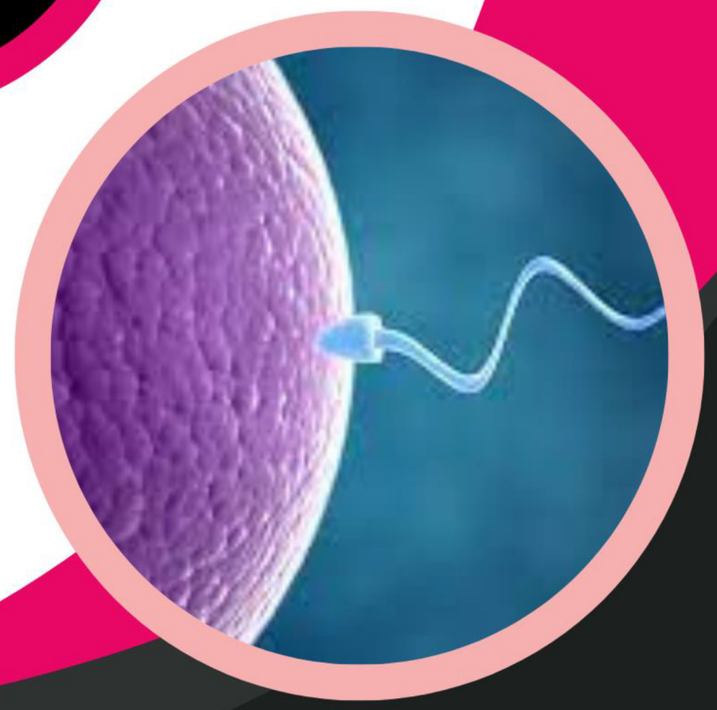
MASLICHAH MAFRUCHATI

INFERTILITY

MANAGEMENT AS A BASIS FOR EMBRYO RESEARCH



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Preface

Alhamdulillah, for all the outpouring of guidance and will, this book can be completed properly. This book is entitled "Infertility Management as a basis for embryo research". This book was written by someone who is an expert in his field and already has scientific publications both nationally and internationally, speakers at national and international seminars related to book material. This book can be used to add to the body of knowledge for all levels of education and the general public. Hopefully the book written by the author will be useful both in this world and in the hereafter, one of the uninterrupted charity is useful knowledge.

Surabaya, January 2023

Foreword

Alhamdulillah, all praise and gratitude to Allah SWT for this book has been completed. This book was compiled with the aim of helping students learn Infertility Management as a basis for embryo research**.** .The preparation of this book is certainly not the work of the author alone, many parties have helped and provided support for the success of writing this book. For this reason, the author expresses his deepest gratitude to all those who have provided moral and material support so that this book has been successfully compiled. The author realizes that in the preparation of this book there are shortcomings, but the author fully believes that no matter how small this book still provides benefits. Finally, in order to improve this book, the writer welcomes criticism and suggestions from readers.

Surabaya 22 January 2023

Writer

List Of Content

Chapter 1

History and epidemiology of human fertility

1. Our understanding of human evolution will be improved by being aware of historical variations in fertility. One of the most challenging issues the human race has faced since the dawn of civilization is the issue of reproduction. Understanding the link between sexual activity and pregnancy must have been one of the earliest ideas that the human brain produced, given that for a significant portion of their early history, humans did not fully understand how a woman became pregnant.
2. When it was first discovered, many people thought that fertility was a superhuman trait. Different fertility deities were revered by different cultures as resources for the study of fertility. The majority of these deities were female goddesses, as traditionally conception and childbirth were attributed to women. Isis and Hathor were the fertility and maternal protection deities respectively in ancient Egypt. 1.1). The goddess of fertility Aphrodite had a name in ancient Greece. Venus was a goddess in Roman mythology who represented sex, love, conception, and beauty. Birthing was aided by the goddess of love, Eros. The goddess is referred to as Ashanti or Mama Oclio in both Inca and African cultures. This person is known as Jiutian Xuanwu and Banka-Mundi in their respective tongues. In Babylonian and Sumerian, she was known as Brigit, respectively. The

lotus, the orchid, and the rose were among the flowers that attracted fertility. Each goddess had a special set of skills that she had developed through a particular ritual [1]. Lack of necessary funding and time-tested scientific methods has frequently slowed the development of more widely accepted infertility treatments. A good historical example is Egypt. The idea of a seed has served as a metaphor for conception for ages. It's important to mention Ghalioungui. Despite the fact that this assertion appears to be supported by science, please be aware that it may not be. Despite the possibility of finding up to 85% of pregnancies, only 70–80% of confirmed pregnancies were discovered [2].

3. Ancient Greek conception and infertility theories do not adequately explain how these processes function now. The writings "On Infertile Women" (Peri Aphoron), "Diseases of Women" (Gynaikeia), and "Diseases of Women," 1 and 2, all address the issue of infertility. Many tried-and-true treatments and recipes can be found in these books. Even the greatest Greek philosopher of all time, Aristotle (384-322 BCE), thought that only male semen was incorporated into the fetus and that women had no place in the generative material. Contrary to Aristotle's theory, Soranus of Ephesus thought that both males and females have the ability to produce the "seeds" needed for conception. He was the first to describe the human uterus thanks to his creative work at the former

Alexandria Medical School. Cervical os blocking is his recommendation for an efficient birth control method [4]. Males with more muscular features and period-free females, he claimed, were unusual.

4. After completing his medical training in Rome, Galen relocated there and served as Emperor Marcus Aurelius' personal physician from 129 to 200 AD. A well-known Roman physician named Galen was seated at his desk. Autophlebotomy allows the removal of potentially harmful circulating humors and other waste products through the use of menstruation, a typical method of elimination [5]. It was understood that the other phrase, "female testes," referred to the testicles of females. The only significant finds made in Andalucia during the Middle Ages, including the Arab/Islamic Golden Age, were the allegedly antiquated obstetric forceps developed by Abulcassis of Cordoba [6].
5. Our knowledge of the processes underlying human reproduction has only recently, following the Renaissance and the ensuing age of enlightenment, improved. He created his first anatomical diagrams in Milan, Italy, in the year 1506. Leo da Vinci, a person, lived from 1452 to 1519. Later, in Pavia, he collaborated with physician-anatomist Marcantonio della Torre to create a precise replica of a growing human [7]. Gabriele Falloppio, an anatomy professor at the University of Padua, is credited with providing the Fallopian tube with the first thorough description and naming. Dutch

entrepreneur and scientist Antonie van Leeuwenhoek (1632–1723) invented the microscope. Once the fundamentals of fertility were understood after the turn of the 20th century, significant progress was made in a remarkably short period of time. They included efficient in-vitro fertilization techniques, understanding of the hypothalamic-pituitary-ovarian axis, familiarity with gonadotrophins and gonadal steroids, and awareness of the hormonal shifts involved in the regulation of the menstrual cycle.

6. After a partial pituitary ablation, adult dogs' genital organs shrank, according to Samuel Crowe's now-famous discovery from 1910 at Johns Hopkins University [13]. The hypophysis and pituitary stalk were equally impacted by illnesses, tumors, and injuries, according to Austrian physician Bernhard Aschner (1883-1966), who made this observation in Vienna in 1912. Young male and female mice and rats that received daily injections of fresh anterior pituitary gland tissue matured sexually too early, according to studies by Philip Smith (1884-1970), a researcher connected to Berkeley and later Columbia.
7. In 1926, Bernhard Zondek (1891-1966), a doctor at the Charite' Hospital in Berlin, implanted anterior pituitary glands from adult cows, bulls, and people in young animals to hasten the onset of sexual puberty [16]. The gonads are thought to be stimulated by the pituitary hormones Prolan A

and Prolan B, according to Zondek's 1929 theory. In the blood and urine of postmenopausal women, he discovered gonadotropins in 1930. In contrast to Prolan B, which caused follicle development and the release of estradiol, he hypothesized that Prolan A caused ovulation, the growth of the corpus luteum, and the release of progesterone [16]. According to him, rhythmic ovarian activity and cyclical endometrial preparation are caused by the anterior pituitary's coordination of Prolan A and Prolan B secretion [17]. He made a similar claim in 1930. Fevold of Wisconsin claims [18] that the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production of the pituitary stopped in 1931.

8. In 1927, a gonad-stimulating substance was discovered in the blood and urine of pregnant women by Berlin Charite Hospital physician Selmar Ascheim (1878-1965). Ascheim (1878-1955) accomplished this while working once more with Bernhard Zondek. Additionally, they demonstrated that the Ascheim-Zondek pregnancy test is reliable by demonstrating that injecting this substance into young female mice resulted in luteinization and follicular maturation [19]. Georgina Seegar-Jones (1912-2005), a scientist at Johns Hopkins University, first used the term "human chorionic gonadotropin" (HCG) to describe the substance after learning that the placenta, not the anterior pituitary gland, controls its

production. The anterior pituitary is thought to be the source of this substance, according to Ascheim and Zondek [20].

9. Since it was discovered how crucial these hormones are for reproduction, gonadotrophin therapy has been used on infertile women. The Hamblen town is a part of it. , 1945. They were first utilized in pregnant mare serum gonadotrophins, or PMSG. Patients received PMSG during the follicular phase of their treatment, and patients with inactive ovaries received HCG 12 to 18 days later [21]. Lunenfeld had that thought. Urine from menopausal women was cleaned up and the HMG was separated. Nothing changed in 1945. What was being fundamentally contested became apparent. in 1962 [22]. Uppsala, Sweden-based researcher Carl Gemzell was the first to isolate human pituitary gland gonadotropins and use them to treat anovulatory disorders. After Creutzfeldt-Jakob disease (CJD), which was first identified in Australia, France, and the UK [16], was reported in four cases, the production of these human pituitary gonadotrophins was subsequently stopped. There were 75 IU of LH and FSH in every HMG ampoule.

10. Researchers were able to track the different ways that each patient responded to stimulation using HMG. The prevalence of ovarian hyper-stimulation syndrome was higher in individuals with polycystic ovary syndrome and high LH/FSH ratios.

When making urofollitropin, also known as immunochromatographic HMG purification, polyclonal antibodies are used to remove LH. After 1982, it underwent a change and turned into a consumable. 25 IU of LH and 75 IU of FSH were combined in one ampoule. The HMG urofolllitropin-HP ampoules were extremely pure, containing less than 1 IU of LH and 75 IU of FSH. The FSH gene was inserted into the nuclear DNA of Chinese hamster ovary cells to produce recombinant FSH in response to a rise in demand and the development of IVF facilities. A substance called estrone that resembles gonadotrophin was recently discovered. Robert Battey, MD, a native of Atlanta, Georgia, invented the oophorectomy between 1928 and 1955. This procedure was used to treat bleeding and dysmenorrhea brought on by the fibroids. Amenorrhea, hot flashes, and vaginal atrophy are some of the allegedly frequent adverse effects of ovary removal. The beginning of the menstrual cycle is thought to be signaled by a chemical released by the ovaries.

11. The Vienna researchers Ludwig Fraenkel (1870-1951), Josef Halban (1870-1937), and Emil Knauer (1867-1935) were the first to observe uterine atrophy in rabbits with removed ovaries. In doing so, he was able to successfully treat this condition. He studied them to show that the ovaries secrete internally. He also observed that the uterus was contracting, which would help with the

ovary removal. Another option is to use ovarian tissue from an alternative source to make up for the obvious uterine atrophy. In 1897, Hubert Fosbery used ovarian extracts to treat a woman who experienced frequent hot flashes [23].

12. Numerous studies on the "estrogen" that the ovary secreted were conducted at the start of the 20th century. Estrone, the estrogen precursor that was initially discovered in 1929, was isolated and purified by biochemists Adolf Butenandt (1903–1955) and Edward Adelbert Doisy (1893–1986), who also co-shared the 1943 Nobel Prize for chemistry. German Butenandt was awarded the Nobel Prize in Literature in that year. Estriol and estradiol were discovered later, more specifically in 1930 and 1933 [23].

13. Progesterone was discovered in more places, though. The first corpus luteum in a pregnant rabbit was discovered in 1929 by Georges Corner (1889–1981) and William Allen (1904–1993), two American scientists. When the extract was given to a second castrated rabbit, the researchers discovered that the pregnancy had continued. "Progestin" is how people refer to it [24]. Adolf Butenandt gave progesterone its name when he discovered that it belonged to the ketone family in 1934 [25].

14. The aromatase system was first identified by scientists from Harvard University and the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts. Androgens become estrogens as a result of the process. Radiolabeled tracer steroids were used in the research of two enzymologists, Ralph Dorfman (1911–1985) and Mika Hayano (1920–1964) [26]. Lewis Engel and Kenneth Ryan of Harvard University did, however, perform the first androgen to estrogen conversion [27]. Armstrong and Dorrington proposed the two-cell, two-gonadotrophin theory to explain the relationship between ovarian hormones and gonadotrophin in the ovary. They were employed at the time in Ontario, Canada.

15. In New York, immunoassay research was carried out by Rosalyn Yalow (1921–2011) and Solomon Berson (1918–1972). Yalow received the 1977 Nobel Prize in Physiology or Medicine. Thus, the concentrations of various compounds in biological fluids (such as blood or urine) can be calculated in nmol and even pmol [29]. No complex interactions existed between progesterone, estrogens, LH, and FSH. The only substances that permit independent measurements are estriol and esttron. the procedures involved in producing pituitary hormones and how the gonadal system develops. The two teams—one from California under the direction of Robert Jaffe

(1933-2020) and the other from Columbia University under the direction of Raymond Vande Wiele (1922-1983)—joined forces to publish the iconic diagram that illustrated these connections and that we now take for granted.

16. Our knowledge of human fertility has improved as a result of more significant recent discoveries. Researchers from Baylor College of Medicine and Tulane University working under Andrew Schally made the initial discovery of gonadotrophin-releasing hormone (GnRH) in 1971.

17. The views on reproduction in our society had hardly changed when Louise Brown was born on Tuesday, July 25, 1978. Each team member contributed significantly to the project's completion. Beginning in the 1960s, Professor Raoul Palmer began receiving visits from Patrick Steptoe (1913–1988), a consultant gynecologist from a nearby city. Steptoe is recognized as the inventor of the ground-breaking laparoscopy procedure. Steptoe was only a small child when his parents moved to Oldham. Steptoe later discussed laparoscopy at the London Royal Society of Medicine while he was in England. The spermatozoa were mocked as "animalicules" by Steptoe's speaking companion [8].

18. The work of the Dutch anatomist and physician Regnier de Graaf in Delft between 1641 and 1703 had a significant influence on reproductive biology. The efferent ducts, corpora lutea, and testicular tubules were also mentioned.

19. 1. The term "hormone" was first used in 1905 by researchers Ernest Starling and William Bayliss at University College London. ". Arnold Berthold (1803–1861) investigated the results of castrating cock chickens at the University of Göttingen to ascertain how this affected the birds' aggressiveness and behavior.

20. 2. Gynecologists allegedly showed no interest in the state-of-the-art method, according to young researcher Robert Edwards [35] from Cambridge University. Edwards concentrated on the fertilization of mammalian oocytes before 1965 [36], the year he began studying human oocytes. Steptoe would frequently make the round trip from Oldham to Cambridge, where Edwards would meet him, to fertilize oocytes that had been surgically harvested. This collaboration is one of the most significant in the field of human reproduction.

21. 3. None of the 40 initial patients Steptoe and Edwards saw were able to conceive despite their groundbreaking study's four years [35]. For the first human transfers,

though, it was made possible. The success of in vitro fertilization was determined by the transfer of a blastocyst in 1976. That I have to inform you of the ectopic pregnancy is unfortunate. Leslie Brown became pregnant after transferring an 8-cell embryo into an unstimulated cycle after two years and 102 failed attempts. Leslie Brown had a caesarean section the following week, giving birth to "Louise," a full-term, typical, fit, and healthy baby, according to The Lancet [37]. Alastair Macdonald was the first boy ever to be born through in vitro fertilization on January 4, 1979. He most likely was the expert on the specifics of how the Fallopian tube impacts reproduction. He also mentioned ovarian follicles, which he later mistook for oocytes and incorrectly referred to as "Graafian follicles" [9]. Italian priest and physiologist Lazzaro Spallanzani of Pavia was the first to realize that physical contact between the sperm and the ovum is necessary for fertilization to take place. In 1770, he was able to control canine ovaries thanks to this knowledge [10]. The first artificial insemination on a human was successfully performed ten years later by Scottish physician John Hunter, who practiced in London between 1728 and 1793 [10]. Karl Ernst von Baer (1792-1866) delivered the first lecture on the discovery of the human oocyte at the Konigsberg University in Kaliningrad. He talked about his 1827 study, which revealed the location of the oocyte within the follicle [9]. The Berlin scientist Oscar Hertwig

(1849–1922) discovered that contact between a sperm and an egg cell is necessary for fertilization through study of sea urchins [11]. Their discovery earned them a portion of the 1977 Nobel Prize in Physiology or Medicine. With the aid of this discovery, we were able to comprehend conception better and produce GnRH agonists and antagonists, both of which have since been proven to be very beneficial in assisted reproduction [32,33]. In contrast, Peter Medawar (1915-1987), a researcher at the National Institute for Medical Research in the UK, received the Nobel Prize in Medicine in 1960 for his investigation into the mechanisms underlying acquired immunological tolerance, which was crucial to our comprehension of the embryonic implantation process [34].

4. 1. In order to avoid any potential endometrial side effects of the stimulation medications, Steptoe and Edwards' original advice that IVF be performed during unstimulated cycles is still valid. The first IVF procedure was successfully carried out in June 1980 by a Monash University team under the direction of Carl Wood and Alan Trounson. The fourth child was born in that month as a result of a cycle caused by clomiphene [38]. The first in vitro fetus was born on December 28 as a result of Howard and Georganna Jones' research at the Jones Institute of the Eastern Virginia School of Medicine [39]. Edwards' illness prevented him from personally accepting the Nobel Prize in 2010, but their

groundbreaking work was still honored with numerous awards, including a CBE from the British Queen [35].

22. 5. 2. The primary method for tracking daily follicleogenesis up until 1981 was plasma estradiol measurements. Linear ultrasound technology has never been able to locate follicles. By routinely monitoring the level of LH in the blood or urine, the best time for oocyte retrieval can be determined. I'm giving each of you my undivided attention. It has been around since 1981, according to Schmidt and von Holst [41]. We talked about hormonal assay-free ultrasound monitoring in relation to initial gonadotrophin therapy. The following year is also included in that time frame. The use of static B-mode ultrasound for the assessment of ovarian follicles was the subject of a ground-breaking study conducted by Dr. Alfred Kratochwil of Vienna, which was published in 1972 [40]. At London's King's College Hospital, he started his professional career in 1982 [42]. also the colleagues of Lens. Described in this article is the first successful transabdominal transvenous ultrasound oocyte retrieval. a citizen of Copenhagen who worked at Rigshospitalet in the 1980s [43].

6. 6. Dellenbach was someone they knew well.

7. 7. The lab underwent more adjustments. Embryos can now be frozen for later transfer thanks to developments in cryopreservation. According to a 1983

study by Alan Trounson and Linda Mohr (45), the first pregnancy made possible by using a frozen human embryo ended spontaneously at 10 weeks. In the Netherlands, twins made from frozen embryos were made public on December 26 [46]. There is a brief mention of Handyside and his friends. There is no evidence to support preimplantation genetics. a hospital in Hammersmith, London. Five couples, all of whom only implanted female embryos, produced two twins and one singleton [47]. The initial study on transvaginal ultrasound-assisted oocyte retrieval is available to read right now.

8. 1. To help couples who struggle with male factor and unexplained infertility, the first technique for altering human oocytes was developed at the end of the 1980s. Many research teams have discovered that subzonal insemination (SUZI), a less invasive micromanipulation technique, is the most efficient approach. The first successful SUZI case was reported by Dr. Simon Fishel in 1990 [48], and twin pregnancies were involved. Gianpierro Palermo, a student at the Free University of Brussels, accidentally implanted a spermatozoon into an oocyte to show the mechanism of fertilization and cleavage.

9. 5. 2. Because there are so many definitions and populations that have been studied, it is difficult to estimate the total population of infertile people around the world. Women, couples, singles, and a variety of other people can all experience the effects of infertility.

10. 6. 3. Fewer than half of infertile couples in developed and developing countries receive medical care, and even fewer of these situations result in pregnancy. Couples in less developed countries experience infertility at a rate that is 561 percent higher than that of couples in developed countries. 42 percent is the typical. 512 percent more than in less developed nations. 763 percent of people participated in this activity. The proportion of people in both groups who received care decreased from 42 to just 22 percent [61]. According to the study [62], 40.5 million couples would undergo infertility treatment in 2007. Analysis of the embryo culture medium's genome, proteome, and metabolome in real time. The possibility exists that one of these approaches is more successful than the other, despite the fact that this hasn't been established [50, 51]. Preimplantation genetic testing for aneuploidies, also known as PGT-A, has come to be recognized as the gold standard for detecting aneuploidies. The investigation is still ongoing, though [52].

11. 7. 4. Currently, men and women who want to preserve their fertility may put off having children due to societal pressures or cancer treatment [53]. An ovary and all of its parts can now be frozen before transplantation (see references 54, 55).

12. 8. 5. Before any research on the evolution of human reproduction can start, the epidemiology literature must be thoroughly reviewed. The sections that follow will discuss the prevalence, causes, and consequences of infertility, as

well as the demand for fertility services and whether or not this demand is sufficiently met in both developed and developing countries.

13. 7. proximate to Donth. 340 of the couples in the study used natural family planning, and all of them had children. In a single year, 310 couples gave birth to children, according to the study. The Kaplane Meier analysis of survival at 1, 3, and 6 months after your last experience with regular sex revealed that there were 38 cumulative odds of conception. Overall, humanity ought to gain from this development. A modified embryo and an artificially induced pregnancy resulted in the birth of a healthy child [49]. Intracytoplasmic sperm injection, also known as ICSI, is the treatment method for male infertility. In 1985, the first ultrasound device created especially for gynecology was unveiled. In Strasbourg [44], oocyte retrieval first appeared, and it spread rapidly from there. The 9 percent of married, voluntarily enrolled women between the ages of 20 and 44 who underwent IVF and ICSI had better clinical results when various embryo selection methods were used. With a median estimate of 9% in each case, the sensitive range for both the developed and developing worlds was between 5 and 15 percent [61]. An earlier study [62] that concentrated on genital and STD infections as its primary causes found that infertility was more common there than in developed nations (especially in Africa). The results of this new study contrast with those of those earlier studies and show .s, 68s, 81s, and 92s. Conception was still a possibility,

though less likely [56]. Collis worked alongside them on a project. data demonstrated was accurate. findings from earlier research. Co-defendants work together. This group includes Hull and the rest of the crew. [57e59]. The WHO revised its definition of infertility following the publication of these findings to include the clinical inability to conceive following a period of 12 months of regular, unprotected sexual activity [60]. An illustration of a selectable variable is a woman's potential for becoming pregnant while undergoing treatment [66]. According to numerous studies [63], there could be millions of participants. According to a review of 47 Demographic and Health Surveys funded by the WHO, there are 186 million infertile women in the world, or more than 25% of all women of childbearing age who have previously been married [64]. This has an effect on women in countries besides China. Boivin and his friends. However, 172,413 female respondents (representing populations from both developed and developing countries) reported that there were 72,014 million infertile women in the world in 2007. According to 277 reproductive and health surveys funded by the Gates Foundation and the WHO, there are 48.15 million infertile women in the world. These studies were carried out in 190 nations and territories. The study's definition of infertility stipulates that it must manifest itself after a 5-year exposure period but prior to the conception of a live child [65]. If the waiting

period was shortened from five to two years, there would likely be 121 million more infertile couples, according to the WHO [63].

8. determining the pregnancy that is most likely. The majority of couples think that the ovulation day is the best day for conception. Understanding Faust is challenging. 98,903 women's 225,596 menstrual cycles, totaling 225,596, were examined. As ovulation approached, the likelihood of becoming pregnant through sex increased by 33% and decreased by 27% (Figure). 1.3).

9. As a medical condition, infertility has disadvantages. The likelihood that a couple will become pregnant declines as more infertility treatments are used on them. Along with him were Gnoth's allies. It was made by Gnoth and his companions. ". 80 percent of pregnancies happen within the first six fertile sexual cycles. Over the following six cycles, the remaining 19%, or one in two couples, will conceive naturally. Unexpectedly, 5% of couples still struggle with infertility after 48 months, and an even startling 8% do so after 12 unsuccessful cycles [57]. For these couples, natural conception is practically impossible.

10. age of the female.

main reasons for infertility. An infertility treatment's outcome will differ depending on what caused the issue in the first place. Thonneau runs a company. The 1 850 000 people living in the three French regions were studied. Twenty percent of infertility cases involved men, while thirty percent

involved women. Infertility cases with two underlying causes accounted for 9% of all cases, or 39% [69]. Additional treatments include surrogacy, uterine transplantation, and gamete and embryo donation when other options have failed, such as when the uterus is absent, the ovary is completely failing, or the testicles have been completely destroyed.

Healthcare systems in the nation as well as infertile couples are impacted by the infertility problem. negative effects of infertility, which are widespread and very bad. Female fertility begins to decrease between the ages of 25 and 30. et al. Eijkemans. They employed cutting-edge research techniques for their study. According to studies, the rate of age-related fertility loss increases steadily as people get older, going from 4% at age 25 to 7% at age 30, 13% at age 35, and 20% at age 38. The percentage has almost tripled to almost 100% by the time people are between the ages of 41 and 50 [68]. The graph shows the relationship between reserve oocyte quantity and quality and fertility. 1.4). According to research [66], a lot of women think IVF and other cutting-edge procedures can stop the natural decline in fertility that happens as women get older. Most women are unaware that delaying parenthood raises the chance of infertility. Given how much is still unknown about this fascinating subject, the history of human reproduction appears to have no real beginning.

References

Cohen J, Gilligan A, Esposito W, Schimmel T, Dale B. Ambient air and its potential effects on conception in vitro. Hum Reprod 1997; 12(8):1742e9. https://doi.org/10.1093/humrep/12.8.1742.

Boone WR, Johnson JE, Locke AJ, Crane IVMM, Price TM. Control of air quality in an assisted reproductive technology laboratory. Fertil Steril 1999;71(1):150e4. https://doi.org/10.1016/S0015- 0282(98)00395-1.

Luo Q, Yang J, Zeng QL, Zhu XM, Qian YL, Huang HF. 50-hertz electromagnetic fields induce gammaH2AX foci formation in mouse preimplantation embryos in vitro. Biol Reprod 2006;75(5): 673e80. https://doi.org/10.1095/biolreprod.106.052241.

Genuis, Lipp CT. Brown RH Monitoring vocs in air e the develop- ment of ISO standards and a critical appraisal of the methods. Sci Total Environ 2002;414(6).

Brown RH. Monitoring vocs in airethe development of ISO stan- dards and a critical appraisal of the methods. J Environ Monit 2002;4(6).

Petry T, Vitale D, Joachim F, et al. Regul Toxicol Pharmacol 2014.

Amodio M, Dambruoso PR, de Gennaro G, et al. Indoor air quality (IAQ) assessment in a multistorey shopping mall by high-spatial- resolution monitoring of volatile organic compounds (VOC). En- viron Sci Pollut Control Ser 2014;21(23):13186e95. https:// doi.org/10.1007/s11356-014-2544-1.

Moya J, Howard-Reed C, Corsi RL. Volatilization of chemicals from tap water to indoor air from contaminated water used for showering. Environ Sci Technol 1999;33(14):2321e7. https:// doi.org/10.1021/es980876u.

Malkin J. Medical and dental space planning: a comprehensive guide. 2014.

Loumaye E, de Cooman S, Thomas K. Optimalisation des condi- tions de fe´condation et de culture d'embryons in vitro. Rev Med Brux 1985;6(9):611e4.

Cutting RC, Pritchard J, Clarke HS, Martin KL. Establishing qual- ity control in the new IVF laboratory. Hum Fertil 2004;7(2):119e25. https://doi.org/10.1080/14647270410001709188.

Wieslander G, Norba¨ck D. Ocular symptoms, tear film stability, nasal patency, and biomarkers in nasal lavage in indoor painters in relation to emissions from water-based paint. Int Arch Occup Environ Health 2010;83(7):733e41. https://doi.org/10.1007/ s00420-010-0552-0.

Bayil S, Cicek H, Cimenci IG, Hazar M. How volatile organic com- pounds affect free radical and antioxidant enzyme activity in textile workers. Arh Hig Rad Toksikol 2008;59(4):283e7. https://doi.org/10.2478/10004-1254-59-2008-1918.

Sugai K, Maekawa H. Reutilisation of wool as a thermal insulator for building material. In: Proc 10th IWTRC, Aachen D. 9; 2000. p. 767e8.

James AE. Painting collections in hospitals: humanity in medicine. J Am Coll Radiol 2012;9(11):767e8. https://doi.org/10.1016/ j.jacr.2012.02.017.

Dela Cruz M, Mu¨ ller R, Svensmark B, Pedersen JS, Christensen JH. Assessment of volatile organic compound removal by indoor plants-a novel experimental setup. Environ Sci Pollut Control Ser 2014;21(13):7838e46. https://doi.org/ 10.1007/s11356-014-2695-0.

Cooke S, Tyler JPP, Driscoll G. Objective assessments of tempera- ture maintenance using in vitro culture techniques. J Assist Reprod Genet 2002;19(8):368e75. https://doi.org/10.1023/A: 1016394304339.

Ottosen L, Hindkjaer J, Ingerslev, Pomeroy t o, Reed ML, Hill jr RB, Bensch KG, King DW. Photosensitization of nucleic acids and proteins. The photodynamic action of acridine orange on living cells in culture. J Reprod Stem Cell Biotechnol 1960; 24(2):106e17.

Ottosen LDM, Hindkjær J, Ingerslev J. Light exposure of the ovum and preimplantation embryo during ART procedures. J Assist Reprod Genet 2007;24(2e3):99e103. https://doi.org/10.1007/ s10815-006-9081-x.

Hill RB, Bensch KG, King DW. Photosensitization of nucleic acids and proteins. The photodynamic action of acridine orange on living cells in culture. Exp Cell Res 1960;21(1):106e17. https:// doi.org/10.1016/0014-4827(60)90351-7.

Wang RJ. Lethal effect of “daylight” fluorescent light on human cells in tissue-culture medium. Photochem Photobiol 1975;21(5): 373e5. https://doi.org/10.1111/j.1751-1097.1975.tb06688.x.

Zigler JS, Lepe-Zuniga JL, Vistica B, Gery I. Analysis of the cyto- toxic effects of light-exposed hepes-containing culture medium. In Vitro Cell Dev Biol 1985;21(5):282e7. https://doi.org/ 10.1007/BF02620943.

Barlow P, Puissant F, Van Der Zwalmen P, Vandromme J, Trigaux P, Leroy F. In vitro fertilization, development, and implantation after exposure of mature mouse oocytes to visible light. Mol Reprod Dev 1992;33(3):297e302. https://doi.org/10.1002/mrd.1080330310.

Oh SJ, Gong SP, Lee ST, Lee EJ, Lim JM. Light intensity and wave-length during embryo manipulation are important factors for main- taining viability of preimplantation embryos in vitro. Fertil Steril 2007;88(4):1150e7. https://doi.org/10.1016/j.fertnstert.2007.01.036.

Yamauchi Y, Yanagimachi R, Horiuchi T. Full-term development of golden hamster oocytes following intracytoplasmic sperm head injection. Biol Reprod 2002;67(2):534e9. https://doi.org/ 10.1095/biolreprod67.2.534.

Fischer b, Schumacher A, Hegele-Hartung, et al. The origin, ef- fects and control of air pollution in laboratories used for human embryo culture. Human Reprod. J Assist Reprod Genet 1988;50: 146e55.

J Reprod Stem Cell Biol 2013;3(2):46e54.

Quality and risk management in the IVF laboratory. 2005. https://doi.org/10.1017/CBO9781139680936. undefined.

Hall J, Gilligan A, Schimmel T, Cecchi M, Cohen J. The origin, ef- fects and control of air pollution in laboratories used for human embryo culture. Hum Reprod 1998;13(4):146e55. https://doi.org/10.1093/humrep/13.suppl_4.146.

Nielsen K, Cleal B. Predicting flow at work: investigating the ac- tivities and job characteristics that predict flow States at work. J Occup Health Psychol 2010;15(2):180e90. https://doi.org/ 10.1037/a0018893.

Chapter 2

Setting up an ART unit: planning, design, and organization

A medically assisted reproduction (PMA) center's environment must be carefully chosen for it to be successful [1, 2]. A rough estimate of the number of infertile couples who will need assisted reproductive technology (ART) is required before deciding whether or not to open a center. The areas with the best potential for development, accessibility, and transportation should be given priority.

a Lin family business. Unexpectedly, the incubator used in this study's incubator may increase the risk of DNA damage in in vitro generated embryos. It's important to emphasize how magnetic field strength and square of distance are inversely related. Electrical equipment, especially that used in operating rooms, must adhere to the law in order to prevent electromagnetic fields from interfering with other electronic devices. However, it might be best to keep this equipment apart from incubators. This point of view emphasizes how crucial it is to take lab workers' welfare into account, especially in light of the growing body of evidence suggesting that some people may be electromagnetic radiation sensitive [4].

Wetlands, unstable terrain, porous ground, and still ground are not permitted as site locations. Avoid venturing into areas where there may be hazardous fumes, strong winds, or both [5].

This decision is influenced by the air quality [2,6]. Due to societal and commercial demands, the PMA centers are currently located in the city center to serve a sizable portion of the population. An architect must first decide whether any nearby areas will be developed or destroyed in order to stop the air quality from further declining [7]. It is critical to be knowledgeable about these factors because they may harm the center. Ozone levels in the atmosphere, levels of pollen and dust, wind patterns, and wind direction are a few examples of environmental factors. Actually, volatile organic compound (VOC) particles from building construction, demolition, and remodeling are the main cause of pollution [8].

Take into account how much of this structure is auxiliary, including the parking lots, the streets, and occasionally even the plants. Parking shall be provided in separate, roomy lots set back from the building, both indoor and outdoor parking. The viability of the routes must be taken into account.

Parking and accessibility, despite appearing to be unimportant, are actually very significant considerations. Only those with a history of overcoming challenges should use it. The patient's ability to make decisions may be impacted if the illness is severe enough. It should be simple to access the building with nearby parking lots and bus stops. Accessible parking must be available in every place that a person visits or calls home.

It is important to take into account the communications system's usability and the options for both public and private transportation's accessibility. Driving and using phone and data networks both require effective communication skills. Given that WiFi is currently the most widely used form of communication, the lobby or a nearby location should have a free hotspot. This area should end in the waiting area in order to prevent the WIFI signal from entering the technical areas.

Although estimating the amount of space needed to construct an ART center can be challenging, it may be advantageous to conduct a study that meets American standards [9]. The environment in which a patient is received is one of a professional's tools. You should keep your cool when speaking with patients. Remember that their purpose in being there is to complete a challenging task.

Establish a calm and serene ambiance as soon as guests arrive using delicate colors, plush furnishings, background music, and the most recent issues of newspapers. To keep the kids occupied, safe, and away from the other adults who are waiting, we set up a sideline area with cartoon videos or comics, if there is room. Large seats are also necessary. During routine examinations, you should be able to speak with the patient or the patient's companion. Both a patient-accessible exam table and a quiet area should be available nearby.

The location, or more specifically the bathroom where the sperm is extracted, should be especially comfortable and have a video device that enables one to choose movies that can aid with performing the act itself. Sometimes, patients will be unable to provide the sample due to mental health issues; in these circumstances, they will not be able to.

They must be able to submit this sample in a welcoming, secure environment if we are to be of any assistance to these patients. Direct communication, though it may initially seem unimportant, is regarded as a safety measure that is actually very helpful. It's in the middle, between the sampling area and the main laboratory. The patient need not always ask about how to properly dispose of the sample once it has been collected. It is not necessary to have a connection to the in vitro fertilization lab, but it must be close by because some of the operators travel back and forth between the two locations frequently.

The lab needs to be situated in a quiet, safe neighborhood with few close neighbors. Picture an embryology research facility. One of them is egg collection, which also requires preparing a tiny catheter for the transfer, processing oocytes in an incubator and a laminar flow hood, and potentially injecting sperm using an inverted microscope and a micromanipulator.

The available space cannot accommodate the required hardware for the IVF lab and operating room. Since cardboard contains a lot of volatile organic compounds (VOCs), it produces a lot of dust when first used. Consumables

must be transferred from plastic storage containers kept outside of labs to cardboard boxes that can be left outside. Another example would be consumables. g. In the packaging of food, plastic is frequently used. g. It is important to consider whether products made of plastic contain VOCs. Don't enter the lab with more supplies than are absolutely necessary. The operating room, cryoroom, and IVF lab will all be restricted to authorized personnel only to maintain the security of the area. Consider the use of emergency vehicles, such as ambulances and fire trucks, when selecting potential escape routes. Paramedics may ask for access to the operating room if a patient develops a complication that calls for more medical equipment than the clinic has on hand. Stretchers must be easy to maneuver through doors and hallways when transporting patients. This law applies to every entrance that a firefighter may enter. It is essential to have a plan in place to ensure that the gametes and embryos stored in the cryoroom can be accessed in case of an emergency or evacuation.

One of the biggest problems at work is controlling and avoiding contamination. For the patient, it is a secure setting.

safety precautions for employees.

ensuring the protection of the environment.

The likelihood of the materials' effects on cell cultures should be given the utmost importance. They are very aware of their surroundings, and there are

additional passages everywhere. Cell culture is done in incubators and IVF labs. We would seriously jeopardize the integrity of our research if we used substances that produce cellular toxins [2]. The aforementioned goals must be attained before "controlled contamination" conditions can be met. They are positioned in locations with specific operational and preventative measures in place to lessen the risk of crop contamination and operator exposure [5,11].

The ceiling must have a uniform texture, be completely fireproof, and be completely hygienic. The floor needs to be strong, non-slip, attached to the walls, and resistant to abrasion from physical and chemical agents.

There is a possibility that formaldehyde and volatile organic compounds (VOCs) will be released during the installation of some building materials, such as those used for walls, floors, and ceilings. These pollutants also harm cell cultures. Some of these materials have the capacity to absorb odors and chemical waste from additional construction processes, which can then be released once more and pollute the air [8,10,12]. Moreover porous and absorbent, these materials. The best place to prepare and manage sperm is somewhere else.

The primary substances used in the production of these items are PVC, rubber, or linoleum. PVC is a trustworthy, economical material that can be disposed of with ease and is unlikely to trigger allergic reactions in people. The fact that it is stable means that it satisfies the requirement for an organic polymer.

Formaldehyde emissions, poor indoor air quality, and humidity issues may be made worse by thermal insulation in buildings [12e–14]. Due to the possibility of hazardous materials being released, impermeable synthetic insulation and waterproofing products like polystyrene panels and urea-formaldehyde foams should be avoided. These substances lessen both wall permeability and ventilation.

The ceiling is frequently used as a false ceiling in healthcare facilities. Because of the fixtures that are already there, the false ceiling can be used. In the unlikely event that a problem does arise, it is easy to fix. But because of the way it was built, the false ceiling is more likely to collect dust and act as a source of airborne disease.

Since paint produces a lot of VOCs, fewer should form. Before being used in medical facilities, false ceilings must pass rigorous testing and certification requirements. This can be accomplished using a variety of methods, such as the use of paints that release little solvent [15]. Non-water-based paints should never be used to build a PMA center because they have the highest concentrations of volatile organic compounds (VOCs).

In order to develop an ecological system that would purify the air inside spacecraft that would be launched into orbit, NASA spent a lot of time studying various plant species in the 1980s. The majority of this knowledge can be found

in B's "Friendly Plants" online book. ". ". ". ". ". C. The work of NASA researcher Wolverton was useful for this endeavor.

Compared to temperature [17], pH, and the components of the culture medium, light's potential functions and effects have not received as much research. Oocytes, zygotes, and early embryos do not, in the opinion of the majority of scientists, physiologically respond to light. Researchers have concluded that light is not always harmful because it has a variety of long-term effects on oocytes, sperm, and embryos in different an- imal species [18,19].

There are no significant barriers preventing the evaluation of the potential effects of light type, exposure time, and exposure to various wavelengths on gametes and human embryos grown in vitro at this time. Animal models are frequently used in studies to apply the results. Although a mammal's environment outside can change significantly, the uterus is built to maintain homeostasis. Modern incubators at the PMA labs can almost perfectly mimic this internal environment.

The incubator's controls for pH and temperature are currently the main source of worry. This is as a result of the wider and quicker excursions these parameters exhibit in IVF labs compared to other settings. During ART procedures, light of different wavelengths is all exposed to oocytes, sperm, and embryos. At every stage of in vitro fertilization, oocytes and embryos are thought to be susceptible to irreversible damage because they lack a light-

protection system [18]. Light can be harmful to a cell for a variety of reasons. Because light ionizes DNA, prolonged exposure to it can be bad for cells [20e22]. Oil and other components of the culture medium are subjected to light, which causes a chemical reaction called photooxidation [23e25]. Mammalian cell structures could unintentionally be harmed by this reaction. The components of a culture medium photooxide, releasing the infamously toxic byproduct H2O2. Sperm and membranes may undergo similar changes to those noted in relation to the components of the culture medium [25].

Gametes or embryos can frequently suffer damage from a brief exposure to light. It is common knowledge that hamster embryos are sensitive to light. The first intracytoplasmic sperm injection using hamster oocytes was actually made possible by red-filtering the microscope's light in a low-light setting [19,26]. Examples are the ability to stop the development of the embryo in hamster oocytes at the two-cell stage after just 30 minutes of exposure to light (380-760 nm) and the ability to resume normal meiosis after just one hour of exposure to cold fluorescent light. An embryo's development can be hampered by even five minutes of exposure to 2-8 cells [27]. He accomplished this by explaining indoor plants in detail (Fig. to provide support for his assertions. Levels of benzol and formaldehyde must be cut in half in enclosed spaces. Microorganisms can only remove pollutants after they have been consumed by the leaves, stem, and roots [16]. We must encircle ourselves with "friendly"

plants if we want to keep everything in our daily lives, including our centers and departments, as spotless and ideal as possible. In three widely dispersed plant species, the conversion of CO2 into formaldehyde and oxygen is especially effective. The Hort Science journal published a list of plant species compiled by the University of Georgia in October 2009. These microbes could prove to be extremely helpful in the fight against toxic VOCs and benzene, which are found in tap water, adhesives, clothing, clothing dyes, solvents, building materials, paints, and even clothing. The incredibly stringent lighting requirements for sterile environments and hospitals call for luminaires with unusual lighting and construction features. Some components, however, ought to be reserved for lab use. Culture-specific adaptation is the type that happens and is most likely to happen. Environmental factors, however, can have a negative effect on critical aspects of postnatal development, growth, and offspring.

The production of reactive oxygen species in mouse and hamster zygotes has also been demonstrated to increase after 15 minutes of exposure to either warm or cold fluorescent light at 37 degrees Celsius. These findings imply that warm light is less harmful to oocytes and embryos than cold light, which is the type of light produced by incandescent and fluorescent lights.

The two most frequent and typical effects of exposure to light are the appearance of a significant number of small pronuclei and an irregularity in

chromosomal development after the metaphase. Infrequently does it detach from the second polar globule of the body. Using these techniques, the human cell cycle can also be turned around. How well these systems will work in IVF patients exposed to potentially harmful light is unknown. It is ideal to expose oocytes, zygotes, and embryos to very little, if any, visible light in order to make in vitro development as similar to what occurs in vivo as possible [27]. Low-wavelength light, or light that is close to the UV spectrum, is the best illumination for this. Warm white fluorescent lighting, which in this situation emits light with shorter wavelengths, seems to be the safest and most sensible choice. Every procedure carried out in an IVF lab requires electricity. If the standard incandescent light used in microscopes doesn't cause any harm, there shouldn't be a problem. The clinic should be concerned about the quality of the power delivered in addition to any possible power outages. Electronic device problems could occur if the power sources are unstable. Generators and uninterruptible power systems (UPS) are your two options in the event of a power outage. To reduce the likelihood of problems caused by spikes and surges, power filtering components are frequently used in backup systems. Large UPS groups can go without power for a respectable period of time because they operate on alternating current, which is produced by converting direct current and doesn't emit VOCs.

Generators are frequently kept outside the building in a secure location for maintenance purposes, frequently near the parking lot. Generators typically run on two fuel types: diesel and gasoline. To prevent breathing potentially dangerous volatile organic compounds (VOCs), keep as much distance as you can between the fuel and the air conditioner vent. In addition to anesthetic gases for the operating room, a specific N2 and CO2 gas mixture is needed for the incubators in the IVF lab. Unattractive, heavy, and difficult to move gas cylinders. The best place to store cylinders is near the parking lot or a location where used cylinders can be collected and kept; it should also be a place that the delivery service can easily access. An area with shade, like a parking lot, is the best setting for this. Cylinders and regulators are the only items that should be stored in a cage or other small area. Because gases frequently experience thermal excursions, gas fitting leaks frequently have a temperature cause. As a result of these things, environmental concerns are growing. There are limitations on who is permitted to use the lab (e. g. g. Maintaining order, obtaining authorization (via a badge), and dressing appropriately are all requirements. In operating rooms, these rules are also in effect.

If the shelving is strong enough to support the cylinders, fewer employee falls will happen. To ensure that even if one gas cylinder runs out of gas, the other can still provide gas, any gases that are introduced into the lab or operating room must be connected via an automatic switch system. The most powerful

regulators must enjoy the trust of the market participants. Some of them could have VOC leaks due to neoprene diaphragms. A gas supply system and plumbing will be put in place in the lab. The two materials choices are stainless steel and copper-nickel.

PTFE is a different kind of pipe material. Inert, safe for developing embryos, and unable to pass through carbon dioxide, PTFE is preferred by some gas mixtures. The preservation of gametes and embryos depends heavily on liquid nitrogen. Even though silicone is an inert material that can absorb carbon dioxide, it shouldn't be used with mixed gas. It is expected that the CO2 concentration will drop as the tube lengthens. It also needs to be handled carefully because of how dangerous it is. LN2 must always be available for lab cryopreservation. Common dewars with six to ten compartments are the most popular containers; however, larger containers with larger sample capacities are also available. Large cryobanks would benefit from having a sizable storage container on the premises, ideally outside the lab and in a location that is convenient for delivery personnel. In this situation, it is important to carefully consider where to put the storage container for liquid nitrogen, which must be outside the building. Keep it secure and out of direct sunlight is the best course of action. Dewars can now be topped off or fed into storage tanks via an automated top-up system since LN2 can now be introduced into the cryoroom via the pipes. A delivery truck will fill an external LN2 tank for high-

volume utilities rather than delivering LN2 in smaller tanks based on the required volume. In both cases, a transport vehicle must be able to leave the interior and follow a pre-planned route.

When designing, one must take into account the cryolab or other location where LN2 will be applied and used. Because there is a chance that some LN2 will leak from dewars, the flooring needs to be resilient to sudden temperature changes. Staff members will be notified if an oxygen meter is installed if nitrogen gas is present and the oxygen level starts to drop. Forced ventilation is necessary to add fresh air quickly and remove LN2 vapor. If you did that, you could even end up dying.

The significance of remote liquid nitrogen level alarm controls for various dewars cannot be overstated. Sadly, unless the loss is sufficiently significant, even the most sensitive probes won't detect a decline. Infrared cameras can now quickly find even the smallest leaks as a result of recent technological developments. According to research by Kukadia and Palmer, the quality of the air inside and outside may be connected. The majority of air pollution originates from exterior sources, such as buildings like homes, offices, and other establishments that release volatile particles and air pollution (Fig. 1). These pollutants frequently enter the environment through ventilation ducts and other openings. Carpets, paints, resins, fiberglass, and sealants are just a few of the product categories that the construction industry naturally produces

[28]. More than 90% of human activity takes place indoors, where there are internal sources of pollution. Some dangerous substances may exist at concentrations that are two to five times higher than those that are typically seen in the environment, according to studies done by the American Environmental Protection Agency.

It has been found that healthcare facilities have slightly worse indoor air quality than other public and private settings (like homes, businesses, and schools), despite the fact that there aren't many studies on the air quality inside PMA centers. Chlorhexidine, a sperm toxin, airborne lab worker particles, ethylene oxide-based cleaning and sterilization products, and even anesthetic gases that can dissolve in culture media and affect embryonic development are some of the causes of this [12, 29]. Avoiding essential building materials like chipboard, wood panels, dry stone walls, adhesives, carpets, and paint that contain VOCs, aldehydes, or compressed gases can help prevent potentially harmful effects on fetus growth in vitro and pregnancy rates [13].

The vast majority of in-vivo studies have focused on the toxicologic effects of VOCs on developing humans and animals. Following implantation, the mother's immune system protects the embryo from pollutants. Because in vitro embryos lack defenses like an epithelium, excretion systems, and respiratory capabilities, they might also be more vulnerable to contamination [11]. The immune systems of these people are weak.

Despite the fact that air toxicity is frequently a concern for PMA facilities, little is known about the toxicological effects of the phenomenon prior to, during, and after reproductive procedures. The same is true for laws that set limits on gas emissions or establish particular standards for air quality.

To reduce VOC exposure in IVF laboratories, a second air-purification system that can aid in removing particle pollution from labs and check for contaminants in PMA centers is required [5]. Additional factors must be taken into account, such as the exchange of air pressure, inspection of the facility's ventilation and filtration systems, and others, to ensure measurement, monitoring, and maintenance. Microbiological control is also used for contamination particle level measurement, monitoring, and maintenance.

Facilities for ART must maintain relative humidity at a comfortable level, or about 40%. For the ART lab and operating room to receive air, positive exterior air pressure is also necessary.

Telemedicine's emergence is probably influenced by the communication sciences' effects on medicine. From a methodological and technological standpoint, it forges new connections based on "geographical axes," and from an organizational standpoint, it provides a strong and useful tool for linking various care levels. In situations where direct intervention may be challenging for a variety of reasons, the doctor must be able to provide essential support while working remotely. But in order to make things better and emphasize the

need for a solution (i. e. e. Imagine a time when medical systems had been rationalized and reorganized to take full advantage of the opportunities these technologies present.

All of the client's needs, from the most obvious to the latent and unspoken, must be taken into account when designing a fully or partially home automated PMA center. Home automation, it is claimed, can reduce overloaded current, avoid blackouts, enable safe load operation, and save 20 to 30 percent on electricity. In buildings, there are automatic security and fire alarms. The various solutions exhibit a wide range of adaptability while maintaining their full modularity, effectiveness, and efficiency. They are very adaptable and can live in both very big spaces and more laid-back ones. It is difficult to design a PMA center with home automation integration because the healthcare sector presumes the existence of particular safety precautions. A difficult process can be entirely automated using one of the many home automation services available. We'll go over some of the most common uses so that you can see how adaptable the system is. health-related and oximeter control alarms. Every area of the center has a controlled microclimate and humidity. The administration, audio, camera, and intrusion detection settings for the security camera system are entirely under your control.).).

interaction with specific particle counters and VOC-type sensors to make sure the air in the operating room and lab is sufficiently sterile. restricting access

and keeping an eye on it there. the ability to adjust the alarms on the incubator. Be prompt when reporting in telemedicine. The operating room and lab should be kept separate from the UPS and generators. g. When we interact with people, we frequently make snap judgments about them, particularly when their signals can immediately catch our attention. Once this is done, one can exhibit admirable traits like helpfulness, kindness, and physical fitness. Any facility, regardless of size, is evaluated based on its organization, hygienic conditions, and cleanliness. The latter impression seems to be the most significant one that users have, and it serves as a way to gauge the quality of the service because customers initially contact a provider with no additional needs. The patient and his family don't have much faith in the center because of how disorganized it appears and because they are concerned that it might not be able to meet its own needs.

It is essential to at least fully comprehend the potential problems with disorganization that could arise when there are conflicts between the various competences, whether they relate to doing or not doing the capital goods that an organization needs in order to carry out its work or whether they relate to doing or not doing the human resources. The typical picture that comes to mind when thinking about workflow is a series of routine tasks that frequently take place over the course of a workday and produce a largely predictable outcome. It is obvious that various groups have been formed for the various functions

because it is crucial to carefully examine the flows in order to avoid unnecessary crossings and waiting. the main life-giving organs and nerve centers of the organization, i. e. e. or the beginning of the patient flow, significant organizational nodes. Take these important factors into careful consideration as quick success will physio- logically increase the advantageous course of action and the capacity for problem-solving. Each focal point should go through at least three to four months of problem-sharing before introducing a plan that begins moving forward right away.

We start the process of creating value flow diagrams so that these evaluations can be applied to specific disease, surgical, or trauma management profiles. Students need to be reminded of the procedures frequently enough (every two to three months) to learn how to apply the aforementioned principles as effectively as possible. Controlling patient flow is undoubtedly not one of the most common skills in a hospital setting if the number of people waiting, which includes patients, doctors, nurses, technicians, and support staff, is the best indicator of waste [33e35]. The next steps are to create improvement indicators, review your priorities, streamline your work flow, and standardize your group activities. Ergonomics places a strong emphasis on the interactions between human activity and the external physical, technological, and organizational contexts. Modifying these circumstances to better suit a person's needs in light of their personality and activities is the goal of ergonomics. If

the organizational, instrumental, and environmental circumstances are compatible with the individual characteristics and professional objectives of the system's employees, ergonomic principles are used [36]. Compliance is assessed using data on the system's efficacy, efficiency, and user satisfaction. An ergonomist is in charge of creating functional and user-friendly environments, tools, products, services, and procedures [37,38]. They are assessed for effectiveness in addition to design.

He will therefore try to get involved in order to change the situation.

The goals of the ergonomic intervention can be determined using the classification of A. (Anthropometric, Physiological, Psychological, and Sociocultural Characteristics of the Operators and Users Processes, as well as Life and Work Activities that Support the Enhancement of the Overall Quality of the System) by Identifying Environments, Tools, Products, and Services with Physical and Cognitive Interfaces That Are In Line With The Operators and Users Processes. Chapani people.

Increased output, improved safety, and a decrease in errors are the main goals of operations.

2. Standards that are efficient, strong, and durable.

3. The objectives include enhanced working environments, operator usability, and user comfort.

4. updated specifications to cut waste.

The lab must be put in a secure location with minimal traffic and controlled access. It is crucial to closely examine the lab's workflows for embryology. Egg collection should be the first step, followed by oocyte cleaning under a laminar flow hood and incubators, potential sperm injection with an inverted microscope and micromanipulator, again in an incubator, and microscopic preparation of the transfer catheter. There must be restrictions on who can enter the lab (e.g. g. g. Only those who are properly identified (by badge), groomed, and dressed (as in a sterile operating room) are allowed entry. Experts in academic reproductive medicine were probably involved. According to the expanding body of research based on the available data, reproductive medicine should be treated differently than obstetrics and gynecology. Whether they are standalone companies or a division of an obstetrics and gynecology department, assisted reproductive facilities require a highly skilled and committed workforce. The lack of formal education among ART program administrators suggests that either few institutions, like universities, provide this kind of training or that it is difficult to access.

The lab staff, directors, and embryologists must balance their prior experience with the demands placed on them in order to produce the best results. The Human Fertilization and Embryology Authority and the College of American Pathologists, respectively, are regulatory bodies that set standards and issue licenses to embryologists in the US and the UK. Although licenses cannot be

transferred across national borders, having one does not automatically imply one is skilled (or successful). It is essential to have a thorough understanding of clinical embryology before starting a new program. Even a sizable number of very competent clinical staff members should answer directly to a sizable number of seasoned embryologists and scientists.

"Traditional" IVF procedures used to only need about nine staff hours, as opposed to "modern" procedures, which can take up to 20 hours. More embryologists must be hired if the lab is to continue operating productively and safely. If success is to be maintained at the high standards required, the workload must not be so heavy as to render time for quality assurance, ongoing education, and training useless. If there are already problems with embryologists' credentials and licenses, it is harder to evaluate and certify medical staff. Only the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) have made an attempt to create guidelines on this subject; there is no consensus regarding which organization must certify the requirements in order to start working. The PMA lab setup requirements at ESHRE and ASRM, however, differ significantly. As opposed to the European model (EM), the American model (ASRM) gives special consideration to the staff and design of the ART center. This is so because the laboratory model's (EM) focus on every element necessary to guarantee an improvement in quality in terms of management,

assistance, control, and results has proven to be accurate. An organizational chart is essential for determining whether a treatment is effective because it makes it easy to identify everyone involved in each step of the process, allowing you to identify any problems and determine what can be done to fix them. For a structure to be considered organized, each member must perform predetermined tasks in accordance with a predetermined organizational chart. For qualified individuals, there are openings at the IVF lab.

The lab should be overseen by someone who is knowledgeable in biological, medical, and clinical embryology. a Ph. D. in terms of education. MSc (Ddot), MD. D. made the findings of an ESHRE survey on clinical embryologists' employment and education available. D.), with at least six years of verifiable experience in human embryology, and preferably holding an ESHRE certification as a senior clinical embryologist or a title equivalent.

The laboratory director is accountable for a number of other tasks in addition to managing the workforce, choosing qualified candidates, monitoring the quality management system, lowering risks, and assessing the outcomes. In some places, you might find a portrait of the lab manager. conditions that are particular, like e. g. A bachelor's degree in biomedical sciences is needed, along with three years of documented experience in human embryology, and passing the clinical embryologist certification exam given by the ESHRE or a similar organization would be ideal. The manager is in charge of establishing

work phases, creating a trustworthy communication system, carrying out staff training programs, and making sure that improvement is ongoing. Medical institutions frequently employ clinical embryologists. New hires are required to successfully complete an organized training course under the guidance of seasoned clinical embryologists. In addition, the clinical embryologist is responsible for overseeing student embryologists, ensuring that they follow SOPs, taking part in lab decisions, and interacting with a variety of people. Nowadays' construction is impossible without LAN networks. Every piece of scientific equipment housed in an ART center has a network port that enables remote equipment management, which is an important concept to comprehend. Since WIFI mode should only be used in a few locations, possibly excluding sensitive ones like the operating room and laboratories, the entire building should be wired. The application of quickly changing technology is one aspect of the new paradigm in medical practice. The amount of human error should be reduced as much as possible. Because of the use of computer and communication systems, medical science now has access to possibilities that were previously unthinkable. Consider clinical data collection from numerous independent diagnostic techniques, clinical parameter remote monitoring, or extensive medical knowledge dissemination. The availability of healthcare services may improve greatly in effectiveness, equity, and efficiency as a result of technological advancements. The number of embryologists employed and

the number of cycles carried out ought to be correlated. It is typically advised to employ a minimum of two clinical embryologists who are qualified to carry out up to 150 egg retrieval and/or cryopreservation cycles annually. This starting value will increase based on the methods employed and the number of cycles. Biologists must manage, coach, instruct, train, check for quality, educate, and communicate in order to successfully complete their work. An essential additional factor is the availability of sufficient staff to support embryologists.

Employee information is kept private, including names, titles, and positions. Having enough staff on hand is essential to guaranteeing that operations can continue even if someone is not present. One or more academic disciplines will allow you to prove your superiority. You must enroll in an ART program if one of the following applies to you. Male reproductive specialists must also be board-certified in either gynecological endocrinology or obstetrics and gynecology. A consultant urologist must be reachable, regardless of whether they are employed by the facility.

Nursing staff with ART licenses can provide patients who require prenatal care with nursing care, counseling, and support. The director of an embryology lab should have at least two years of professional experience and be knowledgeable in reproductive physiology, cell biology, biochemistry, and experimental design. They must have a PhD in a chemical, physical, or

biological science in addition to an MD or DO from an accredited university and a laboratory director certification that dates back before July 20, 1999. Every two years, participants must successfully complete an ongoing ART training course that takes at least 24 hours. By January 1, 2006, all new laboratory directors had to be ELDs working in high complexity clinical labs, embryology labs, or both.

The protocols must be created by the embryology lab director, who is also responsible for informing the other physicians of laboratory results that are essential to a specific course of treatment. Any incident that could have an impact on how the lab runs must also be reported to this person by the medical director. Lab operators must receive ongoing training, a quality management program must be in place and implemented, and the workload must be organized so that there is always enough staff available to complete the tasks. The lab manager is in charge of ensuring that all of these conditions are true, including that the lab is clean, that everything is in working order, and that the staff has access to manuals of standard operating procedures. Make a backup strategy as well. A bachelor's or master's degree in physical or biological science, medical technology, or clinical or reproductive laboratory science must be granted by an accredited college or university. At least 30 successful ART procedures must be carried out before becoming certified as an ELD. A licensed registered nurse with experience in reproductive medicine must

oversee the clinical ART care. The lab staff needs to be skilled in handling tiny objects, cryopreserving embryonic gametes, and analyzing hormones. The progress of the follicles is monitored by a gynecological ultrasound specialist. An ultrasound technician, nurse, or doctor might carry out this. Specialists in mental health and genetics must be available; ideally, they should have experience as consultants or ongoing fertility counselors. Even though the director has no medical background, interaction with ASRM and the registers is crucial. The medical director of a PMA cycle must be certified as of January 1, 2000, or be a candidate for certification, according to the American Board of Obstetrics and Gynecology (ABOG) REI Board. The medical director is required to validate the information per a request from SART, the Society for Assisted Reproductive Technology. The egg retrieval and transfer procedures must be performed by physicians who satisfy the required standards for education, experience, and training. They must also be carried out frequently enough and under close supervision. The training's successful completion must be attested to in writing by the Medical Director. These procedures must be performed by doctors on a predetermined number of occasions each year in order to keep their licenses. The science behind ultrasound follicular monitoring is something that doctors need to be familiar with.

References

Cohen J, Gilligan A, Esposito W, Schimmel T, Dale B. Ambient air and its potential effects on conception in vitro. Hum Reprod 1997; 12(8):1742e9. https://doi.org/10.1093/humrep/12.8.1742.

Boone WR, Johnson JE, Locke AJ, Crane IVMM, Price TM. Control of air quality in an assisted reproductive technology laboratory. Fertil Steril 1999;71(1):150e4. https://doi.org/10.1016/S0015- 0282(98)00395-1.

Luo Q, Yang J, Zeng QL, Zhu XM, Qian YL, Huang HF. 50-hertz electromagnetic fields induce gammaH2AX foci formation in mouse preimplantation embryos in vitro. Biol Reprod 2006;75(5): 673e80. https://doi.org/10.1095/biolreprod.106.052241.

Genuis, Lipp CT. Brown RH Monitoring vocs in air e the develop- ment of ISO standards and a critical appraisal of the methods. Sci Total Environ 2002;414(6).

Brown RH. Monitoring vocs in airethe development of ISO stan- dards and a critical appraisal of the methods. J Environ Monit 2002;4(6).

Petry T, Vitale D, Joachim F, et al. Regul Toxicol Pharmacol 2014.

Amodio M, Dambruoso PR, de Gennaro G, et al. Indoor air quality (IAQ) assessment in a multistorey shopping mall by high-spatial- resolution monitoring of volatile organic compounds (VOC). En- viron Sci Pollut Control Ser 2014;21(23):13186e95. https:// doi.org/10.1007/s11356-014-2544-1.

Moya J, Howard-Reed C, Corsi RL. Volatilization of chemicals from tap water to indoor air from contaminated water used for showering. Environ Sci Technol 1999;33(14):2321e7. https:// doi.org/10.1021/es980876u.

Malkin J. Medical and dental space planning: a comprehensive guide. 2014.

Loumaye E, de Cooman S, Thomas K. Optimalisation des condi- tions de fe´condation et de culture d'embryons in vitro. Rev Med Brux 1985;6(9):611e4.

Cutting RC, Pritchard J, Clarke HS, Martin KL. Establishing qual- ity control in the new IVF laboratory. Hum Fertil 2004;7(2):119e25. https://doi.org/10.1080/14647270410001709188.

Wieslander G, Norba¨ck D. Ocular symptoms, tear film stability, nasal patency, and biomarkers in nasal lavage in indoor painters in relation to emissions from water-based paint. Int Arch Occup Environ Health 2010;83(7):733e41. https://doi.org/10.1007/ s00420-010-0552-0.

Bayil S, Cicek H, Cimenci IG, Hazar M. How volatile organic com- pounds affect free radical and antioxidant enzyme activity in textile workers. Arh Hig Rad Toksikol 2008;59(4):283e7. https://doi.org/10.2478/10004-1254-59-2008-1918.

Sugai K, Maekawa H. Reutilisation of wool as a thermal insulator for building material. In: Proc 10th IWTRC, Aachen D. 9; 2000. p. 767e8.

James AE. Painting collections in hospitals: humanity in medicine. J Am Coll Radiol 2012;9(11):767e8. https://doi.org/10.1016/ j.jacr.2012.02.017.

Dela Cruz M, Mu¨ ller R, Svensmark B, Pedersen JS, Christensen JH. Assessment of volatile organic compound removal by indoor plants-a novel experimental setup. Environ Sci Pollut Control Ser 2014;21(13):7838e46. https://doi.org/ 10.1007/s11356-014-2695-0.

Cooke S, Tyler JPP, Driscoll G. Objective assessments of tempera- ture maintenance using in vitro culture techniques. J Assist Reprod Genet 2002;19(8):368e75. https://doi.org/10.1023/A: 1016394304339.

Ottosen L, Hindkjaer J, Ingerslev, Pomeroy t o, Reed ML, Hill jr RB, Bensch KG, King DW. Photosensitization of nucleic acids and proteins. The photodynamic action of acridine orange on living cells in culture. J Reprod Stem Cell Biotechnol 1960; 24(2):106e17.

Ottosen LDM, Hindkjær J, Ingerslev J. Light exposure of the ovum and preimplantation embryo during ART procedures. J Assist Reprod Genet 2007;24(2e3):99e103. https://doi.org/10.1007/ s10815-006-9081-x.

Hill RB, Bensch KG, King DW. Photosensitization of nucleic acids and proteins. The photodynamic action of acridine orange on living cells in culture. Exp Cell Res 1960;21(1):106e17. https:// doi.org/10.1016/0014-4827(60)90351-7.

Wang RJ. Lethal effect of “daylight” fluorescent light on human cells in tissue-culture medium. Photochem Photobiol 1975;21(5): 373e5. https://doi.org/10.1111/j.1751-1097.1975.tb06688.x.

Zigler JS, Lepe-Zuniga JL, Vistica B, Gery I. Analysis of the cyto- toxic effects of light-exposed hepes-containing culture medium. In Vitro Cell Dev Biol 1985;21(5):282e7. https://doi.org/ 10.1007/BF02620943.

Barlow P, Puissant F, Van Der Zwalmen P, Vandromme J, Trigaux P, Leroy F. In vitro fertilization, development, and implantation after exposure of mature mouse oocytes to visible light. Mol Reprod Dev 1992;33(3):297e302. https://doi.org/10.1002/mrd.1080330310.

Oh SJ, Gong SP, Lee ST, Lee EJ, Lim JM. Light intensity and wave- length during embryo manipulation are important factors for main- taining viability of preimplantation embryos in vitro. Fertil Steril 2007;88(4):1150e7. https://doi.org/10.1016/j.fertnstert.2007.01.036.

Yamauchi Y, Yanagimachi R, Horiuchi T. Full-term development of golden hamster oocytes following intracytoplasmic sperm head injection. Biol Reprod 2002;67(2):534e9. https://doi.org/ 10.1095/biolreprod67.2.534.

Fischer b, Schumacher A, Hegele-Hartung, et al. The origin, ef- fects and control of air pollution in laboratories used for human embryo culture. Human Reprod. J Assist Reprod Genet 1988;50: 146e55.

J Reprod Stem Cell Biol 2013;3(2):46e54.

Quality and risk management in the IVF laboratory. 2005. https:// doi.org/10.1017/CBO9781139680936. undefined.

Hall J, Gilligan A, Schimmel T, Cecchi M, Cohen J. The origin, ef- fects and control of air pollution in laboratories used for human embryo culture. Hum Reprod 1998;13(4):146e55. https:// doi.org/10.1093/humrep/13.suppl_4.146.

Nielsen K, Cleal B. Predicting flow at work: investigating the ac- tivities and job characteristics that predict flow States at work. J Occup Health Psychol 2010;15(2):180e90. https://doi.org/ 10.1037/a0018893.

Chapter 3

Building the assisted reproduction laboratory

It was thanks to Drs. Edwards and Steptoe's pioneering work that the first in vitro fertilization (IVF) procedure was used to conceive a child in England in 1978. Since then, in-lab IVF procedures have advanced significantly. Replicating the first few weeks of an embryo's life in the mother's womb is crucial for an in vitro embryo culture facility [1]. A stable environment is necessary for development to occur and for good clinical results [2,].

Over the past 40 years, advances in assisted reproductive technology (ART) have been made by gynecologists, embryologists, and geneticists in an effort to increase patient numbers and treatment efficacy. More than 200,000 children are born each year as a result of ART worldwide [3]. Worldwide, ART has resulted in the birth of five million children [4]. The need to guarantee the quality of laboratory supplies like disposables, culture media, and equipment specifically designed for assisted reproduction is becoming more and more important. A reliable lab is necessary for a successful IVF program, according to the Cairo Consensus Guidelines on IVF Culture Conditions [5]. In an IVF lab, each small detail matters. Understanding the clinic's intended clients and services is essential before beginning an analysis of the ART project concept. These variables must be defined for space planning and allocation to be effective [6,].

The clinic's objectives must be made clear, and it is essential to choose which services it will offer from a variety of choices: whether it will offer comprehensive services that range from straightforward diagnostic procedures to the use of cutting-edge technologies, whether it will have a small team to provide individualized care, or whether it will be a clinic able to handle a high volume of patient demand [6].

For the project, it is important to consider both the anticipated volume of services and the required procedures. The disciplines that will be used must be chosen with care. A size estimate for the laboratory is also required, taking into account the projected growth and expansion over the next ten years or the time period specified in the strategic plan. The project's design must be flexible in the event that a future expansion necessitates moving the rooms [6]. The location is one of the first considerations when creating the fundamental structure of a new laboratory. Due to the possibility that stress and other environmental factors could affect the efficacy of reproductive treatments, some clinics have been built outside of urban areas. Given the difficulty in separating certain factors, accessibility might be more significant to some prospective customers. These days, it is more common to find laboratories in urban or metropolitan areas with high population densities. The service will be simpler to access as more people use it [6].

Additionally, not every construction site will be ideal for cell culture. Both within and outside the lab walls, there are various levels of pollution and VOCs that need to be considered. The mother's kidneys, liver, and lungs detoxify and filter VOCs, which reduces the embryo's ability to protect itself from impurities in the uterine tract. An in vitro embryo is not protected by these precautions, so it is necessary to actively lower the levels of toxic substances in the incubator and the lab as a whole [7,8]. Although laboratory air quality can be controlled, depending on the size of the proposed laboratory, installation and maintenance costs may make this form of protection from the outside world ineffective or unworkable [8,9]. In vitro fertilization (IVF) outcomes in assisted human reproduction facilities are significantly influenced by the laboratory [6]. The importance of taking into account any potential problems that might have an immediate or long-term impact on patients and healthcare professionals cannot be overstated when designing a facility of this kind. Given the design of the laboratory and the requirement for close coordination with the clinical staff, the workflows for the clinic must be precisely defined to ensure process effectiveness.

When designing a new laboratory or remodeling an existing one, it is important to consider how personnel, supplies, and clinical procedure samples will be moved. The project must place the highest priority on a structure that values

an appropriate and constrained workflow in order to guarantee the security of the samples and proper laboratory procedures.

When designing the various lab spaces, the typical workflow must be taken into account. The first two steps of this process are sample entry, receipt, and delivery. The use of cryopreservation chambers, incubators, and a laboratory must be physically separated from the processing of seminal samples. Air flow control systems are required in order to maintain a constant pressurizing level [1].

Incubators, gamete handling stations, and other micromanipulator stations should be available in labs to keep embryologists close to one another. During a procedure, an embryologist should not move more than 10 feet at a time. As a result, the risk to gametes and embryos is reduced, and workplace productivity and safety both rise [9].

Managers, engineers, and architects all agree that the clinical and laboratory teams need to be involved in the layout definition process [10]. In the difficult environment of an IVF lab, there are at least 200 confounders that could compromise the success of IVF [11]. Most of them have to do with setting up how the embryology lab's tasks, materials, workers, and personnel are organized. Establishing the conditions necessary to produce embryos with the same developmental potential as embryos that develop in vivo is the goal of this laboratory [8].

Even though some men might find it uncomfortable, the collection of seminal samples is an essential component of infertility treatment. However, at least one room is typically used for this purpose in medical facilities. You can start a collection right at home. In order for patients to enter the collection room without feeling uncomfortable, it must be placed in a specific location. Buildings need to be soundproof in order to ensure the security and comfort of patients [6].

Diagnostic andrology laboratories are likely to contain a range of additional potentially dangerous chemicals in addition to pathogens like the human immunodeficiency virus, hepatitis C virus, or hepatitis B virus. Equipment breakdowns, sample contamination, and organism contamination are frequently less likely in ART labs [12]. They must be physically isolated from other labs and given access to their own air conditioning systems to stop toxins from moving between these locations and harming the system [6]. When freezing gametes and embryos, liquid nitrogen is a common substance that needs to be handled carefully [6]. Storage facilities for liquid nitrogen should be situated as close as is practical to the lab in order to minimize waste and evaporation during transport. Tanks may be used frequently as storage in smaller cities even though larger local reservoirs in larger cities may be easier to maintain. Pipelines could be used in this situation to supply the vicinity of

the nitrogen tanks. By giving shorter, better insulated pipes top priority, transit losses can be reduced [6].

Today, many hospitals routinely perform reimplantation testing, also referred to as PGT. This idea has developed significantly as a result of cryopreservation techniques. Every embryo used in the procedure must be in cryopreserved form, and this practice may continue even after [13]. This came about as a result of careful genetic investigation. The location of the gas supply and storage area needs to be far away from the IVF laboratory and easily accessible to authorized personnel from the outside or inside fireproof shelters. Blocking power transmission lines is also prohibited by law. The ignition of liquid oxygen and nitric oxide cannot ignite composite flooring made of incombustible materials. Steel gas supply pipes are required to transport N2 and CO2 from the hub to the usage points. The cylinders must be connected to pressure-control valves in order for the system to function at its maximum continuous flow.

The lab's materials come in a variety of sizes and shapes, so storage space is necessary. Not only do cardboard packaging materials contain a lot of volatile organic compounds (VOCs), but they can also harbor bacteria, gather dust, and accumulate dirt. Consumables must be kept in tiny plastic containers outside the lab complex and kept apart from the cardboard packaging [6]. They will only work during the day. Large objects must be accommodated in the storage

area, along with mobile shelves and easily accessible containers. To maximize logistical efficiency and avoid having an excessive amount of consumables there, if at all possible, the storage location should be close to the lab [9]. Making the right decision is essential because the main source of VOCs in labs—which may affect the outcomes of cell cultivation—is building materials. Each component, including the flooring, paints, and furniture, must meet clean room standards in order to lessen the toxicity of a building's materials to gametes and embryos [14]. It's essential to have flooring that is non-slip, non-gassing, hygienic, and spill-proof in laboratories. The most widely used vinyl flooring has an artificial or monolithic appearance. There must be heat-welded tiled sections with straight corners that extend to the walls. It can be produced using polyurethane or epoxy, respectively. It is intended to fill in any gaps there in order to prevent the growth of dust, bacteria, or fungi [1,6,14]. The lab management must use an environment and air purification system that are different from those found in primary laboratories [9].

For the sake of preventing dust and other debris from entering, ceilings must be sealed and made of hygienic materials. The most popular choices are coated steel and plasterboard. The material used to seal the walls needs to be impermeable, completely decontaminatable upon request, hygienic, and hygienic. Aluminum, plaster, and plasterboard are common building materials

along with coated steel. If the clinic had the cash, the best option would be one of the numerous zero VOC paints listed in the paints category [6]. Unaffected by the type of lighting system employed, the lab must have two distinct types of lighting installed: total lighting for cleaning and maintenance when the gametes and embryos are not exposed, outside the incubators; and yellow incandescent lamps for the laboratory routine, with adjustable intensity grading. Despite being present in many light spectra, reactive oxygen species can be detrimental to cellular growth. the leaders.

A licensed company must check the lab's air flow once every six months. The ceiling filters should ideally be changed every three months [15]. The filters in a filtering system regulate the quantity of contaminants. A combination of activated carbon filters and high efficiency particulate air (HEPA) filters is used to capture volatile organic compounds (VOCs), which are released into the air as vapors. Thin (F8 and F9), thick (G3 and G4), and hybrid are the three different thicknesses available for HEPA filters. An inflation flow system that also certifies the cleaning class and, as a result, the particulate material filtrated supplies the rooms' hourly air volume changes, or m3/h x m2. The presence of outside air causes environments to condense [14]. By circulating sterile air at the ideal temperature and humidity into the surrounding area through diffusers and grilles, the pressure in the lab will rise from the cleanest areas to the least clean areas, producing a positive pressure. As a result, materials from less clean

rooms or rooms that have been abandoned cannot contaminate clean rooms [14]. Temperatures must be kept below 54°C (129°F) by keeping heat sources sufficiently apart from temperatures [14].

Cabinets and countertops are frequently made from MDF, or medium-density fiberboard. One of the main resins used to bind the wood particles together in this substance is formaldehyde, which the International Cancer Research Agency has classified as a known carcinogen and possibly toxic to developing embryos. Plywood and MDF both suffer from this issue due to their widespread use. The unfinished surface will be painted, and any lab-related VOC emissions will stop. Therefore, it is preferable to use gas-free materials to create countertops, such as stainless steel and both natural and synthetic stones [6].

Mobile chairs aren't often used in labs because of the risk of accidents. Experts should be able to use a raised bench and a microscope while standing. This adjustment is typically advised. The plastic construction of the chairs would reduce volatile organic compounds (VOCs) in addition to giving workers more space and a more orderly workspace [6].

In areas with high prices per square meter, facilities for assisted human reproduction should be kept to a minimum. Time-lapse systems, for instance, can be useful on incubators or benchtops. The best outcomes must be guaranteed by providing architects with information on the ideal locations and

all equipment specifications [9]. If equipment is to meet the needs and specifications, it must be carefully specified. Spare tools and equipment need to be considered as well [9] if a sudden failure puts operations in danger. Incubators and additional micromanipulators are not necessary in excess. The gadget will eventually require sterilization, upkeep, and replacement. To accommodate the necessary temporary movement of samples, nitrogen tanks in cryopreservation labs should be expanded [16].

Every piece of equipment should typically go through a functional test every day, and any required maintenance should be scheduled in accordance with the instructions each manufacturer provides [9].

The labs for andrology and embryology require a temporary electric emergency power system. Equipment disconnects during procedures can be avoided by connecting everything to a system with constant power [14]. It's crucial to reduce the likelihood that errors will be made as a result of distraction, fatigue, or other factors when creating a safe working environment. Bench height, adjustable chairs, enough workspace for everyone to work in, the height at which microscopes and magnifiers are in relation to the operator, efficient use of space and surfaces, and adequate lighting are just a few factors to take into account when it comes to workplace safety [17].

Protecting the lab staff is a top priority. When choosing a layout, this must be taken into account to guarantee that infectious waste and sharps are properly

disposed of close to the workstations. This waste must be gathered and stored in a safe outdoor area before being properly collected by a licensed business [6]. To maintain safety, in vitro fertilization and diagnostic laboratories must have close-by eyewash, hand, and safety shower facilities [6].

In vitro fertilization (IVF) procedures require the knowledge and expertise of medical and laboratory staff. Without a thorough evaluation of each patient's capabilities, clinical results are useless [9]. If you're curious about the growth and preservation of gametes and embryos, speak with an embryologist. It must also abide by the requirements for quality assurance, which include regular testing and inspections as well as painstakingly documenting any changes, problems, or corrective actions [10]. It is crucial to review fundamental concepts in genetics and to buy, keep, and get [9, 10].

Director, supervisor, senior embryologist, embryologist, intern, assistant, technician, and supervisory position are all currently open positions. The tasks an embryologist assigns applicants determines who gets selected for these positions. The clinic, however, has the power to modify these rules [10]. Even seasoned embryologists need to be judged on their level of knowledge and suitability for a particular task. Better outcomes are attained as a result of the accreditation and audits carried out by laboratories in support of quality control and standardization [9]. Modern cycles can last up to 20 hours as opposed to the typical 9 hours needed by a skilled physician to complete one traditional

IVF procedure. In order to complete lab procedures successfully and accurately, more embryologists are now required [10]. An interactive calculator was developed to help managers choose the right number of employees to assign to each task after a thorough analysis of the tasks performed in a laboratory and their complexity. Since they perform not only technical tasks but also management, ongoing education, and training with the aim of upholding the high standards, it is generally safe to assume that the proportion of embryologists to all procedures must be equal.

It's crucial to success [10].

As a result of PGT's widespread use, there is an increased need for knowledgeable genetic counselors [13]. Today, understanding genetic counseling is still essential. Effective communication of uncertainty, the complexity of genetic theories and methodologies, and the clinical relevance of data requires at least three of these abilities. To make using genetic data as decision-making evidence easier, genetic counselors decode complex genetic data [18, 19].

There are many reasons why running an assisted reproductive clinic can be difficult. Although it is preferable for physical structures to be designed with workflow in mind, clinics frequently go through renovations before being specifically adapted to an existing space. When planning the laboratory's spaces, keep in mind the air circulation system, the required number of

professionals, their level of education, and their level of training. Having a well-run lab can affect the working environment, clinical and laboratory findings, and lab results, all of which can improve employee satisfaction.

References

[1] Gilligan AV. Establishing the IVF laboratory: a systems view. In: Carrell D, Peterson C, editors. Reproductive endocrinology and infertility. New York: Springer; 2010. p. 569e78.

[2] Swain JE. Decisions for the IVF laboratory: comparative analysis of embryo culture incubators. Reprod Biomed Online 2014;28: 535e47.

[3] de Mouzon J, Lancaster P, Nygren KG, Sullivan E, Zegers- Hochschild F, Mansour R, et al. World collaborative report on assisted reproductive technology, 2002. Hum Reprod 2009;24: 2310e20.

[4] Kissin DM, Jamieson DJ, Barfield WD. Monitoring health out- comes of assisted reproductive technology. N Engl J Med 2014; 371:91e3.

[5] Cairo Consensus Group. There is only one thing that is truly important in an IVF laboratory: everything Cairo Consensus Guidelines on IVF Culture Conditions. Reprod Biomed Online 2020;40(1):33e60.

[6] Spittle J. IVF unit location, design, and construction. In: Fleming S, Varghese A, editors. Organization and management of IVF units. A practical guide for the clinician. New York: Springer; 2016. p. 3e25. https://doi.org/10.1007/978-3-319-29373-8.

[7] Mortimer ST, Mortimer D. Quality and risk management in the IVF laboratory. 2nd ed. Cambridge, UK: Cambridge University Press; 2015.

[8] Palmer GA, Kratka C, Szvetecz S, Fiser G, Fiser S, Sanders C, Tomkin G, Szvetecz MA, Cohen J. Comparison of 36 assisted reproduction laboratories monitoring environmental conditions and instrument parameters using the same quality-control application. Reprod Biomed Online 2019;39(1):63e74.

[9] Cohen J, Alikani M, Gilligan A, Schimmel T. Setting up an ART unit: planning, design, and construction. In: Nagy Z, Varghese A, Agarwal A, editors. In vitro fertilization. Switzerland: Springer; 2019. p. 9e19.

[10] Cohen J, Alikani M, Gilligan A, Schimmel T. New guidelines for setting up an assisted reproductive technology laboratory. In: Gardner DK, Weismann A, Howles CM, Schoam Z, editors. Text- book of assisted reproductive techniques. 5th ed. Boca Raton: Imprint CRC Press, Taylor & Francis Group; 2017. p. 1e9. https://doi.org/10.1201/9781351228237.

[1] Pool TB, Schoolfield J, Han D. Human embryo culture media comparisons. In: Smith GD, Swain JE, Pool TB, editors. Embryo culture: methods and protocols. New York: Humana Press; 2012. p. 367e86.

[2] Shapiro H, Zaman L, Kennedy VL, Dean N, Yudin MH, Loutfy M. Managing and preventing blood-borne viral infection transmis- sion in assisted reproduction: a Canadian Fertility and Andrology Society clinical practice guideline. Reprod Biomed Online 2020; 41(2):203e16.

[3] Hreinsson J, Iwarsson E, Hanson C, Grøndahl ML, Løssl K, Hyde´n-Granskog C, Ingerslev HJ, PGTstudy group. Preimplanta- tion genetic testing practices in the Nordic countries. Acta Obstet Gynecol Scand 2020;99(6):707e15.

[4] Campos ALM, Fujihara LS, Oliveira TV. Laborato´rio de fertiliza-c¸a˜o in vitro (FIV): estruturac¸a˜o, materiais, manutenc¸a˜o e equipamentos. In: Azambuja R, et al., editors. Reproduc¸a˜o Assis- tida: Te´cnicas de Laborato´rio. 1◦ edic¸a˜o. Porto Alegre: AGE; 2017. p. 269e82.

Chapter 4

Workup of female infertility

The inability to conceive after either 12 or 6 months is referred to as infertility, depending on the woman's age and the length of unprotected sexual activity [1]. Up to 15% of couples trying for children experience infertility [2]; pathologies may be present in 30% of these circumstances. Using an efficient and scientific diagnostic approach is highly recommended in infertility cases to increase the likelihood of identifying an underlying condition. In order to prevent this, a comprehensive gynecological exam is necessary, and it is essential to pay close attention to any potential cues in the woman and her partner. While building their methodology around the fundamental test objectives, test questions, and examinations, technical approaches prioritize empathy [3,4]. The various forms of female infertility will be covered in this chapter. We'll focus on the test's useful features, like techniques for detecting infertility. For a thorough explanation of the diagnosis of male infertility, please refer to the pertinent chapter in this book. The infertility interview affects the evaluation's objectives and timing. During the "first infertility interview," which primarily concentrates on gathering anamnestic data and making exam recommendations, the couple will have the chance to go to an IVF clinic for the first time. The primary objective of the second access, also referred to as the "secondary interview" or "decision interview," is to determine

the recommended course of treatment. ". ". ". A second or third interview may be required if the first round of infertility treatment is unsuccessful. The medical interview should adhere to the steps listed below, according to our research.

1) It should be possible to locate a gynecologist with extensive experience in identifying and treating infertility. To reduce "white coat stress" for the couple entering the interview room, additional medical staff members such as residents or fellows should only occasionally be present when tutoring.

2) Only when absolutely necessary should a nurse or midwife be present during an echography or gynecological visit.

Reduced anxiety and other psychological issues that might make it difficult for women to respond to questions should be the main goal. Keep in mind that discussing infertility exposes the couple's most intimate interactions.

4) A welcoming and knowledgeable atmosphere is necessary for the interview. The ultrasound machine and gynecological table should have a curtain drawn over them. Keep any extra items hidden if you can. Gynecologists and their patients should make open, unrestricted eye contact (i. e.

5) At some point, you ought to be able to buy necessities for stationery like paper and stamps. The desk, however, must be as spotless as is physically possible.

Infertility clinics are required to provide mental health services because the WHO defines "health" as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.". ". ". ". ". ". ". When making recommendations, fertility specialists are urged by the European Society of Human Reproduction and Embriology (ESHRE) to consider the psychological effects of infertility [3]. There are difficulties with conception's unpredictability and a diagnosis and treatment process that typically takes time for those who are particularly infertile [6]. Throughout the therapy process, decisions need to be made with the input of both partners. The medical staff can reduce wait times by offering infertility counseling or psychotherapy before, during, and after IVF treatment. When providing information, you must be very exact. When discussing treatments or informed consent, for example, use simple language.

The anamnestic record and the suggested exam were the main topics of the initial interview. Each suggested test must address the issue of infertility, and the results must either support a diagnosis or change the recommended course of treatment.

Each and every trustworthy anamnestic record must include this information. The minimum requirements are age and marital status.

2) A gynecological anamnesis to determine whether pain is present, persistent, frequent, and severe. its power. The menstrual cycle should be taken into

account when conducting an evaluation. Additionally considered are previous pregnancies and miscarriages.). Any prior assisted reproductive technology (ART) treatment needs to take hormonal treatments into account more fully. A fertility specialist should take into account the patient's sexual history, coitus frequency and timing, potential sexual dysfunction, endometriosis, leiomyomas, and STDs in addition to checking for these conditions.

The focus of a well-known anamnesis should be on psychiatric disorders, cardiovascular pathologies, genetic diseases, and oncological diseases. Get to know your female relatives who have dealt with infertility and the challenges they faced, as well as the outcomes. The risk of cardiovascular disease must be considered when treating inherited thromboembolic disease [9]. Oncologic conditions and genetic mutations like BRCA1 may be related either causally or by coincidence. Women who have pathogenic BRCA gene mutations lose their ovarian reserves more frequently after chemotherapy. e. e. e. e. Hardware examples include computers, printers, and other appliances.).

According to recent research [10], inadequate DNA repair may have an impact on the mechanisms underlying aging, cancer, and infertility. As a result, they should be carefully assessed before being administered. It is crucial to thoroughly examine genetic disorders that are congenitally transmissible before starting ART. Mental or psychiatric disorders could be affected by hereditary factors, such as the FMR1 mutation that causes fragile X mental

retardation. It is possible that triplet expansion of the FMR1 gene and POI, a condition that can cause mental retardation in both sexes when triplet expansion of the FMR1 gene occurs, are related.

1) Personal anamnesis: Details about a person's chronic pathologies, previous hospitalizations, serious illnesses or injuries, prior surgery (especially if it was done on the abdomen and pelvis), actual therapies, potential allergies, and physiological lifestyle should be retrieved. Consider hormonal therapies if you're treating the patient's allergies. Before deciding whether to use alcohol or nicotine, it is a good idea to do some research. Any environmental risks connected to the person's line of work should be taken into account. After the initial interview, there may or may not be a physical examination that includes a gynecologic examination. If the gynecologic exam is taken into consideration, delaying the ovarian reserve assessment may be preferable in some circumstances. A fertility specialist should decide the best time based on the amenities the IVF facility offers.

Testing is required.

Two different types of tests were required of you.

1) the results of diagnostic procedures like imaging and laboratory examinations.

In accordance with the specific goals of the question, both first- and second-line evaluations of fertility are provided.

Only an ovarian reserve test is capable of determining a woman's fertility [15]. How many ovarian oocytes are present before follicle development can be determined using this test. It is possible to forecast how well-timed ovarian stimulation will function by reducing ovarian reserve for ART. Along with measuring serum hormone levels, this exam also uses transvaginal ultrasound echography.

The second to fifth day following the start of menstruation must be used to complete the serum hormone assessment. The following are requirements.

a. This substance is referred to as "anti-Mullerrian hormone.". ". ".

The serum AMH concentrations have the biggest an impact on the ovarian follicle reserve. AMH is typically produced by the granulosa cells of the antral follicles, and its blood concentration is typically constant throughout the menstrual cycle. Now, administering it whenever you want is simple [16]. More specifically, it gets worse as a woman ages and changes throughout her lifetime. When using a conversion factor of 7.14, both pmol/L and ng/mL are acceptable units of measurement. Use the 7.14 formula to convert a value from pmol/L to ng/mL or vice versa. It is advised that at least one AMH value have been seen in the previous 12 months for women who are under or over 35. The AMH value needs to be assessed by a certified lab before choosing a potential infertility treatment.

b. FSH is the name of the folic acid-stimulating hormone.

c. E2 is the name of an estrogen subtype.

FSH, the second-most significant hormone, is detected through serum testing. To calculate the reserve of ovarian follicles, a prior hormone that wasn't present with AMH was necessary. It is therefore limited to screening tests for counseling [17]. It cannot, however, predict a poor ovarian response until very high threshold levels. It is currently specifically associated with E2 because of a negative reaction. In order to prevent the hypophysis inhibitor from unintentionally lowering the FSH value, the baseline E2 concentrations must be less than 60e80 pg/mL. This E2 value must be hormonally evaluated between the second and fifth day post-menstruation [2].

a. The term "luteinizing hormone" is denoted by the letters LH and the number 1.

On the first and fifth day after ovulation, exact measurements of LH levels are taken. Its application could be beneficial in the next two scenarios.

In this situation, it may be possible to see an inversion, which could help with PCOS diagnosis.

The FSH/LH ratio Poretsky [18] calculated is shockingly low, being less than 1. PCOS was unknown before this finding. Research [19,20] has shown that PCOS must be properly managed because it reduces fertility.

It is crucial to check the hypophysis to see if another LH deficiency also exists if both an LH and an FSH deficiency have been identified. The importance of

a GnRH test cannot be emphasized enough. In the absence of a positive test result, hypogonadotropic-hypopituitarism is the diagnosis.

If a pathology is suspected of being the cause of the infertility, a second-line hormonal assessment ought to be requested. This means that they shouldn't come first in an infertility interview.

b. One of its additional names is TSH, which stands for thyroid-stimulating hormone.

Depending on the circumstance, hypothyroidism or hyperprolactinemia may be the cause of ovulatory dysfunction. A few symptoms and signs of the condition include amenorrhea, oligo-ovulating, and a lack of luteal support. Serum thyrotropin (TSH) levels should be checked in females with thyroid disease, infertility, or dysfunctional ovulation symptoms in order to rule out dysthyroidism [21]. In most cases, the preferred range is between 2 and 0 mU/L [22]. You must give more levothyroxine if the numbers are higher.

c. Prolactin is also known by the acronym PRL.

It is advised, however, that infertile women with irregular periods, galactorrhea, a pituitary tumor, or other symptoms related to hyperprolactinemia have their PRL assessed. For any issues relating to hypopituitarism, the PRL is routinely assessed. Any punctual value greater than or equal to 25 ng/mL should warrant close attention. The recommended initial PRL dosage is three points. This particular cannula insertion allows the

collection of three samples at time intervals of 0, 200 and 400. According to this experiment, stress has no impact on the PRL value. A three-point PRL dosage that confirms the PRL value is higher than the threshold is advised in order to perform a cerebral magnetic resonance scan to look for any potential adenoma that may be affecting the hypophysis [23,24].

Using ultrasound technology, the reserve ovarian follicle count must be performed precisely. Using it between the first and fifth days of the menstrual cycle yields the best results, though it can be used at any time. In order to give a bleeding woman the greatest possible level of comfort, transvaginal ultrasounds are frequently carried out. It would be best to use practical, water-resistant drapes. The following conditions are primarily screened for during an ultrasound examination. Women-specific factors such as height, weight, body mass index, blood pressure, and heart rate must be covered during the initial interview. Hirsutism is the second, more severe symptom of androgen excess after acne. The person's weight must be taken into account. Obesity has been proven to negatively impact the mother, developing fetus, and female fertility [11]. As soon as a couple walks into an IVF clinic, it is crucial to notice and address any increase in male weight. However, hypogonadotropic hypogonadism may be supported by an eating disorder. Calorie restriction, significant weight loss, and primary or secondary amenorrhea are all indications of anorexia nervosa. Menstrual disorders are under the control of

the hypothalamic-pituitary-gonadal axis, which is dysfunctional in anorexics [12,13]. Treatment ought to concentrate on other pathologies (such as vulvodynia and dyspareunia, which can both have an adverse effect on a woman's sexual health and are connected to one another). g. g. Always when endometriosis is an issue) [14]. Equally important factors in determining the nodules, masses, and tenderness of the adnexa are the uterus' size, shape, location, and mobility. Any irregularities, secretions, or discharge involving the vagina or the cervical area must be taken into account and handled properly [4].

a. Both uterine and endometrial thickness must be measured. Myomas should be examined and measured because they might be larger than anticipated. To ascertain whether a myoma is present in the endometrial cavity, a secondary line or 3D ultrasound is required. Polyps should always be taken seriously, whether they are on the cervix or in the uterus. In a healthy uterus, unexpected patterns frequently surface. Numerous factors can lead to adenomyosis.

b. In order to determine whether the ovaries are normal, retrouterine, or above the uterus, it is imperative to evaluate their size, depth, and location. The need to increase ovarian reserve is the most pressing issue. Additionally, in 5 preantral follicles, the ovarian response is unexpectedly average or weak when AMH >1 point 2 ng/mL is present. these people.

perhaps further divided into:.

a. Only up to four oocytes could be successfully retrieved by subgroup 1a patients.

b. Then, four to nine oocytes were removed during a typical controlled ovarian stimulation (COS) procedure on the patients in subgroup 1b.

II. The AFCs of more than 35 patients in Group 2 are satisfactory.

Unexpectedly weak or negligible ovarian response, AMH >1 ng/mL, and >5. These people.

maybe further broken down into:

a. In patients in subgroup 2a, the oocyte retrieval rate was below four.

b. Four to nine retrieved oocytes were administered to subgroup 2b patients who received standard ovarian stimulation.

III. Patients in Group 3 (AFC 3) are older and have inferior ORT.

According to [28], the main objective of this new classification is to individualize COS. The COS proposal requires that a patient be categorized into one of these groups by an infertility specialist. There will likely be a benefit of experience in the form of an increase in ART efficacy when the POR classification is combined with other patient characteristics. If a woman experiences unexplained ovarian insufficiency or failure, an elevated FSH level, or both before the age of 40, it is advised that she undergo fragile X carrier screening to test for a FMR1 premutation [29]. An occurrence known as anovulatory failure raises the possibility of infertility. Even though serum

evaluations and analyses are required, amenorrhea may be a symptom of this condition [30]. Measuring midluteal progesterone (P4) and LH serum will reveal the precise time of ovulation. The biphasic cervical mucus variations and baseline body temperatures are unreliable indicators. P4 levels are measured during the luteal phase to determine whether ovulation has taken place and whether the corpus luteum progesterone supplement is sufficient to support pregnancy. Progesterone levels over 3 ng/mL can be used to determine ovulation [31]. The P4 assessment should be postponed if a woman's cycle lasts more than 28 days, and she should retake it once per week until the serum peak is found. Lack of progesterone prevents the luteal phase (LPD) of the endometrium from secreting normally, which prevents the endometrium from allowing an embryo to implant [32]. One might be on the lookout for this condition if the luteal phase begins less than nine days after ovulation, which is abnormal. If you start spotting a few days prior to your period, you should also take LPD into account [33]. Uncertainty surrounds the LPD diagnosis today. It is well known that the substantial serum fluctuation that takes place during the midluteal phase makes precise progesterone measurement difficult [34]. The histologic changes in the secretive endometrium cannot be detected by endometrial biopsy [32]. Genetic tests that are thorough and precise are now accessible [35]. A LH test can be used to pinpoint the exact time of ovulation. Because of its short half-life, the LH surge can be challenging to detect, but its

direction can be established. To pinpoint the precise time and location of ovulation, this knowledge could be used in the P4 evaluation [36]. Recent SARS CoV-2 outbreaks necessitate the use of phone calls and video consultations, despite the preference for in-person interviews [7,8]. Because of the advantages they offer and the popularity they enjoy among patients, couples should be suggested to each of them.

On whether or not she conceives, her coagulation has a major influence. When determining whether estro-progestin therapy is safe to administer while receiving COS therapy, it can be used to determine whether anticoagulation is required. The following fundamental tests should be carried out, in particular:. Blood platelets are inspected throughout this process.

Only PT and INR serve as examples of b).

The term "activated partial thromboplastin time" would be more accurate.

Another name for the AT III protein is antithrombin III protein.

Discussions are had regarding the MTHFR enzyme, factor II, and the Leiden V factor.

The flowchart below shows the steps you should take to request the additional tests so you can determine whether you're infertile:.

1) During each initial interview, the primary illness should be established as cystic fibrosis. If the gene analyses of both partners are normal, no further study is required. If one of the partners has changed, though (for instance, g. g.

g. g. g. supporting information (e.g. g. The DeltaF 508. The geneticist will discuss any risks related to conceiving a child who has cystic fibrosis or a specific mutation linked to the condition.

2) Karyotype: It is suggested that this test be used as the initial assessment when IVF therapy is required. Karyotype analysis is not required for intrauterine inseminations (IUIs).

The karyotypes 46XX and 26XY are the most prevalent. After the discovery of aneuploidies, infertility could develop. The couples should be informed that a genetic interview is necessary in order for them to fully defend themselves. Couples should be aware of the dangers because some mutations, particularly those that have been identified, can be passed on to the next generation.

Genetic testing might also be necessary before implant implantation in cases where IVF/ICSI cycles cause karyotype aneuploidy. The benefits and drawbacks of this technology should be fully explained to couples. Not all couples will benefit from therapy, despite its importance [39].

The hemoglobin profile test, despite not being a genetic test in the conventional sense, can still diagnose a patient because it is connected to a change in the hemoglobin genes. At this time, there are no first-line treatments for the hemoglobin profile test. For the test to be able to detect potential changes in hemoglobin, a blood count with an average red cell corpuscular volume is

necessary. To ensure safety, at least one of the two partners must be prescribed the hemoglobin profile. Thalassemia needs to be handled carefully.

When recommending a procedure for assisted reproduction, a fertility expert asserts that it is crucial to carefully consider any genetic changes. It is essential to contact a geneticist right away.

Each couple should be aware of the advantages of getting a serologic panel before going to an IVF clinic. The major viral families on which in-depth research has been focused are listed below.

•HIV.

The acronym for the hepatitis B virus is HBV.

Hepatitis C virus, also known as HCV.

•syphilis.

Negative serologic test results shouldn't cause women to postpone receiving their rubeovirus vaccination. Wait 28 days after receiving the final dose of the vaccine before attempting to become pregnant. If the patient's serologic panel is positive, the best course of action should generally be discussed with an infectious disease specialist.

A sonohysterosalpingography (SHSG) should be used to inspect each woman's fallopian tubes. This evaluation is required to decide whether intrauterine inseminations can be suggested for a young woman with a healthy ovarian reserve and a partner who is normozoospermic [40]. If the SHSG test is

negative, the underlying reason for tubal infertility can be discovered. However, an explicit tubal occlusion must be considered during IUI [41]. When determining whether an SHSG is advantageous in an IVF facility, an infertility specialist advises also taking this into account. A 40-year-old woman with a low ovarian follicle reserve is exempt from SHSG testing because she has the best chance of becoming pregnant through an IVF/ICSI cycle. This is significant because it allows for the precise determination of the ideal SHSG weight for each woman.

In addition, if a comorbidity (such as an illness, e.

If uterine morphology (e.g., abnormality) is present, g. , a uterine polyp) is either unidentified or not thought to exist (e. g. g. g. g. Obtain a 3-dimensional transvaginal ultrasound (e. g. a uterine polyp, as an example). g. g. Didelfus, septate, and T-shaped uteri are a few of the recognized uterine shapes.). A 3D ultrasound can be used to both confirm the existence of suspected polyps or myomas and to ascertain whether they have protruded into the endometrial cavity. Finding a 3D ultrasound can be challenging, especially in developing countries. As a result, it's possible that the test won't be performed during a diagnostic hysteroscopy [42]. Women who are having trouble getting pregnant frequently receive orders for hysteroscopy (HSC). The main diagnostic tool, however, shouldn't be an HSC. usually advised in cases where a condition that may affect fertility is present. HSC assumes even more significance in the

event that endometrial cavity-blocking myomas are detected during an ultrasound screening. A diagnostic HSC can be used to gauge the extent of the myoma's cavity invasion. It is frequently recommended to perform a surgical HSC in order to remove it and restore the appropriate cavity. For diagnostic purposes, an HSC must confirm a transvaginal polyp discovered by ultrasound. Following that, a functional HSC is used to treat the polyp (Salazar [43]).

The shape of the uterus, such as whether it is septate, didelfus, or bicornual, can also be identified using an HSC if morphologic anomalies are found during an ultrasound. An earlier ultrasound and an HSC can be used to tell a septate uterus apart from an arcuate uterus [42]. Additionally, a HSC can help in the detection of chronic endometritis (CE), which has just recently been linked to a higher risk of unsuccessful embryo implantation [7,8]. In this case, the infertility specialist must look for the HSC markers micropolyps and red spots. Despite not being diagnostic tools, these markers can help with the diagnosis. To verify it, an endometrial biopsy is required. Due to their rarity and importance for the diagnosis of CE, the histologic examination will specifically look for CD 138 plasma cells. If CE is found, a fresh endometrial biopsy must be performed before determining whether the patient requires the appropriate antibiotic therapy [44]. Exams for PAP or HPV. g. e. when specific conditions (e. g. g. pelvic inflammatory disease, endometriosis, and an earlier extrauterine

pregnancy.). Using laparoscopy or salpingocromoscopy, pelvic conditions and tubal patency can be assessed.

It must be done during the initial interview to administer the PAP test, an HPV-DNA test, or both. The majority of medical experts concur that a test that was recently completed—within 1 to 5 years, or sooner if a person's condition requires it—is reliable. A more thorough follow-up is required when dealing with L- or H-SIL.

Ultrasounds and breast imaging are frequently unnecessary. But if the patient's or a family member's anamnestic history raises concerns about a breast tumor, this should be taken into account. If a radiology specialist doesn't specifically request something different, validation should be limited to 1.5 years. The need for (and usual recommendation for) a needle biopsy arises when a nodule is discovered but no definitive diagnosis or oncologic ruling has been made.

Prior to the second interview, each test must be completed and administered according to the instructions provided during the first interview. In this chapter, the ideal time period for a 28-day menstrual cycle with a 5-day blood loss is discussed.

1) The ovarian follicle reserve is used from the first to the fifth day, according to antral follicular count and hormone analysis using transvaginal ultrasound.

2) A hysteroscopy, which also involves taking an endometrial biopsy, is carried out between days 6 and 12 to assess CE and SHSG. Concurrent PAP testing

can be done easily. Breast imaging is only permitted in a predetermined number of group exams.

1) Begin monitoring serum P4 on day 21 to confirm an accurate and spontaneous ovulation. An increase in serum blood progesterone levels, which is thought to typically occur during the luteal phase, is another sign of insufficient luteal support.

Each additional test's results, including those from imaging and blood work, are evaluated impartially. You can save time and ensure that they all start at the same time by carefully scheduling your exams. The goal of the second interview is to confirm the findings of each test the couple underwent for the first interview and to determine the best course of action for managing infertility. There could be a number of contributing factors, and each one might call for a different strategy. The fertility specialist stresses the value of allowing the couple enough time to talk about the suggested assisted reproductive method. It is imperative that the next action plan be completed as soon as possible.

The tests need to be reviewed by the couple first. Be open to new concepts at all times. The couple's clinical condition must be carefully taken into account because new exams take time.

2) The treatment plan must be fully explained, and every query must receive a satisfactory response.

(3) The couple's free and informed consent is required prior to the start of treatment. Similar reasoning should be used when developing a treatment plan. The consultation should have included a thorough discussion of the couple's treatment plan and the next steps.

If a treatment is ineffective, a second interview is frequently conducted. One can create a completely new strategy by focusing on the prior failure. The odds of success and any possible risks should be fully disclosed to the couple. Spend some time concentrating on the new approach while responding to the couple's queries.

In spite of this, identifying female infertility can be difficult.

Gynecologists should make an effort to describe the diagnostic process and define the frequently ambiguous causes as they navigate this difficult path. It is critical to take into account both the risks posed by anatomical, endocrinological, infectious, and environmental risks as well as any potential psychological side effects of different issues. Before being recognized as infertility experts, gynecologists must complete extensive, practical training. Infertility diagnosis techniques and tests are briefly covered in this chapter. It's important to keep in mind that the couple's infertility may not have an official diagnosis in 30% of cases. The infertility assessment, which offers a framework before beginning ART therapy, is another essential element in these circumstances. Delivering more specialized and individualized medical care is

the main objective of the new clinical practice era, which is covered by this feature. Genetic testing is necessary to determine whether one of the partners is a mutation carrier. Children usually don't have many issues when one parent is ill and the other is healthy.

References

[1] Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2013;99(1):63. https://doi.org/ 10.1016/j.fertnstert.2012.09.023. Epub 2012 Oct 22. PMID: 23095139.

[2] Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a commit- tee opinion. Fertil Steril 2015;103(6):e44e50. https://doi.org/ 10.1016/j.fertnstert.2015.03.019. Epub 2015 Apr 30. PMID: 25936238.

[3] Gameiro S, Boivin J, Dancet E, de Klerk C, Emery M, Lewis- Jones C, Thorn P, Van den Broeck U, Venetis C, Verhaak CM, Wischmann T, Vermeulen N. ESHRE guideline: routine psychoso- cial care in infertility and medically assisted reproduction-a guide for fertility staff. Hum Reprod 2015;30(11):2476e85. https:// doi.org/10.1093/humrep/dev177. Epub 2015 Sep 7. PMID: 26345684.

[4] Infertility workup for the women's health specialist: ACOG committee opinion, number 781. Obstet Gynecol 2019;133(6):e377e84. https://doi.org/10.1097/AOG.0000000000003271. PMID: 31135764.

[5] World Health Organization. Basic documents (Constitution of the World Health Organization). 46th ed. 2007.

[6] Klonoff-Cohen H, Natarajan L, Klonoff E. Validation of a new scale for measuring concerns of women undergoing assisted reproductive technologies (CART). J Health Psychol 2007;12(2): 352e6. https://doi.org/10.1177/1359105307074282. PMID: 1728 4498.

[7] Buzzaccarini G, et al. A single Italian medically assisted reproduction center organization: efficacy and optimization during the COVID-19 pandemic. Fertility and sterility dialog. May 6, 2020. Available from: https://www.fertstertdialog.com/users/16110-fertility-and-sterility /posts/a-single-italian-medically-assisted-reproduction-center-orga nization-efficacy-and-optimization-during-the-covid-19-pandemic.

[8] Buzzaccarini G, Vitagliano A, Andrisani A, Santarsiero CM, Cicinelli R, Nardelli C, Ambrosini G, Cicinelli E. Chronic endome- tritis and altered embryo implantation: a unified pathophysiolog- ical theory from a literature systematic review. J Assist Reprod

[9] Kuperman A, Di Micco P, Brenner B. Fertility, infertility and thrombophilia. Womens Health 2011;7(5):545e53. https:// doi.org/10.2217/whe.11.61. PMID: 21879823.

[10] Oktay KH, Bedoschi G, Goldfarb SB, Taylan E, Titus S, Palomaki GE, Cigler T, Robson M, Dickler MN. Increased chemo- therapy-induced ovarian reserve loss in women with germline BRCA mutations due to oocyte deoxyribonucleic acid double strand break repair deficiency. Fertil Steril 2020;113(6). https:// doi.org/10.1016/j.fertnstert.2020.01.033. 1251-1260.e1. Epub 2020 Apr 22. PMID: 32331767; PMCID: PMC7339936.

[11] Broughton DE, Moley KH. Obesity and female infertility: poten- tial mediators of obesity's impact. Fertil Steril 2017;107(4): 840e847. https://doi.org/10.1016/j.fertnstert.2017.01.017. Epub 2017 Mar 11. PMID: 28292619.

[12] Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode´ C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadismepathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2015;11(9):547e64. https://doi.org/10.1038/nrendo. 2015.112. Epub 2015 Jul 21. PMID: 26194704.

[13] Mun˜oz MT, Argente J. Anorexia nervosa: hypogonadotrophic hypogonadism and bone mineral density. Horm Res 2002; 57(Suppl. 2):57e62. https://doi.org/10.1159/000063953. PMID: 12065929.

[14] Lagana` AS, La Rosa VL, Rapisarda AMC, Valenti G, Sapia F, Chiofalo B, Rossetti D, Ban Frangez˘ H, Vrta˘cnik Bokal E, Vitale SG. Anxiety and depression in patients with endometriosis: impact and management challenges. Int J Womens Health 2017;9: 323e30. https://doi.org/10.2147/IJWH.S119729. PMID: 28553145; PMCID: PMC5440042.

[15] Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril 2015;103(3):e9e17. https:// doi.org/10.1016/j.fertnstert.2014.12.093. Epub 2015 Jan 10. PMID: 25585505.

[16] La Marca A, Stabile G, Artenisio AC, Volpe A. Serum anti-Mulle- rian hormone throughout the human menstrual cycle. Hum Reprod 2006;21(12):3103e7. https://doi.org/10.1093/humrep/ del291. Epub 2006 Aug 21. PMID: 16923748.

[17] Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006;12(6):685e718. https:// doi.org/10.1093/humupd/dml034. Epub 2006 Aug 4. PMID: 16891297.

[18] Poretsky L., Piper B. Insulin resistance, hypersecretion of LH, and a dual-defect hypothesis for the pathogenesis of polycystic ovary syndrome. Obstet Gynecol 1994;84(4):613e621. PMID: 8090402.

[19] Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: a review. J Assist Reprod Genet 2017;34(2): 167e77. https://doi.org/10.1007/s10815-016-0836-8. Epub 2016 Nov 5. PMID: 27817040; PMCID: PMC5306404.

[20] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ, International PCOS Network. Recommen- dations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110(3):364e79. https://doi.org/10.1016/j.fertn- stert.2018.05.004. Epub 2018 Jul 19. PMID: 30033227; PMCID: PMC6939856.

[21] Venables A, Wong W, Way M, Homer HA. Thyroid autoimmunity and IVF/ICSI outcomes in euthyroid women: a systematic review and meta-analysis. Reprod Biol Endocrinol 2020;18(1):120. https://doi.org/10.1186/s12958-020-00671-3. PMID: 33239046; PMCID: PMC7687721.

[1] Orouji Jokar T, Fourman LT, Lee H, Mentzinger K, Fazeli PK. Higher TSH levels within the normal range are associated with unexplained infertility.

J Clin Endocrinol Metab 2018;103(2): 632e9. https://doi.org/10.1210/jc.2017-02120. PMID: 29272395; PMCID: PMC5800836.

[2] Hu Y, Ding Y, Yang M, Xiang Z. Serum prolactin levels across pregnancy and the establishment of reference intervals. Clin Chem Lab Med 2018;56(5):838e42. https://doi.org/10.1515/ cclm-2017-0644. PMID: 29194037.

[3] Chahal J, Schlechte J. Hyperprolactinemia Pituitary 2008;11(2): 141e6. https://doi.org/10.1007/s11102-008-0107-5. PMID: 18404389.

[4] Broer SL, Do´lleman M, van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PM, Eijkemans MJ, Mol BW, Broekmans FJ, IPD-EXPORT Study Group. Prediction of an excessive response in in vitro fertil- ization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta- analysis. Fertil Steril 2013;100(2). https://doi.org/10.1016/j.fertn- stert.2013.04.024. 420e429.e7. Epub 2013 May 28. PMID: 23721718.

Chapter 5

Work-up of male infertility

Even after regularly having unprotected sex without any interruption for at least a year, infertile couples still have difficulty getting pregnant [1,2]. Infertility affects 8 to 12% of fertile individuals. Male factor infertility (MFI), which affects 50% of these cases, is a problem [2, 3]. Infertility prevalence increased steadily among both men and women, according to the Global Burden of Disease study from 1990 to 2017 [4]. Between men and women, there is currently a 0 point, or 37%, gender gap.

A couple's psychological and social wellbeing is negatively impacted by infertility, in addition to having a high financial cost for patients and healthcare systems [5, 6]. As a result, for the best clinical and social outcomes, an early diagnosis and the appropriate course of treatment are essential. Compared to their fertile age-matched counterparts, infertile men have worse overall health and a higher risk of cancer and cardiovascular disease, according to MFI, a reliable indicator of men's general health [7,8,9]. Today, it is possible to identify and treat two medical conditions: infertility, as well as general health and wellbeing. This also enables precise estimation of male fertility potential and early identification of male infertility.

Three factors: inherited (e. g. g. g. digestive issues as well as exposure to gonadotoxic substances. Conditions [10], [ii], and [iii] are examples of

idiopathic illnesses. A few instances include bilateral anorchia, the Robertsonian translocation, the absence of the vas deferens, the Kallmann syndrome, the Klinefelter syndrome, and cystic fibrosis. These signs and symptoms can be caused by a number of genetic diseases. To name a few of these diseases, generic endocrinopathies can present with a wide range of symptoms.). They function best in tandem. g. g. The thyroid and hypothyroid conditions are the congenital causes of MFI that are most frequently mentioned.

Thirty percent of couples experiencing infertility have idiopathic causes. Semen analysis may still reveal pathological findings even though these men underwent routine physical examinations in addition to the typical genetic, endocrine, and biochemical laboratory tests. These guys have never had issues with infertility. Idiopathic conditions are the actual cause of many risk factors for men's fertility that were once thought to be harmful [17,22,23,24]. A few risk factors for infertility and poorer sperm quality include mental stress, alcohol use, smoking, using recreational drugs, being obese, and being overweight [21,25,26,27]. As oxidative stress and sperm DNA fragmentation (SDF) are likely to be significantly impacted by these factors [28,29,30], this is probable. Unexplained male infertility, which is infertility with normal sperm parameters and partner evaluation but caused by an unidentified cause, is another issue that many couples deal with. 20–35 percent of infertile couples

struggle with marital problems [10]. Every male patient seeking medical assistance for infertility, according to World, must go through a thorough assessment that includes a review of his medical and reproductive history, a physical examination, and a semen analysis.

hormone evaluation, suggestions from the World Health Organization (WHO), and hormone evaluation. If you are able, broaden your research. g. Consider including more activities, for instance. g. g. Examples include imaging and genetic testing. possibly essential. g. 10.11. 12.13. 14.15. The numbers 16 and 17 are very important in the Prader-Willi syndrome. Without a doubt, a variety of interrelated, related factors have an impact on both acquired and idiopathic cases [10,17]. Varicocele is one of the causes and it affects 25 percent of all men, 40 percent of men who are infertile, and 80 percent of men who have abnormal semen parameters. Varicocele research suggests that dysregulated spermatogenesis could be brought on by the spermatic cord's inability to drain blood properly and exchange heat countercurrently. drug use, these diseases, testicular injury, torsion, and cancer. g. Chemotherapy is also brought up. comparable to many systemic diseases. g. I. It makes use of radiation. g. Diabetic kidney disease, diabetes, and cirrhosis of the liver) [10,11,21.

A complete medical history must be compiled before infertility can be evaluated. choosing the first (i. e. e. e. e. e. e. e. e. e. e. e. being incapable of having children in the future (i. e. e. , previously fertile, currently infertile)

should always be carried out [10]; despite the fact that treatment and diagnostic testing are frequently comparable between the two categories, there are some notable differences regarding the person's baseline health conditions (e. g. a functional family tree.

The partner's age and gynecological history, including her ovarian reserve, should be noted at the beginning of the infertile couple's evaluation as these elements may affect the timing of and the therapeutic strategies themselves (e. g. Technology for assisted reproduction, or ART. Surgery must be performed right away. Semen parameters, which are affected negatively by the length of infertility [32] and depend on the ages of both partners [10], call for immediate action. Men should also have their genitourinary (GU) systems checked for infections, diseases (such as tumors and cardiometabolic disorders), and a history of any kind of testicular surgery because these conditions could all affect a man's ability to conceive.

Any testicular damage, including that brought on by trauma, torsion, cryptorchidism, postpubertal measles, or other conditions, must be taken into consideration. Each of these issues has been shown to reduce the potency of sperm and the likelihood of conception. According to studies [33,34,35,36], children with undescended testes have lower sperm counts, sperm quality, and fertility rates. Also more likely to affect them is testicular cancer. The inability to conceive in both men and women has been linked to numerous GU

infections. Estimates [33] indicate that up to 35 percent of the general population may experience male GU infections. The findings of the following studies [29,37] showed that 20 percent of male infertiles who weren't aware they had a seminal infection actually did. Among the patient's many cardiometabolic disorders, diabetes is just one of them. g. In addition to the illnesses already mentioned, diabetes, obesity, the metabolic syndrome, insulin resistance, dyslipidemia, and other conditions are all directly attributed to low sperm quality [8,21,38,39,40,41,42]. Due to the fact that the peripheral aromatase enzyme converts testosterone to estrogen more frequently in this population, obese men are known to have higher peripheral estrogen levels. For better sperm quality, the hypothalamic-pituitary-gonad (HPG) axis must be in balance [16]. Infertile men have worse overall health (i. e. e. e. e. Co-morbidities are disproportionately common [8, 42]. The finding that patients with poor general health had lower testosterone levels, higher levels of the hormone follicle stimulating hormone (FSH), and lower sperm counts than counterparts who were fertile supports the idea that a dysfunctional male reproductive system may be connected to poor general health [8]. Consideration should be given to a person's lifestyle choices, including whether or not they drink, smoke, or use recreational drugs. According to a notable meta-analysis [43] that included 20 studies and 5865 patients, smoking allegedly made semen parameters worse. It was found by a subsequent meta-

analysis of 15 studies [27] that there was sporadic correlation between alcohol consumption and sperm analysis. Smoking and drinking have been shown to have a negative impact on sperm parameters [44]. Men who use recreational drugs have a harder time conceiving, according to research. Sperm function is influenced by spermatogenesis, the HPG axis, and cannabis, the most popular recreational drug [45,46].

There is evidence that spermatogenesis can be stopped by a number of frequently prescribed drugs. Antipsychotics, endocrine modulators, antihypertensives, and antibiotics have all been connected to improved sperm quality when used less frequently [16,46,47]. A man's testicles may sustain permanent harm if he receives chemotherapy, radiation therapy, or both [48,49,50]. Therefore, cryopreservation is advised before beginning any oncologic therapy in all urological guidelines [10,51,52].

Any previous vasectomies, vasectomies reversed, orchiectomies, retroperitoneal or pelvic surgeries, and prostatic/bladder neck procedures should be routinely reviewed in infertile men [11]. This is because the sperm quality and fertility may be negatively impacted by these procedures. With regard to hereditary disorders, family history is crucial. One of them is Cystic Fibrosis (CF), a widespread genetic disorder associated with MFI. Serious systemic conditions like inflammation, gastrointestinal changes, recurrent lung infections, and pancreatic insufficiency can affect CF patients.

Men who have mutations in the CF transmembrane conductance regulator (CFTR) gene experience male fibroid syndrome (MFS). The impaired semen in these men could only be explained by gene mutations and not by the clinical symptoms of CF [55]. One of the most perplexing aspects of the wide range of genital phenotypes in clinically affected CF patients is the absence of congenital vas deferens and severely impaired spermatogenesis, which can range from normal fertility to severe impairment. One common genetic modification in male infertility is microdeletions on the Y chromosome. Even though they exhibit a typical clinical phenotype, these men typically have a much lower likelihood of becoming pregnant [56,57]. The couple's sexual activity, the time of coitus, and a man's sperm count and erection are just a few of the significant factors that must be considered. One in six non-fertile men experience erectile dysfunction (ED), early ejaculation, or low/reduced sexual desire (LSD) [58].

Your chances of fertilization during the ovulatory cycle can be increased by engaging in sexual activity every 48 hours [59]. It has been shown that doing so makes it more difficult for the couple to start and keep a healthy relationship, and it causes psychological distress for both partners. The sexual histories of these relationships are therefore extensively discussed in [58].

You should carefully read the following list, paying close attention to items 10 and 11.

General. Skin discoloration could be a sign of a metabolic condition. Despite occasionally being connected to iron overload syndromes, diffuse, patchy hyperpigmentation is a well-known side effect of these conditions that can also cause infertility. The moon-shaped face, thin skin, purple striae, and ecchymoses are additional Cushing syndrome symptoms. Among other symptoms, low testosterone can cause oily skin and pubic or axillary hair loss. The absence of facial and body hair, wide hips, tall stature, and long hands are what distinguish Klinefelter syndrome.

Penis. To check for signs of STDs, phimosis, short frenulum, nodules, ulcerations, scars, and nodules, the foreskin must be retracted. The density and pattern of pubic hair greatly affect secondary sexual characteristics.

respectively, the testicles. The position, size, consistency, and makeup of the testes must all be taken into account. The quickest removal is recommended for any swelling or potential nodules. The Prader's orchidometer is used to gauge testicular volume in medical settings.

Epididymis. When compared to those of normal development, the shape and/or consistency can be used to determine whether atresia brought on by a CFTR mutation. It might be blocked, longer than usual, or neither. Spermatoceles and epididymal cysts are also two more potential issues. The cord carries pregnancy. Pampiniform plexuses can be visually inspected if they are substantial, palpable masses. To check for varicocele, perform the Valsalva

maneuver while still lying on your back. In clinical practice, there are two types of varicocele: subclinical and clinical. Subclinical varicocele cannot be felt or seen when lying still or when performing the Valsalva maneuver; only specialized tests, such as Doppler ultrasound [US], can identify them.

Grade 1 can be felt when performing the Valsalva maneuver, but Grade 2 can only be felt when at rest.

By third grade, they have become fixed, audible, and palpable. Congenital obstructive azoospermia, which renders CF men infertile 97–98 percent of the time, is in fact caused by bilateral vas deferens absence [53,54]. Medical professionals should look at the urethral meatus' aperture, position (epispadias or hypospadias), and any suggestive discharge. Having vaginal sex may be challenging if you suffer from plaque or penile curvature linked to La Peyronie disease.

Vas behaves honorably and with consideration. To rule out agenesis brought on by a CFTR mutation or abnormal Wolffian duct embryogenesis, look at the consistency and/or shape of normal development and contour. Granuloma defects and vasectomy are prohibited. technologically examining the rectus. To check for obstruction, a doctor may inspect midline prostatic cysts or growing seminal vesicles.

As part of the diagnostic process, a semen analysis should be performed on every infertile man or woman who asserts primary or secondary infertility. The

characteristics of the sperm can give the physician important information, such as whether or not additional diagnostic tests are required and how well the sperm is functioning generally. A woman's fertility cannot be accurately predicted using semen parameter values that are either above or below the lower limit. In the real world, only 41 percent of fertile men and 13 percent of infertile men, respectively, had normal sperm parameters, according to recent research. In these studies, the baseline characteristics and sperm of 1957 infertile men who were unable to conceive were compared to those of 103 age-matched fertile controls. Ejaculate analysis procedures are detailed in the sixth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen [64]. It is essential to follow the recommendations in Table 5point 2 in order to standardize all laboratory procedures in accordance with reference values. Couples dealing with unexplained male infertility, recurrent miscarriages following natural conception, or after ART may require men to undergo additional tests in addition to "pure" macroscopic semen analysis [65]. Due to the increased risk of sperm DNA damage, which can cause infertility in these patients, additional tests, such as the SDF index, may be helpful [10]. One test is adequate when semen analysis is normal, according to the most recent European Association of Urology (EAU) Guidelines on Sexual and Reproductive Health [10]. Three months after the initial test, a second semen analysis must be done in case the sperm were altered, which is highly unlikely.

If the results of at least two tests are anomalous, further andrological research should be conducted.

These categories [64] can be used to classify the various sperm modifications.

•oligozoospermia:.

Everywhere you look, you can see the genital system [77]. ICSI is still thought of as an experimental procedure despite clinical trials examining the viability of testicular sperm for ICSI in nonazoospermic men with elevated SDF. SDF testing is not advised for infertile men by medical professionals. According to the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) Guidelines [52], SDF is frequently disregarded during the initial evaluation of the infertile male.

Before figuring out the underlying cause of infertility and coming up with a treatment plan, it is imperative to take the patient's hormonal profile into consideration. International organizations warn against administering it to everyone, particularly men who may have endocrinopathy, oligozoospermia, azoospermia, or diminished sexual function. All infertile men have their hormone levels checked, even though this is a common practice among physicians.

Total testosterone and FSH are two important parts of the fundamental hormonal assessment. To differentiate between primary and secondary hypogonadism when there is low testosterone, an LH assay is required. A

second total testosterone test is necessary in this situation. Checking prolactin levels is recommended for men who have low libido or hypogonadotropic hypogonadism. 7 a. There's testosterone's place of birth. till 11 a. m. m. m. M. It is suggested that anyone who is fasting take it. Even though mass spectrometry remains the de facto industry standard for testosterone assays, the outcomes from superior immunoassays can still be used to make clinical diagnoses with great success [16]. The EAU and ASRM recommend values of less than 230 ng/dL (8 nmol/L) and less than 300 ng/dL for the diagnosis of low testosterone, respectively. Additionally, research on gynecomastia and breast discomfort in infertile men is required. The average testicular volume of infertile individuals, according to several studies [60,61], is 18.0 5 point0 mL, which is lower than the average testicular volume for all of Europe, which is 20.0 5 point0 mL. Despite the lack of valid comparison points, the testicular volume readings obtained by the Prader orchidometer are accurate. Testicular size and total testosterone levels were positively correlated in infertile men as well. Before it can be determined whether the infertile man has secondary sexual traits, a thorough physical examination is required. Infertility in romantic relationships is typically caused by male or female factors, a combination of both, or idiopathic infertility [10]. As a result, it becomes necessary to assess both partners at once. In this case, it is crucial that all infertile female partners receive care from specialists with specialized

gynecologic education and training, and that all infertile male partners receive a medical assessment from a doctor with experience in male reproduction.

People with high SHBGs, such as. g. g. Patients with thyroid disease, diabetes, and 80-year-old men) [79]. In this case, we respectfully request that you get a free testosterone reading.

Contrary to popular belief, FSH may be normal in some instances of spermatogenic arrest at the spermatocyte or spermatid level [83]. Combining FSH with spermatogenesis may be more advantageous in some situations.

Male hypogonadism is a problem that many infertile men face. Primary or hypergonadotropic hypogonadism, also known as hypogonadism for testicular failure, is characterized by low levels of total testosterone, LH, and FSH, all of which are below normal.

It is common clinical practice to analyze genomic DNA in peripheral blood samples. One such instance is the discovery of chromosomal variations. g. g. in relation to the structure. Take trisomy as an example.

Chromosome analysis, also known as kyatyping, is a method for detecting errors in the structural and numerical information stored in chromosomes. Usually, it is recommended for men to get a karyotype analysis if they have severe oligozoospermia or azoospermia (sperm count less than 1 million/mL) [52,92]. The EAU recommendations must now be followed by men with sperm counts below 10 million/mL, a family history of spontaneous abortions,

congenital malformations, or intellectual disabilities. The likelihood that genetic abnormalities will be passed on to the next generation is increased by high aneuploidy rates, spermatogenesis problems that result in oligozoospermia or azoospermia, structural chromosomal abnormalities, and DNA damage in the spermatozoa of infertile men [87]. Genetic mutations in embryos must be identified prior to performing ART for diagnostic and counseling purposes. Both ICSI failure and recurrent miscarriages have been linked to these mutations.

Despite sperm concentration, there are still disabilities [10]. Along with the 47,XXY syndrome (also known as the Klinefelter syndrome), translocations, inversions, and deletions are the three most prevalent karyotype defects [93]. Men with Klinefelter syndrome exhibit a specific phenotype that is influenced by biological, genetic, and aging-related factors [94]. Men with androgen deficiency stigmata and men who have undergone typical virilization have different phenotypes. Patients seeking treatment for infertility frequently describe symptoms of Kli- nefelter syndrome. Teenagers' serum testosterone levels fall and their testicular volume decreases as a result of the rapid loss of germ cells, hyalinization of the tubules, Sertoli cell degeneration, and Leydig cell hyperplasia [95]. The testosterone levels in the testicles then start to increase. Along with the main hypogonadistic symptoms, male adults with Klinefelter syndrome frequently have small, firm testicles. Men with Kline-

Felder syndrome are more likely than men in the general population to have both spermatogenic dysfunction and Leydig cell dysfunction, which increases the likelihood that these men will have low testosterone levels [15]. A man is more likely to have spermatogenic foci if he has Mosaicism, 46, XY/47, XXY, or Klinefelter. Testicular sperm extraction (TESE), which can recover spermatozoa in up to 50% of circumstances, may be advantageous for patients with azoospermia [96, 97]. There is currently no way to predict the viability of the sperm from this group of men using clinical, hormonal, or procedural factors [96,97].). g. against a flip, turn, etc.). Men with infertility had abnormalities on 15% of their autosomal and 42% of their sex chromosomes, respectively. These proportions have risen by 58% in comparison to men who are in good health. Patients with severe testicular hypoplasia frequently exhibit more chromosomal abnormalities. When sperm counts are less than 5 million/mL, people are ten times more likely to have autosomal structural abnormalities than the general population [89,90]. especially if they possess unusual sex chromosomes (e. g. Men with NOA have a higher risk (12–15%) compared to men without NOA. g. [91. The Cloth Illness. ". ". Clinicians who work with infertile couples need a thorough understanding of the most common genetic abnormalities linked to infertility in order to effectively counsel infertile couples looking for fertility treatment. Infertility affects about

15% of men, according to studies on the genes and gene mutations related to spermatogenesis [85, 86].

It's important to let men with Klinefelter syndrome who are undergoing fertility treatments know that their children might have genetic defects. In recent studies, the general population and Klinefelter syndrome patients receiving ICSI both had aneuploidy rates that were comparable.

By having their testicles removed, peri- or prepubertal boys with Klinefelter syndrome can produce cryopreserved testicular spermatogonial stem cells. This procedure should only be used in research settings because it is still considered experimental [98]. This also holds true for older boys who gather sperm without thinking about whether or not they will be able to have kids [99].

Men with Klinefelter syndrome are advised to receive the necessary medical follow-up because they are more likely than the general population to develop cancer, metabolic, cardiovascular, and venous thrombo-embolism conditions. A few examples of structural chromosomal abnormalities that increase the risk of aneuploidy or an unbalanced complement of chromosomes in the developing fetus include marker chromosomes, Robertsonian translocations, paracentric inversions, and reciprocal translocations. Translocated men should be treated with IVF/ICSI using preimplantation genetic screening or amniocentesis [100].

Autosomal-recessive CF is the genetic disorder that affects Caucasians most frequently [101]. There is a mutation in the CFTR gene on chromosome 7p that affects 4% of the general population. The vas deferens, seminal vesicle, and distal two-thirds of the epididymis are all affected by the development of a membrane protein that acts as an ion channel. Congenital Bilateral Absence of the Vas Deferens (CBAVD), one of the 2000 mutations that have been identified, may be impacted by CFTR mutations. But only homozygous mutations can cause CF [102]. Infertility affects one percent of men worldwide, and obstructive azoospermia affects up to six percent of men with MFI [103]. Every azoospermic man should have a thorough physical examination to rule out CBAVD, but those with high semen volumes and acidic urine need special attention [104,105]. When vasa is absent, it is simpler to misdiagnose a patient's condition in a medical setting. Testicular sperm aspiration, TESE with ICSI, and microsurgical epididymal sperm aspiration have the three highest success rates for patients with CF or CBAVD. Patients with CBAVD have higher-quality sperm than those with CF, and they are less likely to have difficulties with sperm retrieval [102]. They also function more effectively during ICSI procedures.

The three most common mutations are F508, R117H, and W1282X, but the prevalence and presence of other mutations are greatly influenced by the patient's race [106]. Routine testing is frequently restricted to the mutations

that are most common in a particular community after a mutation panel has been analyzed. e. a less serious clinical manifestation of CF. g. g. g. history of chest infection.). It's important to check for CF mutations in a partner of someone with CBAVD. In cases where the female partner has CFTR mutations, it may be prudent to perform ICSI using the male partner's sperm. The specific mutations that each parent carries determine whether a child is born with CBAVD or CF. If tests for known mutations are negative, it is necessary to rule out the possibility that the female partner may have any unidentified mutations [107].

The unilateral vas deferens and absence of the ipsilateral kidney are common in newborns, in addition to genetic predispositions [108]. It is not recommended to test for CFTR mutations in this fertile population. You should be aware of this if you are a man with normal kidney function and a unilaterally absent vas deferens. Renal anomalies can occasionally lead to the identification of CFTR and CBAVD mutations [109]. In the absence of a CFTR mutation and the absence of either one or both vas deferens directions, abdominal ultrasound is required.

Three minor deletions of the Y chromosome are designated by the letters AZFa, AZFb, and AZFc [110]. Every AZF region is thought to contain numerous spermatogenesis-related genes. Clinically significant deletions that

completely or partially remove one or more AZF regions frequently result in severe oligo-zoospermia and azoospermia [111].

Men with azoospermia (8-12%) have the highest frequency of Y microdeletions, while men with oligozoospermia (3-7%) show a clear cause-and-effect relationship with spermatogenic failure [112]. Y microdeletions are not present in men who have typical azoospermia. Although only 25–30% of Y deletions are located in these regions, 65–70% of Y deletions are located in the AZFb, AZFbc, or AZFabc regions. According to [113], the AZFa region accounts for just 5% of deletions. The gr/gr deletion in the AZFc region, which eliminates 50% of the region's gene content and increases the risk of oligozoospermia by 2.5e8 fold, must be taken into consideration [114]. Few studies have found a connection between the deletion and testicular germ cell tumors, despite the deletion significantly increasing the risk of decreased sperm production [115].

It may be possible for men with factor c deletions linked to azoospermia to have their sperm removed from their testicles in 50% to 75% of cases, but this is not advised given the poor prognosis. Both the fact that Y chromosome microdeletions can be passed on to male offspring and the recommendation for couples to seek counseling before ICSI are crucial to note.

It is critical to determine whether a Y chromosome microdeletion is present in patients with azoospermia or oligozoospermia and a sperm count [10]. Males

with high sperm counts exhibited a tendency toward having more microdeletions, according to a meta-analysis [116]. Patients must be tested even though this kind of testing only has a beneficial effect when the sperm count is high [10].

The integrity, quality, and functionality of sperm are all harmed by oxidative stress, according to research [117]. Oxidative stress increases the risk of poor embryo development, miscarriage, and infertility [118]. It also weakens and damages sperm DNA. By way of illustration, poor lifestyle choices can result in oxidative stress. g. Reduced risk of SDF and improved sperm quality can be achieved by changing one's lifestyle and adopting antioxidant regimens [118]. due to the involvement of environmental exposure (drinking, smoking). There are numerous techniques, including but not limited to: g. Continuous measurement and evaluation should be viewed as experimental (e. g. g. (With aid from techniques such as chemiluminescence, fluorescence, or others) [119. the detection of stronger obstruction signals (e.

Scrotal ultrasounds are routinely performed on patients with oligozoospermia or azoospermia in clinical practice because of the known link between MFI and testicular cancer [121]. Testicular cancer is more likely to occur in infertile men with severe sperm abnormalities (hazard ratio: 3; risk rises with infertility) [122]. A recent systematic review [123] of infertile men found that testicular microcalcifications were linked to an approximately 18-fold increased risk of

testicular cancer. The effectiveness of US as a routine testicular cancer screening technique for infertile men is still up for debate [121].

Without taking the size, vascularity, and echogenicity of the suspected nodule into account, the US is unable to accurately identify testicular tumors. Smaller lesions and nodules have a lower risk of turning into cancer, according to the data.

The use of transrectal and scrotal ultrasounds in patients with severe oligozoospermia or azoospermia, a low seminal volume, an acidic pH, and a potential obstruction should be safe. In order to identify the seminal vesicles (SV) and/or epididymis, you can use this instrument in conjunction with the CBAVD. g. Other examples include developing seminal vesicles, abnormalities/agenesis, cysts blocking the ejaculatory duct, hypoplasia or atrophy [120,126], and cysts.

The genitourinary tract is now easier to see thanks to MRI. Hypogonadism and elevated prolactin levels can occur in infertile men as a result of a pituitary pathology, most frequently a prolactinoma.

Each infertile couple must undergo assessments of both partners at the same time to decide the best course of action. In order to assess male infertility in men, a thorough medical history, physical examination, and sperm analysis are performed. The WHO Laboratory Manual for the Examination and Processing of Human Sperm, sixth edition, should be used when performing a semen

analysis. FSH/LH ratios and total serum testosterone levels should be used to determine the hormones responsible for oligozoospermia and azoospermia. Men who suffer from severe oligospermia or azoospermia should be able to get genetic testing. Men with untreated infertility issues and couples who frequently miscarry following a natural conception and ART should both get SDF testing. Physical examinations and genitourinary tract ultrasounds might be combined if obstruction is a possible issue. g. g. g. g. Varicocele severity varies (e. g. g. increase the size of the testicles and epididymis while covering them in cystic lesions); and. For instance, Prader's orchidometer may not be accurate if there is a significant hydrocele, an inguinal testis, epididymal enlargement or fibrosis, thickened scrotal skin, a small testis, or if the epididymis is disproportionally large in comparison to the total testicular volume [61]. The most expensive, intricate, and accurate method of measuring free testosterone is equilibrium dialysis. It is believed that men who receive a free testosterone reading, which can be obtained at http://www . issam . ch/freetesto . htm [81, 82], will be able to identify hypogonadal symptoms more quickly, accurately, and simply. However, hypogonadotropic hypogonadism, also referred to as secondary hypogonadism or hypogonadotropic hypogonadism, may exist if FSH, LH, and testosterone levels are low or normal [16, 84]. Future erectile dysfunction treatment protocols may need to adjust to the newly discovered categories of primary,

secondary, and compensate hypogonadism (normal testosterone and elevated LH values in infertile men) [84].

References

[1] Barratt CLR, Bjo¨ rndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysis of the evidence to support the devel- opment of global WHO guidance-challenges and future research opportunities. Hum Reprod Update 2017;23(6):660e80. https:// doi.org/10.1093/humupd/dmx021.

[2] Vander Borght M, Wyns C. Fertility and infertility: definition and epidemiology. Clin Biochem 2018;62:2e10. https://doi.org/ 10.1016/j.clinbiochem.2018.03.012.

[3] Zegers-Hochschild F, Adamson GD, Dyer S, et al. The interna- tional glossary on infertility and fertility care. Fertil Steril 2017; 108(3):393e406. https://doi.org/10.1016/j.fertnstert.2017.06.005.

[4] Sun H, Gong T-T, Jiang Y-T, Zhang S, Zhao Y-H, Wu Q-J. Global, regional, and national prevalence and disability-adjusted life- years for infertility in 195 countries and territories, 1990e2017: results from a global burden of disease study. Aging 2017; 11(23):10952e91. https://doi.org/10.18632/aging.102497.

[5] Slade P, O'Neill C, Simpson AJ, Lashen H. The relationship be- tween perceived stigma, disclosure patterns, support and distress in new attendees at

an infertility clinic. Hum Reprod 2007;22(8):2309e17. https://doi.org/10.1093/humrep/dem115.

[6] Wu AK, Elliott P, Katz PP, Smith JF. Time costs of fertility care: the hidden hardship of building a family. Fertil Steril 2013;99(7): 2025e30. https://doi.org/10.1016/j.fertnstert.2013.01.145.

[7] Capogrosso P, Ventimiglia E, Boeri L, et al. Male infertility as a proxy of the overall male health status. Minerva Urol Nefrol 2018;70(3):286e99. https://doi.org/10.23736/S0393-2249.18. 03063-1.

[8] Ventimiglia E, Capogrosso P, Boeri L, et al. Infertility as a proxy of general male health: results of a cross-sectional survey. Fertil Steril 2015;104(1):48e55. https://doi.org/10.1016/j.fertnstert. 2015.04.020.

[9] Ventimiglia E, Montorsi F, Salonia A. Comorbidities and male infertility: a worrisome picture. Curr Opin Urol 2016;26(2): 146e51. https://doi.org/10.1097/MOU.0000000000000259.

[1] Salonia A, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, et al. EAU Guidelines on Sexual and Reproductive Health. EAU Guidelines; 2022. Available at: https:// d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU- Guidelines-on-Sexual-and-Reproductive-Health-2022.pdf.

[2] Agarwal A, Baskaran S, Parekh N, et al. Male infertility. Lancet 2021;397(10271):319e33. https://doi.org/10.1016/S0140-6736(20) 32667-2.

[3] Aksglaede L, Juul A. Testicular function and fertility in men with Klinefelter syndrome: a review. Eur J Endocrinol 2013;168(4): R67e76. https://doi.org/10.1530/EJE-12-0934.

[4] Dode´ C, Hardelin J-P. Kallmann syndrome. Eur J Hum Genet 2009;17(2):139e46. https://doi.org/10.1038/ejhg.2008.206.

[5] Glazer CH, Eisenberg ML, Tøttenborg SS, et al. Male factor infer- tility and risk of death: a nationwide record-linkage study. Hum Reprod 2019;34(11):2266e73. https://doi.org/10.1093/humrep/ dez189.

[6] Pozzi E, Boeri L, Capogrosso P, et al. Rates of hypogonadism forms in Klinefelter patients undergoing testicular sperm extrac- tion: a multicenter cross-sectional study. Andrology 2020;8(6): 1705e11. https://doi.org/10.1111/andr.12843.

[7] Salonia A, Rastrelli G, Hackett G, et al. Paediatric and adult-onset male hypogonadism. Nat Rev Dis Prim 2019;5(1):38. https:// doi.org/10.1038/s41572-019-0087-y.

[8] Gunes S, Arslan MA, Hekim GNT, Asci R. The role of epigenetics in idiopathic male infertility. J Assist Reprod Genet 2016;33(5): 553e69. https://doi.org/10.1007/s10815-016-0682-8.

[9] Practice Committee of the American Society for Reproductive Medicine, Society for Male Reproduction and Urology. Report on varicocele

and infertility: a committee opinion. Fertil Steril 2014;102(6):1556e60. https://doi.org/10.1016/j.fertnstert.2014. 10.007.

[10] Baazeem A, Belzile E, Ciampi A, et al. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. Eur Urol 2011;60(4):796e808. https:// doi.org/10.1016/j.eururo.2011.06.018.

[11] Damsgaard J, Joensen UN, Carlsen E, et al. Varicocele is associ- ated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. Eur Urol 2016;70(6):1019e29. https://doi.org/ 10.1016/j.eururo.2016.06.044.

[12] Boeri L, Capogrosso P, Ventimiglia E, et al. Undiagnosed predia- betes is highly prevalent in primary infertile men - results from a cross-sectional study. BJU Int 2019;123(6):1070e7. https:// doi.org/10.1111/bju.14558.

[13] Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukkou E, Michopoulos J. Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. Fertil Steril 2003;80(4):914e20. https:// doi.org/10.1016/s0015-0282(03)01123-3.

[14] Alfano M, Pederzoli F, Locatelli I, et al. Impaired testicular signaling of vitamin A and vitamin K contributes to the aberrant composition of the extracellular matrix in idiopathic germ cell aplasia. Fertil Steril 2018;111(4):687e98. https://doi.org/ 10.1016/j.fertnstert.2018.12.002.

[15] Muneer A, Pozzi E, Cakir OO. The role of nitric oxide (NO) do- nors in the treatment of male infertility. Curr Pharmaceut Des 2021. https://doi.org/10.2174/1381612826666201112144828.

[16] Guthauser B, Boitrelle F, Plat A, Thiercelin N, Vialard F. Chronic excessive alcohol consumption and male fertility: a case report on reversible azoospermia and a literature review. Alcohol Alcohol 2014;49(1):42e4. https://doi.org/10.1093/alcalc/ agt133.

[17] La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero AE. Diabetes mellitus and sperm parameters. J Androl 2012;33(2): 145e53. https://doi.org/10.2164/jandrol.111.013193.

[1] Ricci E, Al Beitawi S, Cipriani S, et al. Semen quality and alcohol intake: a systematic review and meta-analysis. Reprod Biomed Online 2016;34(1):38e47. https://doi.org/10.1016/j.rbmo.2016. 09.012.

[2] Amiri I, Sheikh N, Najafi R. Nitric oxide level in seminal plasma and its relation with sperm DNA damages. Iran Biomed J 2007; 11(4):259e64.

[3] Boeri L, Capogrosso P, Ventimiglia E, et al. High-risk human papillomavirus in semen is associated with poor sperm progres- sive motility and a high sperm DNA fragmentation index in infertile men. Hum Reprod 2019;34(2):209e17. https://doi.org/ 10.1093/humrep/dey348.

[4] Lopes F, Pinto-Pinho P, Gaiva˜o I, et al. Sperm DNA damage and seminal antioxidant activity in subfertile men. Andrologia 2020; 53(5):e14027. https://doi.org/10.1111/and.14027.

[5] Campbell MJ, Lotti F, Baldi E, et al. Distribution of semen examination results 2020 - A follow up of data collated for the WHO semen analysis manual 2010. Andrology 2021;9:817e22. https://doi.org/10.1111/andr.12983.

[6] Boeri L, Ventimiglia E, Capogrosso P, et al. The duration of infer- tility affects semen parameters in primary infertile men: results of a single-centre, cross-sectional study. BJU Int 2019;123(5): 891e8. https://doi.org/10.1111/bju.14613.

[7] Henkel R, Maass G, Jung A, Haidl G, Schill W-B, Schuppe H-C. Age-related changes in seminal polymorphonuclear elastase in men with asymptomatic inflammation of the genital tract. Asian J Androl 2007;9(3):299e304. https://doi.org/10.1111/j.1745- 7262.2007.00270.x.

[8] Giwercman A, Bruun E, Frimodt-Møller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological ab- normalities in testes of men with a history of cryptorchidism. J Urol 1989;142(4):998e1001. https://doi.org/10.1016/s0022- 5347(17)38967-x. discussion 1001-1002.

[9] Hildorf S, Clasen-Linde E, Fossum M, Cortes D, Thorup J. Fertility potential is impaired in boys with bilateral ascending testes. J Urol 2021;205(2):586e94. https://doi.org/10.1097/ JU.0000000000001350.

[10] Yavetz H, Harash B, Paz G, et al. Cryptorchidism: incidence and sperm quality in infertile men. Andrologia 1992;24(5):293e7. https://doi.org/10.1111/j.1439-0272.1992.tb02655.x.

[11] Boeri L, Pederzoli F, Capogrosso P, et al. Semen infections in men with primary infertility in the real-life setting. Fertil Steril 2020; 113(6):1174e82. https://doi.org/10.1016/j.fertnstert.2020.01.034.

[12] Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Soci- ety clinical practice guideline. J Clin Endocrinol Metabol 2009; 95(6):2536e59. https://doi.org/10.1210/jc.2009-2354.

[13] Cazzaniga W, Candela L, Boeri L, et al. The impact of metaboli- cally healthy obesity in primary infertile men: results from a cross-sectional study. Andrology 2020;8(6):1762e9. https:// doi.org/10.1111/andr.12861.

[14] Cazzaniga W, Capogrosso P, Ventimiglia E, et al. High blood pressure is a highly prevalent but unrecognised condition in pri- mary infertile men: results of a cross-sectional study. Eur Urol Focus 2018;6(1):178e83. https://doi.org/10.1016/j.euf.2018. 07.030.

[15] Pozzi E, Boeri L, Capogrosso P, et al. Infertility as a proxy of men's health: still a long way to go. Turk J Urol 2021. https:// doi.org/10.5152/tud.2021.20561.

[16] Salonia A, Matloob R, Gallina A, et al. Are infertile men less healthy than fertile men? Results of a prospective case-control survey. Eur Urol 2009;56(6):1025e31. https://doi.org/10.1016/ j.eururo.2009.03.001.

[17] Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World health organization laboratory methods for the examination of human semen. Eur Urol 2016;70(4):635e45. https://doi.org/10.1016/j.eururo.2016.04.010.

[1] Boeri L, Capogrosso P, Ventimiglia E, et al. Heavy cigarette smok- ing and alcohol consumption are associated with impaired sperm parameters in primary infertile men. Asian J Androl 2019;21(5):478e85. https://doi.org/10.4103/aja.aja_110_18.

[2] Belladelli F, Boeri L, Capogrosso P, et al. Substances of abuse consumption among patients seeking medical help for uro- andrological purposes: a sociobehavioral survey in the real-life scenario. Asian J Androl 2021. https://doi.org/10.4103/aja.aja_ 13_21.

[3] Gundersen TD, Jørgensen N, Andersson A-M, et al. Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. Am J Epidemiol 2015;182(6):473e81. https://doi.org/10.1093/aje/ kwv135.

[4] Bracken MB, Eskenazi B, Sachse K, McSharry JE, Hellenbrand K, Leo-Summers L. Association of cocaine use with sperm concen- tration,

motility, and morphology. Fertil Steril 1990;53(2):315e22. https://doi.org/10.1016/s0015-0282(16)53288-9.

[5] Scott C, Omar K, Alnajjar HM, Alifrangis C, Ahmed K, Muneer A. A patient-centric pathway for testicular cancer - a multicentre study investigating the uptake of semen cryopreser- vation and impact on treatment. Andrology 2021;9(3):823e8. https://doi.org/10.1111/andr.12984.

[6] Suzuki K, Shin T, Shimomura Y, Iwahata T, Okada H. Spermato- genesis in tumor-bearing testes in germ cell testicular cancer patients. Hum Reprod 2015;30(12):2853e8. https://doi.org/ 10.1093/humrep/dev250.

[7] Yasmin E, Mitchell R, Lane S. Preservation of fertility in teenagers and young adults treated for haematological malignancies. Lan- cet Haematol 2021;8(2):e149e60. https://doi.org/10.1016/ S2352-3026(20)30324-0.

[8] Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Definitions of infer- tility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2019;113(3):533e5. https://doi.org/10.1016/j.fertnstert. 2019.11.025.

[9] Schlegel PN, Sigman M, Collura B, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril 2020;115(1):54e61. https://doi.org/10.1016/j.fertnstert.2020.11. 015.

[10] Anguiano A, Oates RD, Amos JA, et al. Congenital bilateral absence of the vas deferens. A primarily genital form of cystic fibrosis. JAMA 1992;267(13):1794e7.

[11] Kerem B, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922): 1073e80. https://doi.org/10.1126/science.2570460.

[12] Bieniek JM, Drabovich AP, Lo KC. Seminal biomarkers for the evaluation of male infertility. Asian J Androl 2016;18(3):426e33. https://doi.org/10.4103/1008-682X.175781.

[13] Arumugam M, Shetty DP, Kadandale JS, Kumari SN. Y chromosome microdeletion and cytogenetic findings in male infertility: a cross-sectional descriptive study. Int J Reprod Biomed 2021;19(2):147e56. https://doi.org/10.18502/ijrm.v19i2.8473.

[14] Elsaid HOA, Gadkareim T, Abobakr T, et al. Detection of AZF microdeletions and reproductive hormonal profile analysis of infertile sudanese men pursuing assisted reproductive approaches. BMC Urol 2021;21(1):69. https://doi.org/10.1186/ s12894-021-00834-3.

[15] Lotti F, Maggi M. Sexual dysfunction and male infertility. Nat Rev Urol 2018;15(5):287e307. https://doi.org/10.1038/nrurol.2018.20.

[16] Tur-Kaspa I, Maor Y, Levran D, Yonish M, Mashiach S, Dor J. How often should infertile men have intercourse to achieve conception? Fertil Steril 1994;62(2):370e5. https://doi.org/ 10.1016/s0015-0282(16)56893-9.

[1] Boeri L, Capogrosso P, Ventimiglia E, et al. Testicular volume in infertile versus fertile white-European men: a case-control inves- tigation in the real-life setting. Asian J Androl 2021. https:// doi.org/10.4103/aja.aja_93_20.

[2] Nieschlag E, Behre HM. Anamnesis and physical examination. In: Nieschlag E, Behre HM, Nieschlag S, editors. Andrology. Male reproductive health and dysfunction. 3rd ed. Berlin: Springer; 2010. p. 93e100 [Chapter 5].

[3] WHO. WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge: Cambridge Univer- sity Press; 2000.

[4] Boeri L, Belladelli F, Capogrosso P, et al. Normal sperm parame- ters per se do not reliably account for fertility: a case-control study in the real-life setting. Andrologia 2021;53(1):e13861. https://doi.org/10.1111/and.13861.

[5] World Health Organization. Laboratory manual for the examina- tion and processing of human semen. 6th ed. Geneva: WHO; 2021.

[6] Yifu P, Lei Y, Shaoming L, Yujin G, Xingwang Z. Sperm DNA fragmentation index with unexplained recurrent spontaneous abortion: a systematic review and meta-analysis. J Gynecol Obstetr hum Reprod 2020:101740. https://doi.org/10.1016/ j.jogoh.2020.101740.

[7] Santi D, Spaggiari G, Simoni M. Sperm DNA fragmentation in- dex as a promising predictive tool for male infertility diagnosis and treatment management - meta-analyses. Reprod Biomed On- line 2018;37(3):315e26. https://doi.org/10.1016/j.rbmo.2018.06. 023.

[8] Tharakan T, Bettocchi C, Carvalho J, et al. European Association of Urology Guidelines panel on male sexual and reproductive health: a clinical consultation guide on the indications for per- forming sperm DNA fragmentation testing in men with infer- tility and testicular sperm extraction in nonazoospermic men. Eur Urol Focus 2021. https://doi.org/10.1016/j.euf.2020.12.017.

[9] Grimes DA, Lopez LM. “Oligozoospermia,” “azoospermia,” and other semen-analysis terminology: the need for better science. Fertil Steril 2007;88(6):1491e4. https://doi.org/10.1016/ j.fertnstert.2007.04.013.

[10] Haddock L, Gordon S, Lewis SEM, Larsen P, Shehata A, Shehata H. Sperm DNA fragmentation is a novel biomarker for early pregnancy loss. Reprod Biomed Online 2021;42(1): 175e84. https://doi.org/10.1016/j.rbmo.2020.09.016.

[11] Rex AS, Wu C, Aagaard J, Fedder J. DNA fragmentation in hu- man spermatozoa and pregnancy rates after intrauterine insem- ination. Should the DFI threshold Be lowered? J Clin Med 2021; 10(6). https://doi.org/10.3390/jcm10061310.

[12] Simon L, Emery B, Carrell DT. Sperm DNA fragmentation: consequences for reproduction. Adv Exp Med Biol 2019;1166: 87e105. https://doi.org/10.1007/978-3-030-21664-1_6.

[13] Ribas-Maynou J, Yeste M, Becerra-Toma´s N, Aston KI, James ER, Salas-Huetos A. Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis. Biol Rev Camb Phil Soc 2021. https://doi.org/10.1111/brv.12700.

[14] Tan J, Taskin O, Albert A, Bedaiwy MA. Association between sperm DNA fragmentation and idiopathic recurrent pregnancy loss: a systematic review and meta-analysis. Reprod Biomed On- line 2019;38(6):951e60. https://doi.org/10.1016/j.rbmo.2018.12. 029.

[15] Agarwal A, Majzoub A, Baskaran S, et al. Sperm DNA fragmentation: a new guideline for clinicians. World J Men Health 2020; 38(4):412e71. https://doi.org/10.5534/wjmh.200128.

[16] Evenson DP. Sperm chromatin structure assay (SCSA®). Methods Mol Biol 2013;927:147e64. https://doi.org/10.1007/ 978-1-62703-038-0_14.

[17] Nicopoullos J, Vicens-Morton A, Lewis SEM, et al. Novel use of COMET parameters of sperm DNA damage may increase its utility to diagnose male infertility and predict live births following both IVF and ICSI. Hum Reprod 2019;34(10): 1915e23. https://doi.org/10.1093/humrep/dez151.

[1] Xie P, Keating D, Parrella A, et al. Sperm genomic integrity by TUNEL varies throughout the male genital tract. J Urol 2020; 203(4):802e8. https://doi.org/10.1097/JU.0000000000000659.

[2] Esteves SC, Roque M, Bradley CK, Garrido N. Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmenta- tion in semen: systematic review and meta-analysis. Fertil Steril 2017;108(3). https://doi.org/10.1016/j.fertnstert.2017.06.018. 456e467.e1.

[3] Boeri L, Capogrosso P, Cazzaniga W, et al. SHBG levels in pri- mary infertile men: a critical interpretation in clinical practice. Endocrine Connect 2020;9(7):658e66. https://doi.org/10.1530/ EC-20-0183.

[4] Bhasin S, Zhang A, Coviello A, et al. The impact of assay quality and reference ranges on clinical decision making in the diagnosis of androgen disorders. Steroids 2008;73(13):1311e7. https:// doi.org/10.1016/j.steroids.2008.07.003.

[5] Boeri L, Capogrosso P, Ventimiglia E, et al. Does calculated free testosterone overcome total testosterone in protecting from sex- ual symptom impairment? Findings of a cross-sectional study. J Sex Med 2017;14(12):1549e57. https://doi.org/10.1016/ j.jsxm.2017.10.070.

[6] Hackett G, Kirby M, Edwards D, et al. British society for sexual medicine guidelines on adult testosterone deficiency, with state- ments for UK

practice. J Sex Med 2017;14(12):1504e23. https:// doi.org/10.1016/j.jsxm.2017.10.067.

[7] Martin-du-Pan RC, Bischof P. Increased follicle stimulating hor- mone in infertile men. Is increased plasma FSH always due to damaged germinal epithelium? Hum Reprod 1995;10(8):1940e5. https://doi.org/10.1093/oxfordjournals.humrep.a136211.

[8] Ventimiglia E, Ippolito S, Capogrosso P, et al. Primary, secondary and compensated hypogonadism: a novel risk stratification for infertile men. Andrology 2017;5(3):505e10. https://doi.org/ 10.1111/andr.12335.

[9] Krausz C, Riera-Escamilla A. Genetics of male infertility. Nat Rev Urol 2018;15(6):369e84. https://doi.org/10.1038/s41585-018- 0003-3.

[10] Fakhro KA, Elbardisi H, Arafa M, et al. Point-of-care whole- exome sequencing of idiopathic male infertility. Genet Med 2018;20(11):1365e73. https://doi.org/10.1038/gim.2018.10.

[11] Lipshultz LI, Lamb DJ. Risk of transmission of genetic diseases by assisted reproduction. Nat Clin Pract Urol 2007;4(9):460e1. https://doi.org/10.1038/ncpuro0879.

[12] Johnson MD. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. Fertil Steril 1998;70(3):397e411. https://doi.org/10.1016/s0015-0282(98)00209-x.

[13] Clementini E, Palka C, Iezzi I, Stuppia L, Guanciali-Franchi P, Tiboni GM. Prevalence of chromosomal abnormalities in 2078 infertile couples referred for assisted reproductive techniques. Hum Reprod 2005;20(2):437e42. https://doi.org/10.1093/hum- rep/deh626.

[14] Vincent M-C, Daudin M, De MP, et al. Cytogenetic investigations of infertile men with low sperm counts: a 25-year experience. J Androl 2002;23(1):18e22. https://doi.org/10.1002/j.1939- 4640.2002.tb02597.x. discussion 44-45.

[15] Deebel NA, Galdon G, Zarandi NP, et al. Age-related presence of spermatogonia in patients with Klinefelter syndrome: a system- atic review and meta-analysis. Hum Reprod Update 2020;26(1): 58e72. https://doi.org/10.1093/humupd/dmz038.

[16] Jarvi K, Lo K, Fischer A, et al. CUA Guideline: the workup of azoospermic males. Can Urol Assoc J 2010;4(3):163e7. https:// doi.org/10.5489/cuaj.10050.

[15] Krausz C, Giachini C. Genetic risk factors in male infertility. Arch Androl 2007;53(3):125e33. https://doi.org/10.1080/0148501070 1271786.

[16] Augarten A, Yahav Y, Kerem BS, et al. Congenital bilateral absence of vas deferens in the absence of cystic fibrosis. Lancet 1994;344(8935):1473e4. https://doi.org/10.1016/s0140-6736(94) 90292-5.

Chapter 6

Prothrombotic gene polymorphisms and adverse reproductive outcomes in assisted reproductive technology

The word "coagulation of blood" is derived from the Greek verb hemostasis, which means "to stop bleeding" [1e4]. Blood clotting is started and stopped by the coagulation pathway, an intricate web of physiological processes [5]. A dynamic equilibrium between hemolysis, anticoagulation, and coagulation is hemostasis. Both post-injury and spontaneous bleeding can be stopped by this pathway.

A coagulation system typically consists of the fibrinolysis system, vessels, platelets, coagulation/anticoagulation proteins, and other components [6, 7]. All four compartments work in perfect harmony until a blood vessel injury causes excessive bleeding that clots. Every component must be flawlessly coordinated with every other component for the system to operate at its best.

The coagulation process consists of the initial, secondary, and concluding stages. Primary hemostasis, caused by thrombocyte adhesion and accumulation, causes a plug to form at the site of injury. There are two distinct secondary coagulation mechanisms that cause hemostasis: intrinsic and extrinsic mechanisms. These two separate but linked pathways make up the common pathway [5, 8]. At the intersection, each person took a separate turn onto a different street. In the end, the shared pathway is utilized to convert

fibrinogen into fibrin [2,5,9]. The main objective of the procedure is to fibrin net stabilize the platelet plug [5].

The intrinsic pathway, which is the longer of the two secondary hemostasis pathways, contains the clotting factors fibrinogen, prothrombin, Christmas, X, Stuart-Prower, plasma thromboplastin, and Hageman [2, 5, 6, 9]. Factors I, II, VII, and X of the extrinsic pathway are shorter than those of the intrinsic pathway. The factors I, II, V, VIII, and X can each activate the common pathway by themselves [2, 5, 6]. The intrinsic pathway is started by exposed endothelial collagen, while the extrinsic pathway is started by tissue factor, which is secreted by damaged endothelial cells [2,5]. For various reasons, every path starts somewhere. The common pathway, which begins at factor X, leads to the combination of the fibrin monomers to create fibrin polymers. A fibrin mesh is created on the fibrin strands by factor XIII, which then strengthens the thrombocyte plug [2,4,5].

Pathologies of the coagulation system can result in thrombosis, hypo- or hypercoagulation, bleeding, or any combination of these conditions [2]. These pathologies can develop when any of the coagulation components is harmed. The primary focus of this chapter is on coagulation disorders that promote thrombosis. The "thrombophilia" condition is characterized by an elevated propensity for clotting, thrombosis, and venous thromboembolism (VTE) [10,11]. ".

Hereditary coagulation disorders like procoagulation conditions and uncommon bleeding disorders can be brought on by mutations or polymorphisms in the genes that encode particular coagulation factors [1,12]. Numerous studies have focused on the genetic element of coagulopathy development [1]. Growing interest in how genetic variations in the coagulation/anticoagulation factors linked to various pathologies contribute has led to the discovery of numerous mutations [13].

Because they change the concentration of the pertinent proteins, genetic variations in the protein-coding regions of genes and polymorphisms in the regulatory regions of coagulation factors both significantly affect hemostasis [1,14]. The two primary types of mutations are gain-of-function mutations, which include diseases affecting antithrombin, protein C, and protein S. [12], and loss-of-function mutations, which include the 20210AG prothrombin gene mutation and factor V Leiden [15]. Contrarily, autosomal dominant diseases are thought to be the main causes of factor XI and dysfibrinogenemia [12,16]. Thrombotic events frequently occur in the families of patients with inherited prothrombotic coagulation disorders [17]. The most prevalent type of hereditary thrombophilia interacts with factor V Leiden mutations to produce thrombophilic syndromes. The name of the mutation comes from the place where it was found [18]. According to various statistics, between 3 and 7 percent of Caucasians live in Europe. The factor V polypeptide undergoes

arginine conversion from glutamate (G506) to arginine (R506Q). By making plasma resistant to activated protein C's anticoagulant effects, this mutation increases the production of thrombin. The diagnosis could be verified by DNA testing for the mutant factor V gene [19].

A vital protein called antithrombin, which prevents thrombin from performing its function, is produced by the liver. In contrast to type I antithrombin deficiency, which is caused by a decline in the production of biologically healthy antithrombin, type II antithrombin deficiency is characterized by normal levels of antithrombin but decreased functional activity [17]. An homozygous antithrombin defect is frequently fatal.

Only naturally occurring sources contain Protein C, which helps to prevent blood clotting [7,8,10]. How well protein C can carry out its functions depends on how much protein S is present [10]. In the presence of protein S., protein C regulates thrombin synthesis [21]. More than 160 different autosomal dominant mutations can affect the protein C gene. Only 0e1e3 people in 1000 have one of the more than 130 mutations that can result in protein deficiency [21].

The anomaly is the G20210A mutation identified in the prothrombin gene's promoter region. The letter A is transposed to the letter G. Prothrombin levels rise as a result of the mutation's increased thrombin production [18,22,23]. Up to 3% of Caucasians in Europe are thought to be heterozygotes. Prothrombin

levels rise by 70 percent and 30 percent, respectively, in homozygous carriers of the mutation [18]. The G20210A and factor V Leiden mutations both increase the risk of thromboembolism [23e25].

Homocysteine levels are frequently elevated as a result of MTHFR (5,10-methylenetetrahydrofolate reductase) mutations. Studies on the MTHFR gene have found 34 rare mutations and nine polymorphisms [26]. Studies [23,26] have shown a link between hyperhomocysteinemia and the genetic variant 677C/T (A222V), which is the most common.

The type 1 plasminogen activator inhibitor (PAI-1) is one of the main controllers of fibrinolysis. Due to polymorphisms in these genes, the body produces thrombin-activatable fibrinolysis inhibitor (TAFI) and PAI-1 in high quantities. According to available data, some gene promoter polymorphisms may be linked to a tad higher thrombotic risks [28].

High-risk patients for recurrent thrombosis can be quickly identified using elevated factor VIII levels. Although it has a broad range of conditions where it can be used as an acute phase agent, its clinical applicability is in question [29,30].

Hemostasis of blood is difficult, as was already mentioned. In fact, complex feedback mechanisms that operate at different levels affect hemostatic plug development. This process is more difficult because of the numerous changes that the coagulation system goes through during pregnancy [7,8]. During the

last trimester of pregnancy, coagulation factor plasma concentrations vary the most. The activity of factors VII, VIII, and X as well as the von Willebrand factor has all significantly increased [7]. There is also more recent evidence that thrombin is produced. Two additional factors linked to, respectively, physiological changes in coagulation during pregnancy are variations in protein S levels and acquired activated protein C resistance [7,31].

The concentrations of PAI-1 and PAI-2 must rise by a factor of 5 in order to become prothrombotic [7]. Also, during the third trimester, fibrinolytic activity decreases. The blood's coagulation activity is well known to be roughly twice as high during pregnancy as it would be in a non-pregnant state [8]. According to evolutionary theory, all of the aforementioned modifications were created in order to stop postpartum bleeding. Nevertheless, these changes may raise the risk of thrombotic complications in pregnancy for both the mother and the fetus [32,33].

Due to physiological changes in hemostasis during a healthy pregnancy, procoagu-lation markers increase [34]. When pathologic hemostasis occurs during pregnancy, it can be challenging to diagnose hereditary thrombophilia and comprehend the findings of coagulation tests.

However, tests for protein C, protein S, and antithrombin can be obtained [35]. Both factor V Leiden and prothrombin 20210AG are caused by distinct DNA alterations that can be difficult to detect. This is why it is suggested to wait six

weeks after a miscarriage or conception before requesting hereditary thrombophila testing [36].

Negative pregnancy outcomes continue to pose problems for modern obstetrics despite advances in perinatal medicine [37]. Recurrent miscarriage (RPL) has been connected to procoagulation disorders in general and inherited thrombophilias [10]. Factor V Leiden mutation, protein C and protein S deficiencies, prothrombin gene mutation, and anti-thrombin III deficiency are a few inherited thrombophilias associated with poor obstetric outcomes and miscarriage. Hyperhomocysteinemia and MTHFR mutations may play a role in pregnancy-related procoagulation issues. Because of these mutations, thrombotic risks associated with pregnancy are no longer frequently taken into account [36,38].

In RPL patients, thrombophilia is not more likely to be present at birth, according to research [39]. In the literature and in clinical settings, it has been discussed how likely RPL is and how effective treatment is [40, 41]. Unknown percentage of RPL patients have inherited hypercoagulation.

The factor V Leiden mutation has a significant impact on the complications of hypercoagulability related to pregnancy. Pregnancy-related thrombosis occurs in nearly 40 percent of women with heterozygous factor V Leiden. Regardless of their personal or family history, pregnant homozygous women have a 4 percent higher risk of developing venous thrombosis than pregnant non-

homozygous women [22,42]. Contrary to the relationship between factor V Leiden and the prothrombin mutation, the relationship between VTE, protein S, and antithrombin is less obvious. The study [44] was unable to establish a link between RPL and the absence of this protein or factor, just as it was unable to show this association. A more recent cross-sectional study on the subject [36,45] found that both women with RPL and healthy controls have an equal prevalence of the protein S variant.

The MTHFR mutation, which causes thermolabile homocysteinemia, is associated with poor pregnancy outcomes [7]. RPL and MTHFR 677C/T are related, according to the findings of several studies [46,47]. The placental insufficiency linked to thrombophilia is believed to be caused by chorionic or placental vascular thrombosis [7]. There isn't much proof that the MTHFR mutation results in poor pregnancy outcomes, despite more recent studies disputing this assertion [36,44,48].

According to a recent recommendation from the European Society of Human Reproduction and Embryology (ESHRE) [36], there is either no connection at all or a tenuous one between RPL and hereditary thrombophilias. However, the hereditary thrombophilia screening should not be performed on females who test positive for RPL.

Prothrombin mutation and RPL have been linked in a number of studies [36–43]. A female's risk of developing RPL is doubled by the G20210A mutation.

Others have found a connection between prothrombin mutation and RPL in women who have experienced two or more miscarriages, as well as between the mutation and RPL in the first trimester [44].

In the first and second trimesters of pregnancy, protein C activity is at its highest levels [10]. Theoretically, this increase in protein C activity may promote preterm labor by assisting the regulatory systems that regulate inflammation and anticoagulation [10]. Due to the inherited nature of anticoagulant protein deficiencies (protein C deficiencies), treating infertility is difficult in modern reproductive medicine. Despite unlimited sexual activity or therapeutic donor insemination, women of any age, from those under 35 to those over 35, may experience infertility, or the inability to conceive [22,49]. The majority of fertile couples were afflicted, according to reports [50–54] claiming an 8–15 percent prevalence worldwide.

If the root causes of infertility are specifically addressed, infertility can be treated. The use of assisted reproductive technology (ART) has significantly altered the way this condition is currently treated. Diseases that were once incurable can now be successfully treated thanks to significant advancements in ART techniques [50,53,55,56]. Examples of "assisted reproductive technologies" (ART) techniques include preimplantation genetic screening (PGS) and intracytoplasmic sperm injection (ICSI) [57,58]. Another illustration is the transfer of embryos. A few of the prognostic factors that have

been extensively discussed in the literature and are essential for a successful IVF cycle include the mother's age, ovarian aging, diagnosis, and ovarian reserve. Up until recently, the relationship between a person's lifestyle and the success of IVF was largely ignored. The success rates of IVF appear to be impacted by unhealthy eating patterns, caffeine use, physical activity, and exposure to harmful bisphenols [52, 57, 59]. Over four million ART procedures were carried out worldwide between 2008 and 2010 over a two-year period, according to the International Committee for Monitoring Assisted Reproductive Technologies (2008e10) [57]. Delivery rates have increased over the past few decades, going from about 40 percent in the present to 26 percent in the 1990s [57] due to significant advancements in ART. According to a conservative estimate [57,60], ART therapy has aided in the birth of more than eight million children. In the US and Europe, ART-assisted conception is used in more than 2 percent of births.

Consideration must be given to both the significant risks involved with ART procedures and the negative side effects of the drugs used in the procedures. Preterm labor, gestational diabetes, pregnancy-induced hypertension, and low birth weight have received the majority of attention in the literature that is currently available on pregnancy- and perinatal outcomes [56,58]. Ovarian hyperstimulation syndrome (OHSS), ectopic and heterotopic pregnancy, ovarian torsion, and even cancer are a few complications in emergency

medicine that are more serious [56e58,61e63]. A hypercoagulable state and venous thrombosis may be more likely given the complex OHSS pathogenesis [56]. Hemoconcentration, hypercoagulability, and abnormal electrolytes are effects of an OHSS-induced fluid shift into the third space [56e58]. Upper extremities venous thrombosis, which occurs more frequently than arterial restenosis (ART), is the thrombotic event that is discussed the most in academic writing.

Due to the rising use of ART to preserve fertility and the possibility of rare complications brought on by their co-occurring conditions, these patients should be handled with extra caution [64,65]. For example, there is a higher risk of side effects in patients receiving ART to maintain their fertility [58]. Every patient receiving ART should be considered to have had a difficult pregnancy.

However, ART's success rate has increased over time [48,51,57,66]. More than half of couples seeking assisted reproduction give up after several failed attempts because ART has a low success rate (around 40 percent) [57].

The fibrinolytic system is crucial to the implantation process because it contributes to both implantation failure and miscarriage [28]. While some reports and earlier studies [28,67] did yield conflicting findings, others did not. According to one theory, an ART cycle implant could fail due to a microvascular occlusion brought on by thrombophilia. However, the exact

reason for implantation failure is still unknown [44,48]. Thrombophilia may be to blame.

Ovarian stimulation, which is frequently required for ART procedures like IVF or ICSI [28,48,68], affects the pathways that cause coagulation and fibrinolysis. The result is thrombotic-related diseases. Some researchers [48, 69] have proposed low molecular weight heparins (LMWH) as a potential therapy to stop RPL after ART administration. Regarding the potential effect that hereditary thrombophilias may have on the efficacy of ART, various reproductive immunologists and reproductive endocrinologists have differing opinions [32,33,48].

During an embryo's implantation, progesterone ought to harm endometrial stromal cells. By invading the endometrial capillaries with cytotrophoblasts, this physiological process stops bleeding [7]. There is a higher expression of PAI-1, the primary thrombin precursor and initiator of hemostasis. When tissue-type plasminogen activator is inactivated, tissue factor serves as the main initiator of fibrinolysis [7]. To maintain hemostasis, these two components work together.

Hypercoagulation-related mechanisms are shared by RPL and recurrent implant failure after IVF. [7]. IVF failure has been associated with localized thrombosis at the implantation site because it prevents syncytiotrophoblasts from naturally colonizing the maternal vascular bed [7, 69].

The fibrinolytic parameters (clot lysis time P 14 .003; TAFI) were significantly altered by ovarian stimulation in the study by Sticchi and colleagues.

In particular, P14 .009 and P14 .003 of the PAI-1 [27]. values indicating the duration of the clot lysis process.

Between the beginning of the menstrual cycle and days 5 to mid-luteal phase, there was a significant rise in the levels of TAFI and PAI-1 (pb0.0001, P1-dot01, and P1-dot005, respectively). There was a decrease rather than an increase between Day 1 and Day 7.

every two weeks. The investigation's findings demonstrated that polymorphisms in TAFI and PAI-1 had a significant impact on these molecules' concentrations during ovarian stimulation [28]. Variations in fibrinolysis have been connected to mutations in the TAFI and PAI-1 genes, which can take place at various points during the ovarian stimulation cycle.

In a different study of prothrombotic hereditary coagulation disorders, women who tested positive for prothrombin gene mutations, factor V Leiden, or MTHFR C677T were screened for acquired thrombophilias [7,69]. These women attempted IVF or ICSI at least twice, but they were unsuccessful both times.

Testing for thrombophilia was done on 594 women who had previously received ART [70]. Common thrombophilias don't appear to be associated with the prevalence of prior failed ART cycles or reduced fertility [48,70].

There was no correlation between thrombophilia and less favorable reproductive outcomes in this study. Contrary to the results of this extensive retrospective study, it is advised that couples receiving ART have their factor V Leiden mutations tested. The subjects received LMWH starting at the start of the controlled hyperstimulation and continuing until the b-human gonadotropin (b-HCG) test. Mild to moderate homocysteinemia may be brought on by the thermolabile MTHFR variant linked to the 677C/T mutation. Through an autosomal recessive mechanism, this disease is spread. Homocysteine levels in the body have been linked to low levels of folic acid, vitamin B6 and B12, as well as a few enzymes necessary for methionine metabolism [27].

Factor V Leiden mutation patients had a threefold increased risk of ART failure, according to Bates' meta-analysis of data from eight case-control studies (OR 3.08, 95 percent CI 1.77e5.36). Congenital thrombophilias of any kind, including AT, AT, protein C or protein S deficiency, P2 mutation, or AT, have not been found to increase an ART procedure's failure rate [71].

There was no correlation between MTHFR carrier status and the outcomes of an ART procedure in any of the studies [48,72,73] that examined the topic.

Congenital thrombophilias and the effectiveness of ART are controversial topics right now. If a patient has no personal or family history of venous thrombosis, it is recommended that congenital thrombophilia be excluded or

not treated [7,44,48]. Thrombotic markers will increase even in a healthy pregnancy due to changes in the physiological makeup of the coagulation system [7,8,34]. Pregnancy makes it more difficult to make a precise diagnosis of hereditary thrombophilia. When the results could change or improve management, coagulation testing should be done [15]. According to some theories, testing could be useful in the secondary prevention and treatment of hereditary diseases.

Polymorphisms in prothrombin 20210A and factor V Leiden can be found using DNA mutation analysis [36, 44]. Get tested for hereditary thrombophilia because it can affect protein C, protein S., and antithrombin prior to conception, throughout labor, or after a miscarriage [36].

Patients are advised against undergoing a hereditary thrombophilia screening because there is currently no information available about a family history of venous thrombotic events [36,44]. Women with RPL should get tested for hereditary thrombophilia, according to the American College of Chest Physicians' recommendations on thrombophilia, antithrombotic therapy, and pregnancy [36,74].

The findings of additional recent studies [37] have led to the recommendation that women who have previously experienced miscarriages get tested for thrombophilia. According to medical advice, prophylactic anticoagulant therapy is recommended for females with prothrombotic coagulation who have

altered coagulation systems. The D'uski et al. study's inclusion of it. study. encourages women who are most likely to miscarry to have thrombophilia testing done [37].

Preconception counseling and testing are suggested in order to prevent prothrombotic coagulopathy recurrence and unsuccessful pregnancies [41]. Most suggestions encourage taking into account females with RPL. There is much debate over the best time to examine risk factors in relation to RPL [41]. There are currently no known effective treatments for patients who have received abnormal test results. Heparin use during the peri-implantation phase of ART procedures may have an impact on the frequency of live births and clinical pregnancies [15,48,75]. Heparin was used to improve results, but it also had drawbacks like bruising and bleeding, and it was impossible to evaluate its safety because no studies had provided comparison data on side effects [75].

Without weighing the risks and benefits, prophylactic anticoagulation shouldn't be used to prevent thrombotic events during pregnancy [23]. 2 to 3 percent of mothers who use LMWH experience clinically significant maternal bleeding [23]. The most potent risk factors for thrombophilia and pregnancy-associated thrombosis have been identified as homozygous factor V Leiden or prothrombin G20201A mutations [23,76]. Pregnancy increases the risk for

most inherited thrombophilias by about 4%, with the exception of homozygotes for prothrombin G20201A or factor V Leiden [23].

Even though there is a dearth of strong scientific evidence, LMWH treatment is frequently used in thrombophilia carriers who had implant failure [48]. In patients receiving ART, heparin has been shown to enhance endometrial responsiveness, invasiveness, and decidualization of endometrial stromal cells; all of these effects may increase implantation rates [48].

Empirical LMWH may improve pregnancy prospects in women who frequently experience implantation failures during ART but do not have a known cause. One study [77] found that women who had previously undergone an unsuccessful ART procedure had a significantly higher chance of becoming pregnant. According to these findings, hereditary thrombophilia has no bearing on a patient's chance of becoming pregnant if they have a history of unsuccessful IVF implantations. Before utilizing LMWH for ART cycles, the authors advise conducting randomized controlled trials to support their findings [48, 77].

A total of 150 women who had undergone two or more unsuccessful ART procedures participated in Urman's randomized trial [78] to evaluate the results. Participants were also assigned at random to receive controlled ovarian stimulation in addition to receiving the standard luteal phase support, LMWH therapy, or no therapy at all. For participants who became pregnant, LMWH

treatment was extended for an additional 12 weeks [48,78]. In this study, the live birth rate was higher in the LMWH treatment group compared to the control group (34 percent vs. There are 66.7% (or 6%) of the population. The variation did not show any statistical significance. Heparin should not be administered to any woman who repeatedly fails an ART cycle, according to the evidence, which is, at best, of moderate quality [48]. Any additional risk factors or a family history of thrombotic events should be considered when determining whether to screen a person. Early and late pregnancy complications are more frequent in women who have inherited prothrombotic coagulation disorders. The data that are currently accessible do not support the regularity of thrombophilia testing in patients who are pregnant. Most of these tests are completely useless for the patient, and a few even make things worse by pressuring doctors into prescribing patients ineffective medications. For expectant mothers who have never experienced a pregnancy issue, routine testing for thrombophilic defects is not currently advised. It is still extremely difficult to avoid implantation problems, particularly in ART-achieved conceptions. With the exception of preventing RPL and VTE in antiphospholipid syndrome, there is insufficient evidence to suggest the use of LMWH in women with inherited thrombophilia, pregnancy complications, or ART-related implantation failure. The two groups were compared, and it was found that the LMWH group had a higher pregnancy rate among women over

36 than the placebo group. There was just one significant finding. Only 32% of study participants had thrombophilia markers, and 25% of them had the homozygous MTHFR C677T mutation [69]. There were no statistically significant changes in the prevalence of thrombophilia in the general population. The study that was cited suggests that LMWH prophylaxis may lower the risk of an early labor and a failed implantation following ART.

References

[1] Endler G, Mannhalter C. Polymorphisms in coagulation factor genes and their impact on arterial and venous thrombosis. Clin Chim Acta 2003;330(1e2):31e55. https://doi.org/10.1016/s0009- 8981(03)00022-6.

[2] Palta S, Saroa R, Palta A. Overview of the coagulation system. In- dian J Anaesth 2014;58(5):515e23. https://doi.org/10.4103/0019- 5049.144643.

[3] Thornton P, Douglas J. Coagulation in pregnancy. Best Pract Res Clin Obstet Gynaecol 2010;24:339e52.

[4] van der Meijden PEJ, Heemskerk JWM. Platelet biology and func- tions: new concepts and clinical perspectives. Nat Rev Cardiol 2019;16(3):166e79. https://doi.org/10.1038/s41569-018-0110-0. PMID: 30429532.

[5] Chaudhry R, Usama SM, Babiker HM. Physiology, coagulation pathways. Treasure Island (FL): StatPearls Publishing; January 2021. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK482253/.

[6] Chee Y. Coagulation. J Roy Coll Phys Edinb 2014;44(1):42e5. https://doi.org/10.4997/jrcpe.2014.110es.

[7] Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and pregnancy complications. Int J Mol Sci 2015;16(12):28418e28. https://doi.org/10.3390/ijms161226104. PMID: 26633369; PMCID: PMC4691051.

[8] Katz D, Beilin Y. Disorders of coagulation in pregnancy. Br J Anaesth 2015;115(Suppl. 2):ii75e88. https://doi.org/10.1093/ bja/aev374. PMID: 26658204.

[9] Panova-Noeva M, Eggebrecht L, Prochaska JH, Wild PS. Potential of multidimensional, large-scale biodatabases to elucidate coagu- lation and platelet pathways as an approach towards precision medicine in thrombotic disease. Ha¨mostaseologie 2019;39(2): 152e63.

[10] Said JM, Higgins JR, Moses EK, Walker SP, Borg AJ, Monagle PT, Brennecke SP. Inherited thrombophilia polymorphisms and preg- nancy outcomes in nulliparous women. Obstet Gynecol 2010; 115(1):5e13. https://doi.org/10.1097/AOG.0b013e3181c68907. PMID: 20027027.

[11] Dautaj A, Krasi G, Bushati V, Precone V, Gheza M, Fioretti F, Sartori M, Costantini A, Benedetti S, Bertelli M. Hereditary thrombophilia. Acta Biomed 2019;90(10-S):44e6. https:// doi.org/10.23750/abm.v90i10-S.8758. PMID: 31577252; PMCID: PMC7233636.

[12] Jain S, Acharya SS. Management of rare coagulation disorders in 2018. Transfus Apher Sci 2018. https://doi.org/10.1016/ j.transci.2018.10.009.

[13] Jevremovic M, Petronijevic A, Kartaljevic G, Momcilov P, Baklaja R, Terzic M. Immunochemical determination of anti- thrombin III in blood of patients with EPH gestoses. In: Sinzinger H, Vinazzer H, editors. Thrombosis and haemorrhagic disorders. Wurtzburg-Wien: Schmitt & Meyer; 1989. p. 240e5.

[14] Blake GJ, Schmitz C, Lindpaintner K, Ridker PM. Mutation in the promoter region of the beta-fibrinogen gene and the risk of future myocardial infarction, stroke and venous thrombosis. Eur Heart J 2001;22:2262e6.

[15] Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, Lim W, Douketis JD. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis 2016;41(1):154e64. https://doi.org/10.1007/ s11239-015-1316-1. PMID: 26780744; PMCID: PMC4715840.

[16] Peyvandi F, Palla R, Menegatti M, Mannucci PM. Introduction. Rare bleeding disorders: general aspects of clinical features, diag- nosis, and management. Semin Thromb Hemost 2009;35:349e55.

[17] Anderson JA, Weitz JI. Hypercoagulable states. Crit Care Clin 2011;27:933.

[18] MacCallum P, Bowles L, Keeling D. Diagnosis and management of heritable thrombophilias. BMJ 2014;349:g4387.

[19] Walker MC, Garner PR, Keely EJ, et al. Changes in activated pro- tein C resistance during normal pregnancy. Am J Obstet Gynecol 1997;177:162.

[20] Rhe´aume M, Weber F, Durand M, et al. Pregnancy-related venous thromboembolism risk in asymptomatic women with anti- thrombin deficiency: a systematic review. Obstet Gynecol 2016; 127(4):649.

[21] Louis-Jacques AF, Maggio L, Romero ST. Prenatal screening for thrombophilias. Clin Lab Med 2016;36(2):421.

[22] ACOG Committee Opinion. Infertility workup for the women's health specialist. Obstet Gynecol 2019;133:e377e84.

[23] Campello E, Spiezia L, Adamo A, Simioni P. Thrombophilia, risk factors and prevention. Expet Rev Hematol 2019;12(3):147e58. https://doi.org/10.1080/17474086.2019.1583555. Epub 2019 Feb 26. PMID: 30773075.

[24] Connors JM. Thrombophilia testing and venous thrombosis. N Engl J Med 2017;377(12):1177.

[25] Lim MY, Deal AM, Musty MD, et al. Thrombophilic risk of indi- viduals with rare compound factor V Leiden and prothrombin G20210A polymorphisms: an international case series of 100 individuals. Eur J Haematol 2016;97(4):353.

[26] Leclerc D, Sibani S, Rozen R. Molecular biology of methylenetetrahydrofolate reductase (MTHFR) and overview of mutations/ polymorphisms. In: Madame curie bioscience database [internet]. Austin (TX): Landes Bioscience; 2000e2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6561/.

[27] Hague WM. Homocysteine and pregnancy. Best Pract Res Clin Obstet Gynaecol 2003;17:459.

[28] Sticchi E, Romagnuolo I, Cellai AP, Lami D, Fedi S, Prisco D, Noci I, Abbate R, Fatini C. Fibrinolysis alterations in infertile women during controlled ovarian stimulation: influence of BMI and genetic components. Thromb Res 2012;130(6):919e24. https://doi.org/10.1016/j.thromres.2012.07.005.

[29] Jenkins PV, Rawley O, Smith OP, O'Donnell JS. Elevated factor VIII levels and risk of venous thrombosis. Br J Haematol 2012; 157(6):653e63. https://doi.org/10.1111/j.1365-2141.2012.09134.x. Epub 2012 Apr 25. PMID: 22530883.

[30] Tanaka KA, Bharadwaj S, Hasan S, Judd M, Abuelkasem E, Henderson RA, Chow JH, Williams B, Mazzeffi MA, Crimmins SD, Malinow AM. Elevated fibrinogen, von Willebrand factor, and Factor VIII confer resistance to dilutional coagulopathy and activated protein C in normal pregnant women.

Br J Anaesth 2019;122(6):751e9. https://doi.org/10.1016/j.bja.2019.02.012. Epub 2019 Mar 19. PMID: 30916034.

[31] Szecsi PB, Jorgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemostasis 2010;103:718e27. https://doi.org/10.1160/TH09- 10-0704.

[32] Terzic M, Jevremovic M. Immunology of pregnancy. In: Ljaljevic J, editor. Clinical immunology. Beograd: European Center for Peace and Development (ECPD) University for Peace of United Nations; 2002. p. 1107e21.

[33] Terzic M. Immunology of infertility. In: Ljaljevic J, editor. Clinical immunology. Beograd: European Center for Peace and Development (ECPD) University for Peace of United Nations; 2002. p. 1123e34.

[1] Kristoffersen AH, Petersen PH, Roraas T, Sandberg S. Estimates of within-subject biological variation of protein C, antithrombin, protein S free, protein S activity, and activated protein C resistance in pregnant women. Clin Chem 2017;63: 898e907.

[2] Terzic M. Spontaneous abortion. In: Zigic D, Lapcevic M, Popovic J, Ivankovic D, editors. General practice e family medi- cine. Section of general practice of the Serbian Medical Society. Beograd: As Zemun; 2003. p. 153e60.

[3] ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S,

Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2018;2018(2):hoy004. https:// doi.org/10.1093/hropen/hoy004. PMID: 31486805; PMCID: PMC6276652.

[4] Dłuski D, Mierzyn´ski R, Poniedziałek-Czajkowska E, Leszczyn´-ska-Gorzelak B. Adverse pregnancy outcomes and inherited thrombophilia. J Perinat Med 2018;46(4):411e7. https://doi.org/ 10.1515/jpm-2017-0059. PMID: 28792912.

[5] Levin BL, Varga E. MTHFR: addressing genetic counseling di-lemmas using evidence-based literature. J Genet Counsel 2016; 25:901e11.

[6] Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril 2010;93(4):1234e43.

[7] Branch DW. The truth about inherited thrombophilias and pregnancy. Obstet Gynecol 2010;115(1):2e4.

[8] van Dijk MM, Kolte AM, Limpens J, et al. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update 2020;26(3):356e67. https://doi.org/10.1093/ humupd/dmz048.

[9] Bradley LA, Palomaki GE, Bienstock J, Varga E, Scott JA. Can Fac-tor V Leiden and prothrombin G20210A testing in women with recurrent

pregnancy loss result in improved pregnancy out- comes?: results from a targeted evidence-based review. Genet Med 2012;14:39e50.

[10] Gao H, Tao FB. Prothrombin G20210A mutation is associated with recurrent pregnancy loss: a systematic review and meta-analysis update. Thromb Res 2015;135:339e46.

[11] Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003;361:901e8.

[12] Matsukawa Y, Asano E, Tsuda T, Kuma H, Kitaori T, Katano K, Ozaki Y, Sugiura-Ogasawara M. Genotyping analysis of protein S-Tokushima (K196E) and the involvement of protein S antigen and activity in patients with recurrent pregnancy loss. Eur J Obstet Gynecol Reprod Biol 2017;211:90e7.

[13] Chen H, Yang X, Lu M. Methylenetetrahydrofolate reductase gene polymorphisms and recurrent pregnancy loss in China: a system- atic review and meta-analysis. Arch Gynecol Obstet 2016;293: 283e90.

[14] Govindaiah V, Naushad SM, Prabhakara K, Krishna PC, Radha Rama Devi A. Association of parental hyperhomocysteinemia and C677T Methylene tetrahydrofolate reductase (MTHFR) poly- morphism with recurrent pregnancy loss. Clin Biochem 2009;42: 380e6.

[15] Ata B, Urman B. Thrombophilia and assisted reproduction technology- any detrimental impact or unnecessary overuse? J Assist Reprod Genet

2016;33(10):1305e10. https://doi.org/ 10.1007/s10815-016-0771-8. Epub 2016 Jul 16. PMID: 27423663; PMCID: PMC5065550.

[16] Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2020;113:533e5.

[17] Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update 2015;21(4):411e26. https://doi.org/10.1093/humupd/dmv016. Epub 2015 Mar 22. PMID: 25801630.

[18] Bapayeva G, Aimagambetova G, Issanov A, Terzic S, Ukybassova T, Aldiyarova A, Utepova G, Daribay Z, Bekbossinova G, Balykov A, Lagana` AS, Terzic M. The effect of stress, anxiety and depression on in vitro fertilization outcome in Kazakhstani public clinical setting: a cross-sectional study. J Clin Med 2021;10:937. https://doi.org/10.3390/jcm10050937.

[19] Szamatowicz M. Assisted reproductive technology in reproductive medicine - possibilities and limitations. Ginekol Pol 2016;87(12): 820e3. https://doi.org/10.5603/GP.2016.0095. PMID: 28098933.

[20] De Geyter C. Assisted reproductive technology: impact on society and need for surveillance. Best Pract Res Clin Endocrinol Metabol 2019;33(1):3e8.

https://doi.org/10.1016/j.beem.2019.01.004. Epub 2019 Jan 25. PMID: 30799230.

[21] Maroufizadeh S, Navid B, Omani-Samani R, Amini P. The effects of depression, anxiety and stress symptoms on the clinical preg- nancy rate in women undergoing IVF treatment. BMC Res Notes 2019;12(1):256. https://doi.org/10.1186/s13104-019-4294-0.

[22] Boivin J, Bunting L, Collins JA, Nygren KG. International esti- mates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007;22(6):1506.

[23] Grandone E, Villani M. Assisted reproductive technologies and thrombosis. Thromb Res 2015;135(Suppl. 1):S44e5. https:// doi.org/10.1016/S0049-3848(15)50441-6. Epub 2015 Feb 9. PMID: 25903534.

[24] Esteves SC, Humaidan P, Roque M, Agarwal A. Female infertility and assisted reproductive technology. Panminerva Med 2019;61(1): 1e2. https://doi.org/10.23736/S0031-0808.18.03553-X. PMID: 30674179.

[25] Hilbert SM, Gunderson S. Complications of assisted reproductive technology. Emerg Med Clin N Am 2019;37(2):239e49. https:// doi.org/10.1016/j.emc.2019.01.005. PMID: 30940369.

[26] Sarria-Santamera A, Bapayeva G, Utepova G, Krstic J, Terzic S, Aimagambetova G, Shauyen F, Terzic M. Women's knowledge and awareness

of the effect of age on fertility in Kazakhstan. Sexes 2020;1:60e71. https://doi.org/10.3390/sexes1010006.

[27] Ferraretti AP, Nygren K, Andersen AN, de Mouzon J, Kupka M, Calhaz-Jorge C, Wyns C, Gianaroli L, Goossens V, European IVF-Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Trends over 15 years in ART in Europe: an analysis of 6 million cycles. Hum Reprod Open 2017;2017(2):hox012. https://doi.org/10.1093/ hropen/hox012.eCollection.2017.

[28] Terzic M, Arsenovic N. The link between ovarian cancer and infertility drugs. Eur J Gynaecol Oncol 2007;28:160. PMID: 17479686.

[29] Terzic M, Aksam S, Maricic S, Arsenovic N. Acute abdomen caused by adnexal torsion in the first trimester of pregnancy: a case report. Srp Arh Celok Lek 2011;139:239e41. https:// doi.org/10.2298/sarh1104239t.

[30] Terzic M, Bila J, Pilic I, Kocijancic D. Bilateral ampulary pregnancy after clomifen citrate and intrauterine insemination e a unique case report. Gynecol Endocrinol 2013;29(6):619e21. https:// doi.org/10.3109/09513590.2013.777417.

[31] Terzic M, Norton M, Terzic S, Bapayeva G, Aimagambetova G. Fertility preservation in endometrial cancer patients: options, challenges and perspectives. Ecancer 2020;14:1030. https:// doi.org/10.3332/ecancer.2020.1030. www.ecancer.org.

[32] Terzic M, Aimagambetova G, Terzic S, Kongrtay K, Bapayeva G, Gullo G. Fertility preservation management for ovarian cancer (chapter ID: 69089). In: Garzon S, Lagana` AS, editors. Fertility preservation in gynecological cancer: current management and novel insights. New York, USA: Nova Science Publishers, Inc.; 2021. p. 183e219 (Library of Congress Cataloging-in-Publication Data ISBN: 978-1-53619-271-9; ISBN: 978-1-53619-179-0).