitropin α and β)	>99	Mass/μg

Gonadal steroids

As in the case of gonadotrophins, the discovery of estrogens went through various stages. In the 1880s, Robert Battey (1928–1895) working in Atlanta, Georgia, performed oophorectomy as a treatment for dysmenorrhea and bleeding from fibroids. After removal of the ovaries, he observed that patients developed amenorrhoea, hot flashes, and vaginal atrophy. This meant that the ovaries were secreting a substance responsible for menstruation. In 1896, Emil Knauer (1867–1935) working with Josef Halban (1870–1937) and Ludwig Fraenkel (1870–1951) in Vienna removed the ovaries from rabbits and observed uterine atrophy, which he could prevent by transplanting the ovary at a distant site, confirming the theory of internal secretion by the ovaries. Finally, in 1897, Hubert Fosbery successfully used ovarian extracts to treat a patient with severe hot flashes [23].

Thus with the beginning of the 20th century, work started in earnest to isolate this substance secreted from the ovary called "estrogen." In 1929, the German biochemist Adolf Butenandt (1903–95), who received the Nobel Prize in 1939, and the American biochemist Edward Adelbert Doisy (1893–1986), who also received the Nobel Prize in 1943, independently isolated and purified estrone, the first estrogen to be discovered. Subsequently, estriol and estradiol were discovered in 1930 and 1933, respectively [23].

On the other hand, the discovery of progesterone followed a different path. In 1929, Georges Corner (1889–1981) and William Allen (1904–93) working in the United States extracted a substance from the corpus luteum of a pregnant rabbit. They injected the extract into another rabbit that was castrated just after mating and found that the pregnancy continued. They called the substance "progestin" [24]. However, it was again Adolf Butenandt who isolated the same substance in 1934 and discovered that it contained a ketone group and called it progesterone [25].

The discovery of the aromatase system responsible for the conversion of androgens to estrogens involved the collaboration of many scientists from the Worcester Foundation for Experimental Biology, established in 1944 in Shrewsbury, Massachusetts, and from Harvard. They included Ralph Dorfman (1911–85) and the enzymologist Mika Hayano (1920–1964) who used radiolabeled tracer steroids in their experiments [26]. But it was Kenneth Ryan and Lewis Engel at Harvard who utilized human placental microsomal preparations to convert androgens to estrogens in high yields [27]. Subsequently, Armstrong and Dorrington working in Ontario, Canada, suggested the 2 cell 2 gonadotrophin theory to explain the interplay between the gonadotrophin and ovarian hormones in the ovary [28].

Immuno-assays and the female hormonal interplay

Rosalyn Yalow (1921–2011) and Solomon Berson (1918–72) working in New York cooperated in their discovery of immunoassays, and Yalow received the Nobel Prize in 1977. This meant that it was then possible to measure compounds present in biological fluids (blood or urine) in nmol and even pmol concentrations [29]. This immediately opened the door for the discovery of the intricate relations between FSH, LH, estrogens, and progesterone. It was also possible to measure estradiol, estriol, and estrone separately. Thus the temporal relationships between the pituitary hormones and the gonadal hormones became clearer, and the classical diagram showing these relationships and which we now take for granted was published simultaneously in 1970 by two groups: the Columbia University group headed by Raymond Vande Wiele (1922–83) [30] and the California group headed by Robert Jaffe (1933–2020) [31].

Other milestones in the history of fertility

Some other important discoveries supplemented our current understanding of human fertility. In 1971, Roger Guillemin (Baylor College of Medicine) and Andrew Schally (Tulane University) discovered the gonadotrophin-releasing hormone (GnRH) and jointly received the Nobel Prize in 1977. This development helped our further understanding of the fertility process and opened the door for the manufacturing of GnRH agonists and antagonists that proved of great value in assisted reproduction in later years [32,33]. On another front, Peter Medawar (1915–87), while working at the National Institute for Medical Research in the United Kingdom, received the Nobel Prize of 1960 for his discovery of the mechanisms involved in acquired immunological tolerance, which was instrumental in our understanding of the embryo implantation process [34].

The IVF revolution

The birth of Louise Brown on Tuesday July 25, 1978, was an extraordinary milestone in the field of human fertility and was the culmination of numerous years of hard work for all involved. In the early 1960s, Patrick Steptoe (1913–88), a consultant gynecologist in Oldham near Manchester, had paid a visit to Professor Raoul Palmer (1904–85) in Paris who had pioneered the then new technique of laparoscopy. Upon his return to England, Steptoe gave a talk on laparoscopy at the Royal Society of Medicine in London in 1968, and although his fellow gynecologists were not impressed by this new technique, he was approached by Robert Edwards who was a young scientist working in Cambridge University [35]. Edwards had been working on fertilizing mammalian oocytes since 1955 and had started working with human oocytes in 1965 [36]. Following this encounter, one of the most important collaborations in the field of human reproduction started with Edwards regularly traveling from Cambridge to Oldham and vice-versa to fertilize oocytes collected by Steptoe through laparoscopy.

After 4 years of basic research, Steptoe and Edwards started their first human transfers in 1972, but none of their first 40 patients became pregnant [35]. In 1976, they achieved their first IVF pregnancy after a blastocyst transfer, which unfortunately turned out to be an ectopic pregnancy. Two years later and after 102 failed attempts, Leslie Brown became pregnant following the transfer of an 8-cell embryo in a nonstimulated cycle and gave birth to a full-term, normal, fit, and healthy baby "Louise" by caesarean section as reported in the Lancet the following week [37]. On January 4, 1979, they achieved the birth of their second baby, Alastair Macdonald, who was the world's first boy conceived by IVF.

Steptoe and Edwards had originally suggested that IVF should be done in nonstimulated cycles to avoid any negative effect of the stimulation drugs on the endometrium. However, the team of Carl Wood and Alan Trounson in Monash succeeded in achieving the first successful IVF in Australia in June 1980 in a clomiphene-stimulated cycle, and the birth of the fourth baby in the world [38]. And shortly afterward, Howard and Georgeanna Jones working at the Jones institute of Eastern Virginia School of Medicine achieved the birth of the first IVF baby in the United States in an HMG-stimulated cycle on December 28, 1981 [39]. Both Steptoe and Edwards received many honors in recognition of their pioneering work including a CBE from the British Queen and Edwards received the Nobel Prize in 2010, although he could not receive it in person due to his illness [35].

Further developments in assisted reproduction

It is important to note that until 1981, monitoring folliculogenesis was effected mainly by the daily measurement of plasma estradiol, and the time of oocyte retrieval was decided on the basis of serial measurement of LH in blood or urine, as follicles could not be seen by the linear ultrasound machines available then. And although Alfred Kratochwil working in Vienna had reported the visualization of ovarian follicles with static B-mode ultrasound in 1972 [40], follicular scanning became more realistic with the introduction of abdominal sector scanners in the early 1980s, and the first series of monitoring gonadotrophin therapy with ultrasound,

without hormonal assays, was reported by Schmidt and von Holst in 1981 [41] and Sallam et al. in 1982 working at King's College Hospital in London [42]. The first successful attempt at oocyte retrieval by transabdominal transvesical ultrasound was reported by Lens et al. working at the Rigshospitalet in Copenhagen in 1981 [43]. However, by 1985, vaginal ultrasound machines were introduced, and transvaginal ultrasound-directed oocyte retrieval was first reported by Dellenbach et al. in Strasbourg [44], and it rapidly became the universal method of oocyte retrieval.

Simultaneously, other developments were taking place on the laboratory front. Advances in cryopreservation allowed the freezing of embryos for transfer in subsequent cycles. The first ever pregnancy derived from a frozen human embryo was reported by Alan Trounson and Linda Mohr in 1983 but ended in spontaneous abortion at 10 weeks of gestation [45]. The first babies (twins) derived from frozen embryos were born December 26, 1983, in the Netherlands [46]. At the same time, the world's first successful preimplantation genetic diagnosis was performed by Handyside et al. at the Hammersmith Hospital in London. Female embryos were selectively transferred in five couples at risk of X-linked disease, resulting in two twins and one singleton pregnancy [47].

The story of ICSI

Toward the end of the 1980s, micromanipulation of the human oocytes was introduced in an attempt to treat couples with unexplained and male factor infertility. As direct injection of sperm in the cytoplasm of the oocyte had not been tried in animals before, various groups experimented with milder forms of micromanipulation such as subzonal insemination (SUZI). The first successful case of SUZI, a twin pregnancy, was reported in 1990 by Simon Fishel working in Nottingham [48]. Subsequently, in an apparently lucky event for humanity, Gianpierrro Palermo working under the chairmanship of André van Steirteghem at the Free University of Brussels accidently injected a spermatozoon in the cytoplasm of an oocyte, and found that fertilization and cleavage occurred. The embryo was replaced and pregnancy resulted in the birth of a healthy baby [49]. Intracytoplasmic sperm injection (ICSI) was born, starting another revolution in the treatment of male infertility.

Embryo selection, fertility preservation, and the future

In an attempt to improve the clinical results of IVF and ICSI, various methods for embryo selection were introduced including the use of time-lapse systems and the analysis of various components in the spent medium of cultured embryos (genomes, metabolomes, and proteomes). However, so far, none of these methods has proven its superiority [50,51]. Preimplantation genetic testing for aneuploidy (PGT-A) is now being advanced as the method of choice. However, it is still under scrutiny [52].

On another front, fertility preservation is now a real option for men and women who survive cancer treatment or opt for delaying their fertility for social reasons [53]. Advances were made in cryopreserving oocytes, ovarian tissue, and even a whole ovary for future transplantation [54,55]. Indeed, the story of human fertility is a never ending story and each day brings new developments in this exciting field.

Epidemiology of human fertility

No treatise on the history of human fertility is complete without a thorough discussion of its epidemiology. We will now discuss normal fertility trends, the prevalence and causes of infertility, the burden of infertility, and finally the need for fertility services and whether they are adequately met both in developed and developing countries.

Normal fertility patterns and the definition of infertility

In a study of 340 couples practicing natural family planning methods to conceive, Gnoth et al. found that 310 couples achieved a pregnancy within 1 year. The cumulative probabilities of conception based on Kaplan–Meier survival analysis were 38%, 68%, 81%, and 92% at 1, 3, 6, and 12 months of regular sexual intercourse, and although pregnancy could happen afterward, the probability of conception diminished significantly with time [56]. This work confirmed earlier observations by Collis et al., Gleicher et al., and also of Hull et al. [57–59]. Consequently, and based on these findings, WHO defines infertility as the failure to achieve a clinical pregnancy after 12 months of regular, unprotected sexual intercourse [60].

Prevalence of infertility

In a study by Boivin et al., based on surveys involving 172,413 women (52,253 from developed countries and 120,160 from developing countries), the prevalence of infertility ranged from 3.5% to 16.7% with a median figure

of 9% in women aged 20 to 44 in married and consensual unions. This median estimate of 9% was nearly the same in developed as well as in developing countries with a sensible range of 5%–15% in both groups [61]. These data contradict previous reports showing a higher incidence of infertility among developing countries (particularly in Africa) compared to developed countries, where infertility was mainly blamed on genital and sexually transmitted infections [62].

At the same time, the total worldwide population of infertile people is very difficult to estimate due to the heterogeneity of the definitions used, the populations studied, and whether infertility is defined as being located in women, couples, people, or individuals. Nevertheless, various studies put the figures in the many millions [63]. For example, a WHO-supported study of 47 Demographic and Health Surveys had found that more than 186 million women in all of the developing countries surveyed (except China) were infertile, more than one-quarter of ever-married women of reproductive age in these countries [64]. However, the more realistic estimate based on the aforementioned study by Boivin et al. of 172,413 women from 25 populations (from developed and developing countries) estimated that there were 72.4 million infertile women in 2007 [61]. More recently, the 2010 Global Burden of Disease Study supported by WHO and the Gates Foundation analyzed 277 reproductive and health surveys from 190 countries and territories and estimated the number of infertile women at 48.5 million. However, this study defined infertility as the inability to achieve a live birth after a 5-year exposure period [65]. According to WHO, reducing the time frame from 5 to 2 years would increase the total number of infertile couples to 121 million [63].

Seeking infertility treatment

Despite these large numbers of infertile couples, only about half of them seek medical services, and even a smaller percentage succeed in receiving them, both in developed and developing countries. In their same study, Boivin et al. found that the proportion of infertile couples seeking medical care was, on average, 56.1% (range 42%–76.3%) in more developed countries and 51.2% (range 27%–74.1%) in less developed countries. They also found that the proportion of people actually receiving care was substantially less at 22.4% in both groups [61]. Based on these estimates, they calculated that about 40.5 million couples were seeking infertility medical care then (2007) [62].

Factors affecting the success of infertility treatment

Whether pregnancy occurs with or without treatment depends on various factors, which can be summarized as follows [66]:

1. Knowledge of the maximum fertile period. Many couples assume wrongly that the day of ovulation is the best day for conception. In their analysis of 225,596 menstrual cycles from 98,903 women, Faust et al. confirmed previous studies and found that the probability of conception was highest when intercourse took place 1 day before ovulation (42%) followed by 2 days before ovulation (33%), 3 days before ovulation (27%) and 20% when it occurred on the day of ovulation [67] (Fig. 1.3).
2. Time of unwanted nonconception. The chances of a couple in achieving a pregnancy diminish the longer the time they have been trying to conceive. As mentioned before, Gnoth et al. found that 81% of the pregnancies occur in the first six cycles with regular intercourse in the fertile period. One out of two couples of the remaining 19% will conceive spontaneously in the next six cycles. After 12 unsuccessful cycles, 8% of the couples will remain infertile, and after 48 months, 5% of the couples are definitively infertile with a nearly zero chance of achieving a spontaneous pregnancy [57].
3. Age of the woman. Female fertility starts to decline around 25–30 years of age. In their seminal paper, Eijkemans et al. showed that the age-related loss of

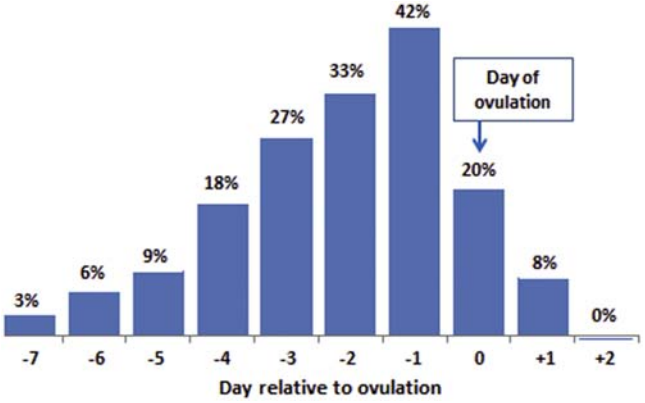

FIGURE 1.3 Chance of conception per day of cycle. *Adapted from Faust L, Bradley D, Landau E, Noddin K, Farland LV, Baron A, Wolfberg A. Findings from a mobile application-based cohort are consistent with established knowledge of the menstrual cycle, fertile window, and conception. Fertil Steril. 2019;112(3):450–457.e3.*

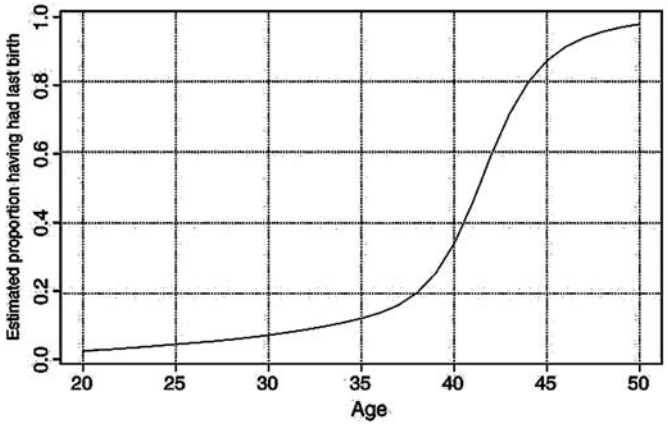

FIGURE 1.4 Cumulative age at last birth (ALB) curves showing declining fertility with age. *From Eijkemans et al. with the kind permission of the Editor of Human Reproduction Eijkemans MJC, van Poppel F, Habbema DF, Smith KR, Leridon H, te Velde ER. Too old to have children? Lessons from natural fertility populations. Hum Reprod. 2014;29(6): 1304–1312. https://doi.org/10.1093/humrep/deu056*

fertility slowly increases from 4.5% at age 25 years to 7% at age 30 years, 12% at age 35 years, and 20% at age 38 years. It increases rapidly afterward to about 50% at age 41, almost 90% at age 45 years, and approaching 100% at age 50 years [68]. This decline in fertility is related both to the continuous depletion of oocytes stored in the ovaries as well as a decline in oocyte quality (Fig. 1.4). Unfortunately, studies show that most women are not aware of the fact that delaying childbearing increases the risk of infertility, and moreover, many women believe that modern treatment modalities such as IVF can treat the fertility decline associated with advancing age [66].

4. Cause of infertility. The success of infertility treatment depends also on the cause of infertility. In their classical study of a population of 1,850,000 in three French regions, Thonneau et al. found that women alone were responsible for infertility in 33% of the cases, while the man alone was responsible in 20% of the cases. The cause resided in both partners in 39% of cases, while in 8%, infertility was unexplained [69]. Most causes of infertility are nowadays amenable to treatment, and even intractable cases such as absence of the uterus, ovarian failure, or absolute testicular failure can be helped by gamete and embryo donation, uterine transplantation, and surrogacy, whenever the law of the land permits.

Burden of infertility

Infertility exerts a burden both on the infertile couples as well as on the national health systems. On a personal level, infertility is known to cause significant psychological and social effects, particularly in low and middle income communities, such as fear, anxiety, depression, self-blame, marital stress, emotional abuse, intimate partner violence, and divorce. Other negative consequences include social isolation, economic deprivation, loss of social status, and in some regions of Africa and Asia, violence-induced suicide and even loss of dignity in death [70]. Unfortunately, in many of these societies, the infertility burden falls disproportionately on women, who are often marginalized, socially excluded, and stigmatized [71].

At the same time, infertility exerts an economic burden on the national systems, and unfortunately, in many parts of the world, authorities still claim that infertility is not a health problem, is not a serious health problem, or that contraception is a more pressing need. As "reproductive rights" are now an integral part of human rights, all governments that are signatories of the Universal Declaration of Human Rights cannot advance these arguments anymore and are obliged to include infertility services in their family health programs [72].

Access to infertility services

Infertility services offered by specialists and institutions can be stratified at three different levels: (a) a basic level offering laboratory investigations, ovulation induction with or without artificial insemination, (b) an intermediate level offering IVF with diagnostic endoscopic services with or without cryopreservation services, or (c) an advanced level capable of offering ICSI with or without preimplantation genetic testing (PGT) as well as operative endoscopic surgeries and other advanced services [71].

At the top of these services, assisted reproduction is considered a state-of-the-art technique capable of solving most infertility problems. However, in many parts of the world, this service is not accessible to those who need it most. In 2001, the European Society for Human Reproduction and Embryology (ESHRE) had suggested that 1500 couples per million population required ART treatment annually [73]. However, with the exceptions of Australia, Israel, and the Scandinavian countries, few developed nations have met this ESHRE benchmark, and even in North America and the United Kingdom, only 25% and 40% of the optimal number of ART cycles were being carried out, respectively, as of 2009 [74]. Unfortunately, in less developed countries, these services are only available to very few people (e.g., only 1.5% of the needs are met in sub-Saharan Africa) [75]. It is hoped that with time, infertility services will be available to more couples in developed as well as developing countries [70].

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